Effects of Methylphenidate on Cognitive Functions in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: Evidence from a Systematic Review and a Meta-Analysis

David R. Coghill, Sarah Seth, Sara Pedroso, Tatiana Usala, John Currie, and Antonella Gagliano

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of neuropsychological impairments. The relationship between these neuropsychological deficits and the defining symptoms of ADHD seems more complex than originally thought. Methylphenidate (MPH) is an effective treatment for ADHD symptoms, but its impact on cognition is less clearly understood.

Methods: With a common systematic search strategy and a rigorous coding and data extraction strategy across domains, we searched electronic databases to identify published placebo controlled trials that compared MPH and placebo on executive and nonexecutive memory, reaction time, reaction time variability and response inhibition in children and adolescents (5–18 years) with a formal diagnosis of ADHD.

Results: Sixty studies were included in the review, of which 36 contained sufficient data for meta-analysis. Methylphenidate was superior to placebo in all five meta-analyses: executive memory, standardized mean difference (SMD) .26, 95% confidence interval (CI): −.39 to −.13; non-executive memory, SMD .60, 95% CI: −.79 to −.41; reaction time, SMD .24, 95% CI: −.33 to −.15; reaction time variability, SMD .62, 95% CI: −.90 to −.34; response inhibition, SMD .41, 95% CI: −.55 to −.27.

Conclusions: These data support the potentially important effects of MPH on various aspects of cognition known to be associated with ADHD. Consideration should be given to adding cognitive outcomes to the assessment of treatment outcome in ADHD, considering the complexity of the relationship between ADHD symptoms and cognition.

Key Words: ADHD, cognition, inhibition, memory, meta-analysis, methylphenidate, neuropsychology, systematic review

Although attention-deficit/hyperactivity disorder (ADHD) is characterized by the symptoms of inattention, hyperactivity and impulsivity (1), there are also considerable data supporting an association with various neurocognitive deficits (2). Implicated domains include aspects of executive functioning including response inhibition (3,4), working memory (5,6), and attentional set shifting and planning (6,7). Barkley (8) proposed behavioral inhibition as the core deficit in ADHD, with other aspects of executive functioning occurring as secondary phenomena. Subsequent studies have not supported this view and found these other executive functions to make an independent contribution that sit alongside rather than occurring as a consequence of poor response inhibition (6). Studies have also emphasized that a broad range of non-executive deficits, including more basic storage aspects of memory (9), timing (10,11), reaction time and reaction time variability (12,13), are associated with ADHD as well as motivational factors such as delay aversion (14,15) and decision making (16). A growing body of evidence strongly suggests that, although each of these domains can impact clinically on those with ADHD, none are essential to the causality of ADHD (17). Initially two- (18) and three-arm (19) pathways were proposed, but more recently even more complex six- and seven-arm (20) pathways have been put forward.

Although it has generally been assumed that the cognitive deficits are the precursors of the symptoms (21,22), several lines of investigation have led us (23) and others (24) to question this relationship. We have proposed that, although the symptoms and cognitive deficits associated with ADHD co-occur, they are not necessarily causally related to each other. Rather they run in parallel at the same level of analysis. This might increase rather than diminish the potential clinical relevance of these cognitive deficits. Effect sizes for many cognitive deficits are, at a group level, in the moderate-to-large range (2), but the proportion of individuals with any one deficit is relatively small (25), and those individuals who do have a deficit are likely to be significantly impaired.

If the clinical and cognitive effects of ADHD treatments are also less strongly associated than is often assumed (26–28), as seems to be the case, it becomes important to identify not only whether symptoms improve with treatment but also whether the associated cognitive deficits improve.

Methylphenidate (MPH) is effective at reducing the symptoms of ADHD with a large effect size (.8–1.0) (29,30). Functional magnetic resonance imaging (MRI) studies in both healthy and ADHD subjects indicate that acute doses of MPH up-regulate and normalize brain regions known to be underfunctioning in ADHD and that longer-term administration enhances the activation of the basal ganglia and frontal regions (31–34). This is the likely

From the Division of Neuroscience (DRC, SS, JC), Medical Research Institute, University of Dundee, Ninewells Hospital; National Health Service Tayside (SS), Child and Adolescent Mental Health Service, Dundee, United Kingdom; Department of Child and Adolescent Psychiatry (SP), Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; UMEE (Unità Multidisciplinare per l'età evolutiva) ASUR (TU), Jesi; and the Department of Pediatric Science (AG), University of Messina, Policlinico Universitario G. Martino, Messina, Italy.

Address correspondence to David R. Coghill, M.D., Ch.B., Division of Neuroscience, Medical Research Institute, Ninewells Hospital, University of Dundee, MACHS2 Building, Dundee, UK DD1 9SY; E-mail: d.r.coghill@dundee.ac.uk.

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mechanism of the effects of MPH on cognition and symptoms. Many naturalistic, open label, and uncontrolled studies have reported positive effects of MPH on a range of cognitive processes. However, placebo controlled studies have provided conflicting results with regard to memory (35,36), reaction time (37,38), reaction time variability (39,40), and response inhibition (41,42), making the data difficult to interpret from a scientific and a clinical perspective. Although there have been narrative reviews of the effects of stimulant medications on cognition (43), these studies have been neither systematically reviewed nor subjected to meta-analysis.

Our aim is to conduct a systematic review and meta-analysis comparing the effects of MPH and placebo on five aspects of cognitive functioning: executive and non-executive memory; reaction time; reaction time variability; and response inhibition in children and adolescents with ADHD. These neuropsychological functions have been chosen because of their strong associations with ADHD and because a pilot search of the literature identified these as the best-studied domains from a neuropsychopharmacological perspective. Specifically, we tested the hypothesis that, compared with placebo, MPH will significantly improve functioning in each of these five domains.

Methods and Materials

A systematic literature search was conducted to identify published studies that investigated the effects of MPH on different cognitive domains (see trial registry information after Acknowledgments).

Inclusion/Exclusion Criteria

Placebo-controlled randomized studies (including both parallel group or counterbalanced crossover designs) published in a peer-reviewed journal that assessed the effects of MPH on neuropsychological outcomes measured with standardized neuropsychological instruments on one or more of five neuropsychological domains (executive and non-executive aspects memory, reaction time and reaction time variability, and response inhibition) were included. The search was limited to published studies to ensure a level of methodological adequacy and rigor among included studies and also to avoid the inevitable difficulties involved in securing access to a full set of unpublished studies and the potential for bias that this would introduce (44). Studies were required to have $\geq$ 10 participants (5–18 years of age) with a formal diagnosis of ADHD, attention-deficit disorder, or hyperkinetic disorder of any subtype made according to either DSM (versions III or IV) or ICD (versions 9 or 10) criteria (minimal brain dysfunction was not included). Given the limited understanding of the way in which comorbid disorders might influence the effect of MPH on cognitive function in children with ADHD, we excluded studies that included ADHD patients with major neurological impairment, chronic physical illness, sensory or motor impairment, psychosis, major depressive disorder, autism spectrum disorders, abuse of any illegal drugs, and intellectual impairment (IQ $<$80). We did not exclude samples with comorbid anxiety, oppositional defiant disorder, and specific learning disorders, because of the high prevalence of these conditions in samples of children with ADHD. Functional MRI imaging studies were excluded on the basis that the functional MRI environment has the potential to add additional confounds. We did not exclude studies with additional nonpharmacological interventions, such as psychoeducation, as long as these were provided to both study groups.

Search Strategy. A common search strategy was used for all cognitive domains and is described in detail in Supplement 1 and the published study protocol (see trial registry information after Acknowledgments). Common terms for participants (e.g. all variants of ADHD, hyperkinetic disorder, attention deficits) and study design were used across domains. In the initial search, both general and specific search terms were used to identify studies with a broad range of neurocognitive outcomes. Only studies addressing executive and non-executive aspects of memory, reaction time and reaction time variability, and response inhibition were included in this review For other neuropsychological domains, there were either too few studies (e.g., delay aversion) or too diverse a range of outcomes (e.g., attention) to be combined in a meta-analysis. Two authors (S.P., A.G.) separately conducted and cross-checked all searches, which were finalized in May 2012.

Study Selection. Studies were blindly double-coded for eligibility. Papers were initially screened on the basis of titles. Two reviewers then independently inspected abstracts of potentially relevant studies and acquired the full article of those studies deemed to be potentially relevant. Potential target papers were independently assessed for final inclusion with full text by two reviewers with a standard data extraction sheet. Disagreements and uncertainty not resolved by coders ($n = 16$) were arbitrated by one reviewer (D.R.C.), who was not involved in earlier stages of coding. Reviewers were not blinded to the names of the trial authors, institutions, or journals of publication.

Data Extraction. Data from included studies were extracted by two reviewers and entered into Revman5 (45). Extracted data were then compared to ensure accuracy. The following data were extracted: study procedures, including recruitment, diagnosis, assessment tools, medication, dosage, duration, and clinical setting; study design; randomization method; inclusion and exclusion criteria for participants; number of participants (total and per group); age of subjects; neuropsychological tasks and outcome measures; method of analysis (intention to treat, per protocol). We included data only for the highest dose, where studies included more than one dose of MPH. We recorded change scores (the difference between score at study end and at baseline) and endpoint scores (score at study end) for the outcomes of interest. Neuropsychopharmacological response to MPH was defined as score change on the primary measures from each task. For studies that included more than one appropriate task for a particular neuropsychological domain, data for each task was entered separately. We analyzed only the available data and made no attempt to impute missing data. Studies with insufficient reported data were not included in the meta-analysis.

Statistical Analysis

All included studies contained continuous outcomes. Because studies within the same domain of interest used varying outcome measures, effect sizes were calculated as standardized mean differences (SMDs). All analyses included all participants in the treatment groups to which they were allocated, if data permitted. Cross-over studies were treated as parallel group studies, because insufficient data were provided to permit analysis of within-individual change (e.g., no correlations of scores between conditions). Even though the results of this approach approximate those from a paired analysis, the resulting confidence intervals (CIs) are likely to be too wide. This approach is considered conservative (studies are under- rather than over-weighted) and is equivalent to setting the between-condition correlation to zero (46). For these studies the baseline SD was used