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Review

Methylphenidate and P300 in attention deficit hyperactivity disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Methylphenidate (MPH) is a stimulant medicine often used to treat attention deficit hyperactivity disorder (ADHD), as it may positively affect behaviour and brain activity. This work aims to systematise the current literature about the effects of MPH on the amplitude of P300 in individuals with ADHD.
Methods: A systematic review and meta-analysis of empirical studies measuring P300 amplitude and comparing MPH administration to either a pre-MPH condition or healthy controls was conducted, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Results: Our results revealed no overall (n = 13) significant differences between individuals diagnosed with ADHD and medicated with MPH and controls. Although, a moderation analysis by region found differences between both groups on frontal sites. When comparing the pre- and post-effects of MPH on the same individuals (n = 17), it appears that P300 amplitude tends to increase post-administration in central and posterior regions. In this second meta-analysis, a moderation by task revealed a larger effect size for go/no-go.
Discussion: In general, MPH was found to increase P300 amplitude in ADHD, somewhat normalising this aspect of their brain activity. The main limitations of the included studies are the insufficiently explained dosages and the skewness for male participants. Future research directions are discussed.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is widely recognized as one of the most common neurodevelopmental disorders (Drechsler et al., 2020; Rocco et al., 2021). Its aetiology has been shown to be complex as it involves a multitude of influencing factors, such as environmental and biological (Gómez-Cano et al., 2023). Further, various traits linked to ADHD might have had evolutionary advantages and are frequently displayed in the general population (Arcos-Burgos and Acosta, 2007; Swanepoel et al., 2017). Previously ADHD was thought to be a male dominant disorder, but recent literature has shown that females are also affected (Faheem et al., 2022). There appears to exist sex differences in the expression of these symptoms and deficits, with females manifesting less hyperactivity and less difficulties in motor response inhibition and with males presenting more cognitive flexibility problems (Carbonneau et al., 2020).

Generally, ADHD encompasses observable symptoms of inattention, hyperactivity, and/or impulsivity (Drechsler et al., 2020). In addition, neurocognitive deficits are commonly observed, particularly in behavioural inhibition and attention, but also in working memory (Townes et al., 2023). These symptoms and deficits are thought to be related to structural abnormalities of the brain, and alterations of its functional networks (De La Fuente et al., 2013). The frontal lobe seems to be the most affected brain region in ADHD individuals, with hypoactivation and reduced overall volume (De La Fuente et al., 2013; Vieira De Melo et al., 2018). This area of the brain is connected to the striatum via fronto-striatal circuitry, which is also a neurological network that appears to play an important role in the pathophysiology of ADHD, as it

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seems to be linked to the previously mentioned neurocognitive functions (Chudasama and Robbins, 2006). The areas involved in the fronto-striatal functional networks appear to showcase reduced volume in patients with ADHD (Cubillo et al., 2012; Cupertino et al., 2020), which can compromise neural circuitry activity and impact dopamine (DA) and norepinephrine (NE; also called noradrenaline) levels (Del Campo et al., 2011).

DA and NE (which is the hydroxylation of DA; Gonzalez-Lopez and Vrana, 2020) are neurotransmitters thought to contribute to the maintenance of attention, working memory, and motor control (Ranjbar-Slamloo and Fazlali, 2020). In ADHD, there seems to be lower extracellular levels of these neurotransmitters as a result of increased reuptake of DA and NE by their respective transporters (Mehta et al., 2019). As such, the modulation of these reuptake processes is often targeted in the pharmacological treatment of ADHD (Posner et al., 2020).

Medications for the treatment of ADHD are categorised as either non-stimulants or stimulants (also known as psychostimulants), with one of the most frequently used stimulants being methylphenidate (MPH; Posner et al., 2020). MPH blocks the DA transporter in the striatum and the NE transporter in the prefrontal cortex, resulting in reduced reuptake of both neurotransmitters and, consequently, in their higher extracellular levels in the prefrontal cortex (Groom and Cortese, 2022). This medication appears to induce improvements in neurocognitive functions, such as working memory, attention, and inhibitory control, in both children (Coghill et al., 2014; Czerniak et al., 2013) and adults (Pievsky and McGrath, 2018) with ADHD. Furthermore, MPH seems to, at least partially, normalise the level of brain activation of children with ADHD to the levels of healthy controls, when performing selective attention and inhibitory control tasks (Pievsky and McGrath, 2018).

Although MPH appears to reduce the severity of ADHD symptoms, it seems to affect both sexes differently (Dafny and Yang, 2006; Kok et al., 2020). Young females with ADHD reported to feel the effect of the stimulant faster, although they also experience an earlier decline of its impact and tend to present greater improvements of their symptoms in the long run (Kok et al., 2020). In turn, for males with ADHD it was reported more improvements in inattention, hyperactivity, and impulsivity than girls with ADHD (Kok et al., 2020). Notwithstanding, there are adverse effects from this medication which are commonly reported, such as insomnia, nervousness, central nervous system side effects (e.g., dizziness, headaches), gastrointestinal problems (nausea/vomiting, weight loss), and cardiovascular effects (tachycardia, and palpitations) (Verghese and Abdijadid, 2023). Although these adverse effects cannot be disregarded, MPH also appears to have positive effects that manifest in both behaviour and brain activity.

Brain activation can be studied through event-related potentials (ERPs), which are the neural responses to stimuli that can be extracted from an electroencephalogram (EEG; Sur and Sinha, 2009). The P300 (or P3) is an ERP component that seems to reflect attentional and memory processes, and can be further divided into P3a and P3b subcomponents (Polich, 2007). P3a is thought to reflect frontal lobe function, occurring when attention is redirected from the frequent target stimuli to a “novel”/less frequent stimuli (Polich, 2003). As such, P3a may be related to earlier cognitive processes, such as attentional mechanisms and working memory, being affected by dopaminergic activity (Polich, 2007). On the other hand, P3b is thought to reflect later processing in temporal/parietal lobe function, associated with memory updating operations and storage (Polich, 2003). Furthermore, the relationship between this subcomponent and the locus-coeruleus-norepinephrine system suggests that P3b is, at least partially, affected by dopaminergic activity (Polich, 2007).

Given that attention and executive functions, such as inhibition and working memory, are processes related to P300 and are impaired in individuals with ADHD (Townes et al., 2023), this ERP and its subcomponents might be the most sensitive biomarkers for ADHD (Kaiser et al., 2020). Additionally, P300 has been an ERP of focus in the context of both the diagnosis and the treatment of individuals with ADHD (Arpaia et al., 2022), although more research is needed to establish concrete criteria for its usage (Gamma and Kara, 2020). In this way, considering that MPH can lead to neurocognitive improvements (e.g., Coghill et al., 2014), it is relevant to explore how this stimulant affects brain activity, namely through the P300.

Generally, the amplitude of P300 and its subcomponents (P3a and P3b) appears to be reduced in individuals with ADHD when compared to healthy controls (Kaiser et al., 2020; Peisch et al., 2021; Szuromi et al., 2011). Moreover, stimulant medication (i.e., MHP) seems to lead to an increase in the amplitudes of these components (Lazzaro et al., 1997; Peisch et al., 2021; Szuromi et al., 2011). However, it is relevant to acknowledge that the efficacy of MPH may be influenced by other factors, such as EEG biomarkers (Loo et al., 2024). For instance, a low baseline alpha peak frequency has been linked to a lesser response to the administered drug in male adolescents (Arns et al., 2008, 2018).

Previous reviews have provided useful insights into the relationship between MPH, ADHD, and ERPs. These reviews focused on: (a) possible effects of MPH in individuals with ADHD in neurocognitive functions, comparing with a placebo condition (Coghill et al., 2014); (b) efficacy of stimulants and non-stimulants in reducing self- and other-reported symptoms of ADHD (Faraone, 2009); (c) possible benefits of using ERPs to clinically differentiate individuals with ADHD from healthy ones (Gamma and Kara, 2020); (d) ERP differences between ADHD and healthy individuals (Kaiser et al., 2020); and (d) effects of stimulants and of neurofeedback in children and adolescents with ADHD (Razoki, 2018). However, not all of these reviews included the analysis of ERPs (Coghill et al., 2014; Faraone, 2009; Razoki, 2018), and those who did fail to specifically target MPH effects in P300 (Gamma and Kara, 2020) or assess the longitudinal impact of this stimulant in the ADHD individuals (Kaiser et al., 2020).

Therefore, the present study aims to systematise the current literature about the effects of MPH on the amplitude of P300, and its subcomponents, in individuals diagnosed with ADHD, when compared to either healthy controls or longitudinal studies with pre- and post-administration outcomes in the same sample.

2. Methods

2.1. Search strategy

The present study was pre-registered in PROSPERO (CRD42024511544) on the 5th of March 2024, and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA; Page et al., 2021) recommendations. The search expression (Methylphenid* OR Metilfenidato) AND (event related OR erp OR P3 OR P300) AND (ADHD OR Attention Deficit Hyperactivity Disorder OR Attention Deficit-Hyperactivity Disorder OR Attention Deficit/Hyperactivity Disorder OR ADD) was used to identify records by their title/abstract, in the PubMed, Web of Science, and EBSCO (PsycInfo, PsycArticles, and Psychology and Behavioral Sciences Collection) databases. Additional records were also retrieved by scanning the reference lists of literature reviews and included studies and by manual search.

The inclusion criteria were the following: (a) empirical studies presenting quantitative data regarding P300, P3a, or P3b amplitude modulation by MPH; and (b) group comparison between pre- and post-administration of MPH in participants diagnosed with ADHD and/or between MPH post-administration and healthy controls. Exclusion criteria are showcased in the PRISMA flow diagram (Fig. 1, Page et al., 2021).

2.2. Study selection

The identified records were added into Rayyan (Ouzzani et al., 2016), and all duplicates were checked for and removed. Three members (FM, CP, and JOP) of the research team were involved in determining eligibility criteria. FM and JOP screened for the inclusion of studies

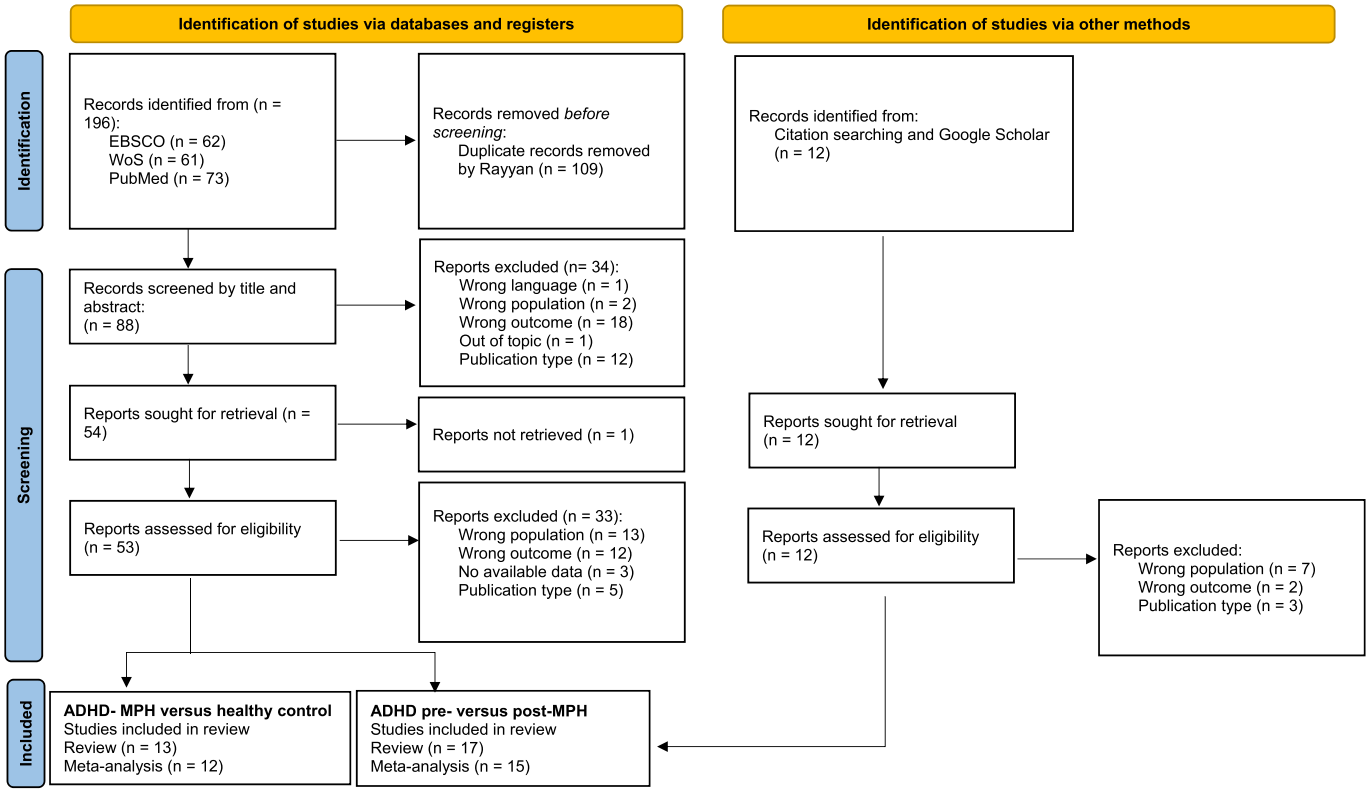

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

using Rayyan (Ouzzani et al., 2016) in two phases (title and abstract screening, and full-text screening). Both coders were blind to the other's decisions until they were revealed in a team meeting where CP solved the emerging conflicts.

2.3. Data extraction and quality assessment

A spreadsheet was built in order to extract the required information from the included studies, namely: (a) study details - authors, name and publication year; (b) sample characteristics - healthy or ADHD group, size and percentage of females, average and standard deviation of group age; (c) ERP component amplitude means and standard deviations, or *t*-test and *p*-value between groups, or p-value and direction of the effect; (d) P300 features - nomenclature of component/subcomponent, time-window, region of interest, measurement technique (peak, mean, or area); and (d) task descriptors - name of the task, modality (auditory or visual), and type of stimuli (e.g., figures).

From the extracted information, P300 amplitude means and standard deviations, sample sizes, t-values, *p*-values, and the direction of the effect, served to compute the effect size. In studies lacking information for the calculation of the effect size, the authors whose contact was available were requested for the needed data. An absence of a reply led to the exclusion of these studies. A total of five authors were contacted for missing information.

Keil et al. (2014) checklist for reporting EEG and MEG research was used to assess the quality of the included studies. As this review has its focus on an ERP component, the topics considered from this checklist were: hypotheses, participants, recording characteristics and instruments, stimulus and timing parameters, description of data preprocessing steps, measurement procedures, statistical analyses, and figures (discarding the last item). Each item was scored as either being present (i.e., "1") or absent (i.e., "0") by BB and FM. The total quality score could, therefore, range from 0 to 29, where the higher the value, the higher the methodological quality of the study. Posteriorly, markings from both members were compared, and conflicts were settled by checking the original studies.

2.4. Analytical strategy and meta-analytic methods

The studies were aggregated into two distinct meta-analyses: 1) Observational studies with one group of participants with ADHD diagnosis treated with MPH and a control group of not-treated ADHD participants; 2) Longitudinal studies with participants diagnosed with ADHD and assessed pre- and post-administration of methylphenidate.

ProMeta 3 software version 3.0 (Internovi, Italy, 2015) was used to analyse the data, and the pooled effect sizes for the ERP amplitudes were estimated as Hedges' g (Hedges, 1981). Effect sizes for Hedges' g values were classified as small ($g \geq |0.20|$), medium ($g \geq |0.50|$), and large ($g \geq |0.80|$) (Cohen, 2009). Each analysis included reported values for Hedges' g, 95 % confidence intervals, and *p*-values. Forest plots were created to visually summarise the data.

Heterogeneity (i.e., variance) between studies was assessed with *Q* statistic (Cochran, 1954) on overall effect sizes. This test was described via I^2 statistic (Higgins et al., 2011), and the significance level used was 0.1 (Egger et al., 1997). Therefore, heterogeneity was classified as either low ($I^2 < 25$ %), medium (25 % $< I^2 \leq 50$ %), or high ($I^2 \geq 50$ %), and random effect models were used in these last two cases. Egger's test of intercept bias was used to assess publication bias (Egger et al., 1997).

For each meta-analysis, subgroup analyses were used for the topographic region and experimental task. Electrode clusters or individual electrodes surrounding Fz, Cz, and Pz were utilised for the topographic region analysis. Moderation analysis was performed if there were at least 3 studies available.

3. Results

3.1. Search results

A detailed flow diagram of study selection was developed using the PRISMA 2020 guidelines (Fig. 1, Page et al., 2021). Initially, 196 records were identified after the electronic search. From those, 109 were removed for being duplicates. The remaining studies were screened by title and abstract ($n = 88$) and then by their full-text ($n = 53$), leaving a total of 20 eligible records. A manual search did not result in additional studies. Hence, the total of records included for data extraction was 20. The agreement between researchers in respect to the decision of inclusion or exclusion of a study by their title and abstract was substantial ($k = 0.71$; Landis and Koch, 1977). The overall characteristics of the reports included are presented in Table 1.

Included studies mainly used the continuous performance task ($n = 5$), the oddball paradigm ($n = 5$), and the go/no-go ($n = 5$). The remaining used an Eriksen flanker task ($n = 2$), a Stroop colour word test ($n = 1$), and a stop-signal task ($n = 1$). This last task, employed by Janssen et al. (2016) was considered to be a go/no-go task, therefore both were combined in only go/no-go ($n = 6$). Most of the studies used visual stimuli ($n = 15$), expressed in figures ($n = 7$), numbers ($n = 4$), letters ($n = 3$), and words ($n = 1$), and 5 studies used auditory stimuli.

The reports for MPH doses were diversified. Some studies reported the dose only in milligrams per day ($n = 5$) or in milligrams per kilogram per day ($n = 7$). Other studies reported the dose in both milligrams per day and in milligrams per kilogram per day ($n = 5$), and the remaining failed to report the dosages ($n = 2$). Overall, the dosages per day varied from 10 to 40 mg per day. The duration of the pharmacological intervention before the EEG record is also inconsistent. In some studies, MPH was only administered on the day ($n = 8$), while in others it was administered for 1–4 weeks ($n = 4$) or 2–3 months ($n = 2$). The duration of the pharmacological treatment is impossible to ascertain in the "usual prescription" studies ($n = 5$).

These studies investigated MPH effects in children (i.e., younger than 13 years; $n = 5$), adolescents (i.e., 13- to 18-year-olds; $n = 1$), youngsters (i.e., sample including both children and adolescents; $n = 13$), and adults (i.e., 18 and older; $n = 1$). Furthermore, the percentage of females in the ADHD participants ranged between 0 % ($n = 5$) and 47 % ($n = 3$).

Based on the samples compared, studies were aggregated into: (a) ADHD individuals post-administration of MPH versus healthy controls ($n = 13$); and (b) ADHD individuals pre- versus post-administration of MPH ($n = 17$).

3.2. ADHD post-MPH versus healthy control

3.2.1. Study characteristics

Thirteen studies meet the eligibility criteria for analysing the ERP differences between ADHD individuals medicated with MPH and healthy controls. Most of the studies reported P300 ($n = 10$), followed by P3a ($n = 2$), and P3b ($n = 1$). The time-window used in P300 ranged between 220 and 550 ms ($n = 5$) or between 400 and 800 ms ($n = 3$), while P3a ranged from 257 to 408 ms ($n = 1$). The remaining studies did not specify the time-window used ($n = 3$). Due to the variability of these time-windows and the possible overlap, the components P300, P3a, and P3b were combined in the analysis. Miller et al.' (1996) study was excluded from the meta-analysis as there was not enough data to compute the effect size.

3.2.2. Meta-analysis

The analysis comprised 12 studies and a total of 279 participants medicated with MPH and 293 controls. Overall, no statistically significant differences were found between groups ($g = -0.07$, 95 % CI [−0.27, 0.13], $p = .499$, Fig. 2). The heterogeneity test identified no significant variance across studies ($Q(11) = 19.23$, $p = .057$, $I^2 = 43$ %). There was no evidence of publication bias in this analysis ($b = 0.86$, $p = .616$).

Although our overall analysis did not identify a significant level of heterogeneity, we performed moderation analysis by task type and region. Regarding reported topographic regions, we separated studies for the electrode or cluster around Fz ($n = 6$), Cz ($n = 6$) and Pz ($n = 8$). All regions reported no significant variance between studies ($p > .479$, Table 2). The cluster around Fz was the only region showing statistically significant differences between groups ($g = -0.39$, 95 % CI [−0.63, −0.15], $p = .001$, Fig. 3), although this effect was small.

The included tasks in this analysis were continuous performance task ($n = 4$), Eriksen flanker task ($n = 2$), go/no-go ($n = 3$) and oddball ($n = 3$). None of the tasks revealed significant differences between groups ($p > .091$, Table 2).

Additionally, we performed a random-effects meta-regression to explore the relationship between the effect sizes of the included studies and the percentage of females in the ADHD sample. The nine studies that disclosed the percentage of females in the ADHD group were included. These reported values between 0 % and 20 % (see Table 1). No statistically significant relationship was found with this covariate ($B = 0.02$, $p = .159$).

3.3. ADHD pre- versus post-MPH

3.3.1. Study characteristics

Seventeen studies meet the eligibility criteria for analysing the ERP differences between ADHD individuals before and after MPH administration. The majority of studies reported P300 ($n = 13$), with P3a and P3b being equally reported ($n = 2$). P300 had time-windows ranging from 220 to 550 ms ($n = 7$) or from 400 to 800 ms ($n = 3$), while P3a ranged from 257 to 408 ms ($n = 1$), and P3b from 280 to 700 ms ($n = 1$). The remaining studies did not specify the time-window used ($n = 4$). Similarly to the previous meta-analysis, P300, P3a, and P3b were combined. Two studies (Miller et al., 1996; Paul-Jordanov et al., 2010) were excluded from the meta-analysis as there was not enough data to compute the effect sizes.

3.3.2. Meta-analysis

This meta-analysis comprised 15 studies and a total of 409 ADHD patients before and after being medicated with MPH. Overall, a statistically significant difference was found between pre- and post-MPH P300 amplitude ($g = 0.38$, 95 % CI [0.17, 0.59], $p < .001$, Fig. 4), with the post-MPH revealing an enhancement of P300 amplitude. The heterogeneity test identified a high level of variance across studies ($Q(14) = 39.98$, $p < .001$, $I^2 = 65$ %). There was no evidence of publication bias in this analysis ($b = 1.72$, $p = .294$).

Moderation analysis by topographic regions included electrode clusters around Fz ($n = 10$), Cz ($n = 10$), and Pz ($n = 11$). An amplitude enhancement post-MPH was found for central and posterior regions ($p < .006$) but not for the anterior cluster ($p = .133$, Table 3). However, variance remained high when studies were grouped in regions ($I^2 > 49$ %, Table 3).

The included tasks in this analysis were continuous performance task ($n = 2$), Eriksen flanker task (1 study), go/no-go ($n = 6$), and oddball ($n = 5$). When grouping for go/no-go and oddball, the moderation analysis found homogeneous results ($p > .161$; Table 3). Both tasks revealed statistically significant P300 amplitude differences between pre- and post-MPH administration, although with different effect sizes, namely a medium effect size for the go/no-go task ($g = 0.55$, 95 % CI [0.30, 0.79], $p < .001$) and a small for oddball ($g = 0.37$, 95 % CI [0.16, 0.58], $p = .001$).

The random-effects meta-regression analysis included 14 studies, which reported percentages of females between 0 % and 47 % (see Table 1). No statistically significant relationship was found with this covariate ($B = -0.003$, $p = .712$).

Table 1
Characteristics of the included studies.

Authors (year)	Quality	Population	n_{sample} (% females)	Age M ± SD	MPH [dosage, duration]			Task [modality; stimuli]	P300 nomenclature (time-window)	Region	Results	
					Washout	Dosage; duration	Time before EEG				Amplitude	Latency
ADHD post-MPH versus *healthy control*												
Jonkman et al. (2000)[a]	18	Youngsters	*n* EG = 14 (7 %) [Exp2] *n* CG = 14 (14 %) [Exp1]	EG: 9.6 ± 2.2 CG: 10.1 ± 1.5	3 days prior	0.36–0.78 mg/kg; on the day	1 h	Eriksen flanker task [Visual; Figures]	P300 (400–800 ms)	Fz, Cz, & Pz	Does not compare	Does not compare
Hermens et al. (2005)[a]	16	Adolescents	*n* EG = 34 (18 %) *n* CG = 34 (18 %)	EG: 13.8 ± 1.6 CG: 13.9 ± 1.5	2^{+} days prior	Usual prescription	1 h	Oddball [Auditory; Tones]	P300 (220–550 ms)	Midline	Does not report the comparison	Does not report the comparison
Miller et al. (1996)	16	Children	*n* EG = 19 (0 %) *n* CG = 13 (0 %)	EG: 9.7 ± NA CG: 9.8 ± NA	18^{+} hours	10 mg; on the day	1 h	Stroop Colour Word Test [Visual; Words]	P3a (225–400 ms) & P3b (400–550 ms)	Posterior	Does not compare	Does not compare
Lawrence et al. (2005)[a]	13	Youngsters	*n* EG = 18 (0 %) *n* CG = 18 (0 %)	EG: 11.3 ± 1.7 CG: 11.3 ± 2.1	24 h	Usual prescription [10–40 mg per day]	1 h	A-X CPT [Visual; Numbers]	P300 (300–450 ms)	Across scalp	EG < CG	EG = CG EG = CG
Groom et al. (2010)[a]	15	Youngsters	*n* EG = 22 (NA %) *n* CG = 28 (4 %)	EG: NA CG: 12.5 ± 1.7	36 h	Usual prescription [M = 1.1 mg/kg]	NA	Go/no-go [Visual; Figures]	P300 (400–700 ms)	Cz & Pz	Does not compare	
Jonkman et al. (1999)[a]	15	Youngsters	*n* EG = 14 (NA %) [Exp2] *n* CG = 14 (7 %) [Exp1]	EG: 9.6 ± 2.2 CG: 10.5 ± 1.4	3 days	0.36–0.79 mg/kg; on the day	0.5–1.5 h	Eriksen flanker task [Visual; Figures]	P300 (400–800 ms)	Pz	Does not compare	Does not compare
Paul-Jordanov et al. (2010)[a]	13	Youngsters	*n* EG = 11 (0 %) *n* CG = 16 (19 %)	EG: 12.4 ± 0.4 CG: 12.5 ± 0.3	48 h	Usual prescription	ca. 2 h	Go/no-go [Visual; Figures]	P300 (260–328 ms)	Fronto-central	EG = CG	Does not report
Sunohara et al. (1999)[a]	13	Children	*n* EG = 20 (20 %) *n* CG = 20 (20 %)	EG: 10.5 ± 1.9 CG: 10.8 ± 1.8	24 h	0.14–0.34 mg/kg per day [Low dose]; on the day	1.5 h	CPT [Visual; Letters]	P300 (NA)	All	EG = CG	EG = CG
Winsberg et al. (1997)[a]	13	Children	n EG = 14 (NA %) n CG = 14 (NA %)	EG: 9.3 ± 1.5 CG: 10.6 ± 1.7	18–24 h	Usual prescription [0.15–0.90 mg/kg per dose]	1 h	CPT [Auditory; Tones]	P300 (250–550 ms)	Pz	EG = CG	EG = CG

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Quality	Population	n_{sample} (% females)	Age M ± SD	MPH [dosage, duration]			Task [modality; stimuli]	P300 nomenclature (time-window)	Region	Results	
					Washout	Dosage; duration	Time before EEG				Amplitude	Latency
Yan-ling and Xuan (2013)[a]	12	Youngsters	n EG = 28 (14 %) *n* CG = 28 (14 %)	EG: 9.3 ± 1.9 CG: 9.2 ± 1.9	All subjects were stimulant naïve	0.3 mg/kg; on the day	2 h	CPT [Visual; Numbers]	P300 (400–520 ms)	Fz, Cz, & Pz	[good & poor performance] EG = CG	
Seifert et al. (2003)[a]	10	Children	*n* EG = 17 (0 %) *n* CG = 20 (0 %)	EG: 9.5 ± NA CG: 9.9 ± NA	NA	0.27–0.47 mg/kg; on the day	1 h	CPT-OX [Visual; Letters]	P3a (257–408 ms)	All	EG = CG	
Taylor et al. (1993)[a]	10	Children	*n* EG = 32 (16 %) *n* CG = 32 (28 %)	EG: 10.3 ± 1.0 CG: 10.3 ± 0.8	NA	0.1–0.3 mg/kg [Low dose]; on the day	1.5 h	Oddball [Visual; Letters]	P3a (NA) P3b (NA)	All All	EG > CG EG = CG	
Ozdag et al. (2004)[a]	9	Youngsters	*n* EG = 23 (0 %) *n* CG = 23 (0 %)	EG: 9.5 ± 1.8 CG: 9.2 ± 1.7	All subjects were drug naïve	0.7 mg/kg per day; 1 month	1.5 h	Oddball [Auditory, Tones]	P300 (NA)	Fz, Fpz & Pz	Does not compare	Does not compare
ADHD pre- versus *post-MPH*												
Aasen et al. (2018)[a]	20	Youngsters	*n* = 57 (30 %)	11.9 ± 2.5	NA	10/15 mg; 0–4 weeks	1 h	Go/no-go [Visual; Figures]	P300 (300–500 ms)	Fz Cz & Pz	Post = Pre Post > Pre	Does not report the comparison Does not report the comparison
Jonkman et al. (2000)[a]	18	Youngsters	*n* = 14 (7 %)	9.6 ± 2.2	3 days prior	0.36–0.78 mg/kg; on the day	1 h	Eriksen flanker task [Visual; Figures]	P300 (400–800 ms)	Fz, Cz, & Pz	Does not compare	
Hermens et al. (2005)[a]	16	Adolescents	*n* = 34 (18 %)	13.8 ± 1.6	2^{+} days prior	Usual prescriptions	1 h	Oddball [Auditory; Tones]	P300 (220–550 ms)	Midline (Fz, Cz, Pz) Right frontal	Post > Pre	Post > Pre
Klorman et al. (1992)[a]	16	Youngsters	*n* = 48 (13 %)	14.1 ± 1.7	NA	M = 0.64 mg/kg per day; 3 weeks	NA	NA [Visual; Numbers]	P3b (280–700 ms)	Fz, Cz, Pz	Post < Pre	Post < Pre
Miller et al. (1996)	16	Children	*n* = 19 (0 %)	9.7 ± NA	18^{+} hours	10 mg; on the day	1 h	Stroop Colour Word Test [Visual; Words]	P3a (225–400 ms) & P3b (400–550 ms)	Posterior	Does not compare	Does not compare
Groom et al. (2010)[a]	15	Youngsters	*n* = 22 (NA%)	NA	36 h	Usual prescription [M = 1.1 mg/kg]	NA	Go/no-go [Visual; Figures]	P300 (400–700 ms)	Cz & Pz	Post > Pre	Does not report the comparison
Janssen et al. (2016)[a]	15	Youngsters	*n* = 25 (24 %)	9.2 ± 1.3	At least 1 week	10/20/30/40 mg per day; 1 week	NA	Stop-signal task [Visual; Figures]	P300 (300–400 ms)	Fz, Cz, & Pz	Pos = Pre	
Rubinson et al. (2019)[a]	15	Youngsters	*n* = 19 (47 %)	12.1 ± 2.5	NA	smaller between 0.5 mg/kg and 20 mg; on the day	1 h	Go/no-go [Visul; Numbers]	P300 (250–400 ms)	Fz & Pz	Pos = Pre	Pos = Pre

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Quality	Population	n_{sample} (% females)	Age M ± SD	MPH [dosage, duration]			Task [modality; stimuli]	P300 nomenclature (time-window)	Region	Results	
					Washout	Dosage; duration	Time before EEG				Amplitude	Latency
Ohlmeier et al. (2007)[a]	13	Adults	$n = 10$ (40 %)	34.8 ± NA	3 weeks	30 mg per day; NA	1 h	Go/no-go [Visual; Letters]	P300 (400–600 ms)	Cz & Pz	Pos = Pre	
Paul-Jordanov et al. (2010)	13	Youngsters	$n = 11$ (0 %)	12.4 ± 0.4	48 h	Usual prescription	ca. 2 h	Go/no-go [Visual; Figures]	P300 (260–328 ms)	[Right hemisphere] Fronto-central	[No-go minus Go] Pos > Pre	[Go] Pos = Pre [No-go] Pos < Pre
										[Left hemisphere] Fronto-central	[No-go minus Go] Pos = Pre	[Go] Pos = Pre [No-go] Pos < Pre
Sunohara et al. (1999)[a]	13	Children	$n = 20$ (20 %)	10.5 ± 1.9	24 h	0.14–0.34 mg/kg per day [Low dose]; on the day	1.5 h	CPT [Visual; Letters]	P300 (NA)	All	Pos = Pre	Pos < Pre
Dolu et al. (2019)[a]	12	Youngsters	$n = 18$ (22 %)	9.6 ± 1.9	NA	0.5 mg/kg incremented up 1.2 mg/kg per day; 3 months	NA	Oddball [Auditory, NA]	P300 (NA)	Fz	Pos > Pre	
										Cz & Pz	Pos = Pre	
Sawada et al. (2010)[a]	12	Youngsters	$n = 10$ (10 %)	9.3 ± 1.9	NA	18–54 mg per day; 8–12 weeks	NA	Oddball [Auditory; Tones]	P300 (250–550 ms)	Fz	Pos = Pre	Pos = Pre
										Cz & Pz	Pos > Pre	Pos = Pre
Yan-ling and Xuan (2013)[a]	12	Youngsters	$n = 28$ (14 %)	9.3 ± 1.9	All subjects were drug naïve	0.3 mg/kg; on the day	2 h	CPT [Visual; Numbers]	P300 (400–500 ms)	Fz & Cz	[good performance] Pos > Pre [poor performance] Pos = Pre	
									P300 (420–520 ms)	Pz	Pos = Pre	
Seifert et al. (2003)[a]	10	Children	$n = 17$ (0 %)	9.5 ± NA	NA	0.27–0.47 mg/kg; on the day	1 h	CPT-OX [Visual; Letter]	P3a (257–408 ms)	All	Pos > Pre	
Taylor et al. (1993)[a]	10	Children	$n = 32$ (16 %)	10.3 ± 1.0	NA	0.1–0.3 mg/kg [Low dose]; on the day	1.5 h	Oddball [Visual; Letters]	P3a (NA) & P3b (NA)	All	Pos = Pre	Pos < Pre
Ozdag et al. (2004)[a]	9	Youngsters	$n = 23$ (0 %)	9.5 ± 1.8	All subjects were drug naïve	0.7 mg/kg per day; 1 month	1.5 h	Oddball [Auditory, Tones]	P300 (NA)	Pz & Fpz	Pos > Pre	Pos < Pre

Note. CG = control group; EG = experimental group; NA = not available; Pos = post-administration of MPH; Pre = pre-administration of MPH. A sample is classified as "Children" when participants are younger than 13 years, as "Adolescents" when they have between 13 and 17 years, as "Youngsters" when both participants are both children and adolescents, and as "Adults" when they are 18 or older. In Jonkman et al. (1999, 2000), the data for the controls was extracted from the "Experiment 1", and for ADHD post-administration of MPH from the "Experiment 2". In Sunohara et al. (1999) and Taylor et al. (1993), only data resulting from the administration of a lower dose of MPH was extracted. In Yan-ling and Xuan (2013), the weighted average for the results for good and poor performance was calculated and used for the analysis.

[a] Articles included in meta-analysis.

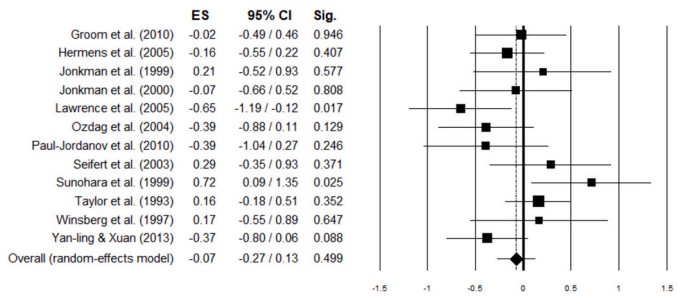

Fig. 2. Forest plot for P300 amplitude in ADHD post-MPH versus healthy controls. Negative effect sizes indicate a lower amplitude in the ADHD post-MPH group.

3.4. Methodological quality assessment

In regard to their quality, studies included in this review scored between 9 and 20, in Keil et al. (2014) checklist. The total average was 14, and the most frequent score was 13 ($n = 5$, Table 1).

4. Discussion

This meta-analytical review aimed to summarise the effect of MPH on P300 and its subcomponents (P3a and P3b) amplitude in individuals with ADHD. To achieve this, two distinct meta-analyses were done: (a) analysis of observational studies, where a group of participants with ADHD diagnosis received an MPH treatment and was then compared to a control group of healthy individuals; and (b) analysis of longitudinal studies, where participants diagnosed with ADHD were assessed pre- and post-MPH.

Most of the included studies used either a continuous performance task, an oddball or a go/no-go task, and the preferred stimuli were visual (particularly figures). The dosage of MPH varied considerably between studies, which evokes the need for a standardised practice in reporting and conducting research with this medicine. In addition, the majority of studies administered MPH in a sample of younger people, while there is a lack of studies focusing on an adult population. Furthermore, a skewness for a higher number of male participants, if not exclusively them, is observed. Both of these aspects beg the question of possible generalisation of the obtained results into the general population, as neither adults nor females are properly represented.

Additionally, the studies included in this review focused on the categorical diagnostic vs non-diagnostic of ADHD, leaving aside community samples only presenting traits of ADHD. Nevertheless, it is relevant to emphasize the necessity of a dimensional approach and analysis of severity of symptoms, particularly considering that various traits tend to present themselves in the general population (Arcos-Burgos and Acosta, 2007). It is worth mentioning that existing dimensional models, namely the HiTOP (Mullins-Sweatt et al., 2021) and the RDOC (Musser and Raiker, 2019), still need a deeper consideration and consistent integration of ADHD symptomatology.

4.1. ADHD post-MPH versus healthy control

Our results revealed no overall significant differences between individuals diagnosed with ADHD and medicated with MPH and controls.

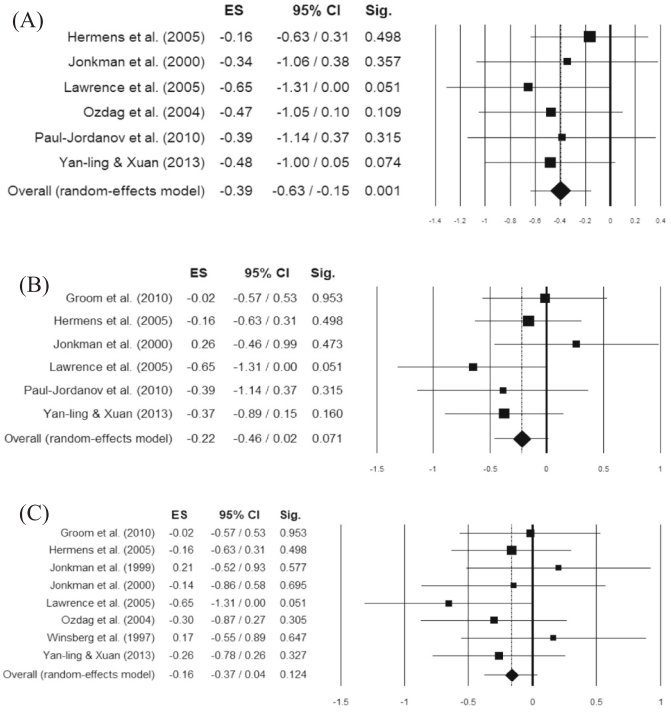

Fig. 3. Forest plot for P300 amplitude in ADHD post-MPH versus healthy controls, divided by topographic region: (A) anterior sites, (B) central sites, (C) posterior sites. Negative effect sizes indicate a lower amplitude in the ADHD post-MPH group.

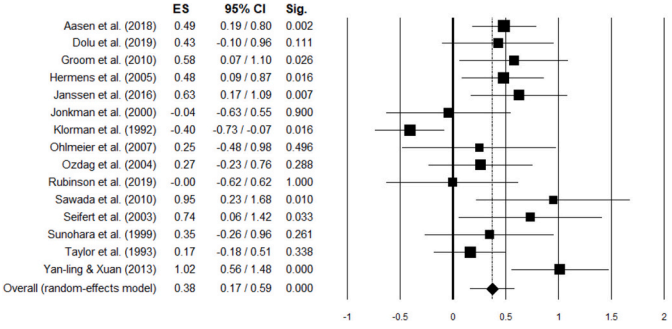

Fig. 4. Forest plot for P300 amplitude in ADHD pre- versus post-MPH. Negative effect sizes indicate a lower amplitude in the ADHD post-MPH group.

Table 2
Statistics for ADHD post-MPH versus healthy controls meta-analysis of P300 amplitude.

	Heterogeneity statistics					Confidence Interval - 95 %		
Moderator	Q	p-value	k	Category	Hedges' g	Lower limit	Upper limit	p-value
Region	1.72	.887	**6**	**Fz**	**−0.39**	**−0.63**	**−0.15**	**.001**
	4.51	.479	6	Cz	−0.22	−0.46	0.02	.071
	4.58	.711	8	Pz	−0.16	−0.37	0.04	.124
Task type	**11.63**	**.009**	4	CPT	0.12	−0.50	0.73	.714
	0.34	.558	2	Flanker	0.04	−0.42	0.50	.869
	1.40	.497	3	Go/no-go	−0.25	−0.53	0.04	.091
	3.53	.171	3	Oddball	−0.09	−0.40	0.22	.560
Overall	19.23	.057	12		−0.07	−0.27	0.13	.499

Note. Values in bold represent significant statistics (< .05).

Table 3
Statistics for ADHD pre- versus ADHD post-MPH meta-analysis of P300 amplitude.

	Heterogeneity statistics					Confidence Interval - 95 %		
Moderator	Q	p-value	k	Category	Hedges' g	Lower limit	Upper limit	p-value
Region	17.59	.040	10	Fz	0.18	−0.06	0.43	.133
	29.65	.001	9	**Cz**	**0.47**	**0.15**	**0.80**	**.004**
	44.67	<.001	10	**Pz**	**0.51**	**0.15**	**0.88**	**.006**
Task type	0.69	.405	2	CPT	0.53	0.07	0.98	.024
	–	–	1	Flanker	–	–	–	–
	7.91	.161	6	**Go/no-go**	**0.55**	**0.30**	**0.79**	**<.001**
	4.32	.364	5	**Oddball**	**0.39**	**0.16**	**0.58**	**.001**
Overall	**39.98**	**<.001**	**15**		**0.38**	**0.17**	**0.59**	**<.001**

Note. Values in bold represent significant statistics (< 0.05).

This is in line with what has been described for stimulant drugs in ADHD, specifically the decrease in ADHD symptoms compared to placebo outcomes (Faraone, 2009). Interestingly, although no significant heterogeneity was found in this analysis, we performed a moderated analysis due to the relevance of topography and task in ADHD assessment with ERP. Kaiser and colleagues (2020) have reported significant differences regarding tasks when comparing ADHD and non-ADHD groups, with higher effect sizes found for the CPT, CPT - flanker version, the go/no-go, and the oddball task. Our results remained the same after this moderation analysis, meaning no differences between groups were found despite the task.

On the other hand, the moderator analysis by topography revealed an interesting pattern between groups, with reduced amplitudes found exclusively in the Fz cluster in ADHD, despite a small effect size. This is in line with what is described regarding the pathophysiology of ADHD, with most alterations, either structural or functional, found in the frontal/prefrontal regions of individuals with ADHD (De La Fuente et al., 2013; Vieira De Melo et al., 2018). While other areas of the brain may be affected in ADHD, the anterior regions appear to take the brunt of it (Vieira De Melo et al., 2018).

Considering that the frontal lobes seem linked to attention and inhibition (Scott and Schoenberg, 2011), which are major symptoms of ADHD, it is expected that the P300 would be more greatly affected due to its relation with these neurocognitive functions. Therefore, it is not surprising that "normalising" the functioning of frontal areas would need a greater rise in P300 amplitude than for the other areas. A moderation analysis by dosage or duration of the pharmacological treatment could have helped clarify if the amplitude of the P300 in the frontal areas would also increase with higher doses/duration. Unfortunately, we were unable to run these moderation analyses due to the high variability in the MPH prescription in the included studies.

The percentage of females in the ADHD group medicated with MPH did not influence the results. This suggests that both sexes showcase higher P300 amplitudes with the administration of MPH, and thus a normalisation of their brain activity. That being said, these results must be seen with caution as there was not a high enough variability, among studies, in the percentages of females to draw concrete conclusions. In fact, the format chosen to evaluate ADHD symptoms (i.e., rating scales or clinical interview) seems to play an important role in the diagnosis of females in particular (Young et al., 2024). Rating scales tend to disfavour the diagnosis of females, while clinical interviews seem to evaluate the severity of ADHD symptoms equally for both sexes (Young et al., 2024). Furthermore, there might be a bias in referring young females to diagnosis only when their externalizing behaviours are prominent (Anckarsäter et al., 2011; Young et al., 2024). In this way, it would be interesting to explore how the P300 amplitude is impacted by MPH in both sexes, while also controlling for the diagnosis criteria used.

4.2. ADHD pre- versus post-MPH

When comparing the pre- and post-effects effects of MPH on the same individuals, it appears that P300 amplitude tends to increase post-administration. However, a high level of variance between studies was found, which prompted the moderation analysis by topographic regions and by experimental task. In regard to the first, similar results to the above case-control meta-analysis were found, with an enhancement of amplitude exclusively found for central and posterior regions. This supports the idea that anterior regions may be more affected, although a high level of heterogeneity in the overall analysis persisted.

In addition, variance across studies was resolved by grouping studies in go/no-go and by the oddball tasks. This is partially in line with what was found by Kaiser and colleagues (2020) when comparing ADHD and non-ADHD groups. In their meta-analysis, larger effect sizes were found for CPT, Eriksen flanker tasks, go/no-go, and oddball tasks. We were not able to replicate their results for the CPT and Eriksen flanker task as less than three studies used these tasks to elicit the P300 component.

Regarding go/no-go, we found a medium effect size, which was larger than the overall effect size. This is particularly interesting considering this task is often used to measure behavioural inhibition ability, as it requires a person to either give a motor response (i.e., "go") or suppress their behaviour (i.e., "no-go"), depending on the stimulus presented (Georgiou and Essau, 2011). In the go/no-go studies group, the medium effect size of the differences between pre- and post-MPH suggests that this medicine can successfully, although not entirely, attenuate the deficits in behavioural inhibition of ADHD individuals. This result is congruent with the fact that MPH limits the reuptake of DA and NE, which are neurotransmitters correlated with impulsive behaviour and the inability to inhibit motor responses (Pine et al., 2010; Sasamori et al., 2019).

On the other hand, the oddball task is frequently employed to study attention and memory processes since participants are required to identify an infrequent or rare stimulus and ignore a frequent one (Polich, 2007). The oddball paradigm is commonly used to elicit P300 or P3b by averaging target stimuli trials. This paradigm has often been used to assess attention and working memory mechanisms. With this in mind, considering attention deficits are a core feature of ADHD, an enhancement in P300 amplitude post-MHP might reflect an improvement in the attentional mechanisms. However, the effect size of this analysis was small ($g = 0.37$), although homogenous and in line with Kaiser and colleagues (2020). After all, oddball tasks depend on selective attention (Mueller et al., 2008), so we would expect at least a medium effect size for this task, similar to the go/no-go subgroup analysis. It is, therefore, important to note that the oddball task also requires sustained attention (Kiat et al., 2018), which may be harder to maintain during tasks involving infrequent responses. Thus, the small effect size of P300 amplitude post-MPH on the oddball may be explained by the lower effects of this medicine on sustained attention (Lufi et al., 2015).

An interesting note can be made regarding the analysed oddball tasks. All studies included in this subgroup used simple auditory pure tones except for one study, which employed visual letters. Also, all studies used midline electrodes or clusters and similar time windows, about 250–500 ms. This probably resulted in a reduction of variance in this subgroup analysis. However, all studies were quite easy at their difficulty level. It has been described that higher discrimination

difficulty between target and standard stimuli appears to engage frontal attentional mechanisms more strongly (Hagen et al., 2006). In this sense, using studies that require different levels of discrimination, namely more difficult tasks, could lead to larger effect sizes reflecting specific differences in attentional mechanisms that might not appear in easier tasks.

In regards to the percentage of females in the ADHD group medicated with MPH, no meaningful influence was found. Thus, it seems that both sexes have improvements in their P300 amplitude after treatment with MPH. However, the small dispersion in the percentages of females in these studies prevents us from further reflections. Therefore, it would be interesting to ascertain if there are differences between males and females' clinical response to the medication.

4.3. Limitations and future directions

The present meta-analysis and review is not without its limitations. Unfortunately, some moderation analyses were not able to be performed due to a lack of studies or high variability of the information available, thus limiting our overall conclusions. With respect to the pharmacological intervention, neither the doses used nor the duration of the treatment appear to be sufficiently explained in the included studies. Moreover, the assessment of ADHD severity seems necessary to deeply understand the effects of MPH. Both of these highlight the need to standardise not only the dosage method and duration for appraisal of effects but also for the neuropsychological assessment of ADHD symptoms and deficits. The small percentage of females is a further cause for concern, bearing in mind that the prevalence of ADHD for males and females appears to be similar. Additionally, it is pertinent to mention that the P300 ERP can be influenced by various neurocognitive processes, which were not individually nor specifically targeted.

Finally, considering the importance of adopting a biopsychosocial approach in neurodevelopmental disorders, future studies could focus on the comparison between the effects of pharmacological, non-pharmacological and combined intervention in ERP components of ADHD individuals. Upcoming research could also focus the study of MPH influences in other ERPs, such as the feedback-related negativity (FRN) component, while also taking into account the baseline EEG frequency pattern and its influence on the drug's efficacy. Finally, it seems relevant for future research to address and explore the impact and efficacy of this stimulant in the female population, in order to determine if specific guidelines should be established for this pharmacological treatment.

4.4. Conclusion

This is the first meta-analysis that systematises the existing literature on the impact of MPH on P300 amplitude. Our findings are consistent with previous research on stimulant drugs in ADHD, notably demonstrating a reduction in ADHD symptoms compared to placebo group outcomes. The analysis uncovered key methodological insights, emphasising the necessity for neurophysiological studies to include a broader range of topographic areas. This would help determine whether the anterior regions continue to be the most significantly affected in ADHD. Additionally, the go/no-go task emerged as the one associated with the largest effect sizes.

It is worth mentioning that prescribing MPH and other medicines requires a comprehensive neuropsychological assessment of the individuals to ensure that they are really necessary based on the severity of ADHD. In particular, it is important to be mindful of the small research with the female population, especially across various age ranges. We also recommend that this treatment be part of a more holistic intervention framed in the biopsychosocial paradigm. Additionally, having in mind the adverse effects of MPH it is important to perform periodical follow-up assessments in order to determine when the washout is appropriate. For this purpose, the measurement of the P300 ERP might aid in the diagnosis of ADHD as a useful biomarker and may contribute to evaluate the efficacy and adequacy of the MPH treatment to the individual.

CRediT authorship contribution statement

Beatriz C. R. Barroso: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Fabiana Mendonça:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Prune Mazer:** Writing – review & editing, Investigation, Formal analysis. **Catarina Prata:** Methodology, Conceptualization. **Joana O. Pinto:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2025.112553.

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