How does methylphenidate affect default mode network? A systematic review

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Introduction. Methylphenidate is a widely-used drug for the treatment of attention deficit/hyperactivity disorder (ADHD) and other neuropsychiatric disorders. Sustained-attention deficits and poorer task performance in these disorders have been associated with default mode network (DMN) dysfunction in fMRI studies. DMN is a set of brain areas more activated during the resting-state. Under the execution of external tasks, there is an attenuation of DMN activity. In healthy individuals, DMN and task-positive network are anticorrelated. It has been suggested that methylphenidate could normalize the attenuated task-related DMN deactivation in attention- and inhibitory control-related disorders and that such normalization could improve task performance.

Patients and methods. To explore the hypothesis of DMN deactivation after methylphenidate administration, we conducted a systematic review of the literature.

Results. After a systematic search, 12 studies were included in this review. For eligibility, studies were required to measure the effects of methylphenidate administration on the DMN activity. Eleven studies showed evidence of MPH-induced improvements in brain areas related to DMN. The results suggest a normalization of brain circuits in individuals with DMN dysfunction.

Conclusions. Our preliminary findings strongly suggest methylphenidate improves DMN dysfunction presented in ADHD and other neuropsychiatric disorders. Further studies are needed to better understand this effect and expand comprehension of methylphenidate action mechanisms.

Key words. ADHD. Attention deficit/hyperactivity disorder. Default mode network. DMN. Methylphenidate. Neuroscience. Psychopharmacology. Resting-state.

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Introduction

Methylphenidate mechanism of action and evidence for treatment

Methylphenidate (MPH) is a widely-used drug for the treatment of attention-deficit/hyperactivity disorder (ADHD) and other neuropsychiatric disorders, in order to enhance attention and cognition, including reducing reaction time, enhancing perceptual sensitivity, working memory, speed of processing, verbal learning, attention and vigilance [1-4]. MPH blocks dopamine and norepinephrine transporters, thereby decreasing presynaptic reuptake following release and increasing extracellular concentration of these neuromodulatory neurotransmitters in the synaptic cleft [5-7]. Basal ganglia, mainly striatum, frontal lobes and cerebellum have been found to be MPH targeted areas in the brain [8,9].

MPH is recommended as first-line pharmacological ADHD treatment by updated guidelines [10]. While the exact pathophysiology of ADHD is not completely understood, treatment with stimulants has long been recognized to attenuate symptoms of inattention and hyperactivity in children with the disorder [11,12]. Furthermore, research on MPH also revealed potential for the treatment of cocaine addiction and narcolepsy and for the recovery from traumatic brain injury (TBI) [13-15]. The prescribing rates of MPH increased dramatically in the past two decades [16]. Awareness to adverse drug reactions must be taken, however, data concerning safety issues shows that, despite being common, adverse drug reactions are mild in severity, both for pediatric and adult populations [17-19].

Default mode network structures and dysfunction-related disorders

Default mode network (DMN) is part of accidental science [20]. Despite being initially neglected [21], DMN functions were progressively hypothesized,

both in emotional and cognitive processes integration and future planning through episodic memory retrieval [22,23]. Regions reported to compound DMN are the ventrolateral and ventromedial prefrontal cortex, the posterior cingulate cortex, the cuneus, and the inferior parietal lobe [24]. DMN is a brain network more activated at rest, when there is no focus on specific tasks, which deactivates when an external task is performed and the magnitude of deactivation is associated to the task demand and engagement, memory load and stimulus rate [24-28]. DMN and task-positive network (TPN) are anticorrelated during an externally oriented task [29-32]. Coordination between DMN and TPN seems to be necessary for efficient inhibitory control [33].

DMN dysfunction has been related to abnormal mental processes and illnesses, including ADHD and TBI [34-36]. Among the main abnormal neuropsychological processes that have been related to DMN dysfunction are attention and inhibitory control deficits. Sustained-attention deficits of ADHD were early associated with altered DMN coherence, particularly intrusive DMN activity [29]. Poorer task performance was associated with the failure to attenuate DMN activity during tasks, particularly if they were attentionally demanding [37-39]. Greater response time variability was reported when DMN and TPN anticorrelation was weaker [30].

Default mode network dysfunction and methylphenidate treatment

MPH has clearly shown its efficacy for ADHD treatment and is recommended as first-line medication on ADHD treatment guidelines [10]. Improvement of symptoms in narcolepsy and TBI has also been reported [14,15]. Dysfunction of DMN activity was also found in ADHD, narcolepsy and TBI [31,36,40].

A few studies reported MPH interactions with DMN activity. Peterson et al demonstrated that MPH normalized the attenuated task-related DMN deactivation in ADHD patients [41]. Additionally, Volkow et al found that decreased brain's glucose demands during a cognitive task in healthy subjects under MPH reflected enhanced DMN regions deactivation [42].

To explore the hypothesis of DMN deactivation after MPH administration, we conducted a systematic-review of the literature. The results may shed light on DMN functions, attention- and inhibitory control-related disorders and expand comprehension of MPH mechanisms of action. To our knowledge, there are no reviews on the subject.

Patients and methods

Search strategy

A systematic search was conducted in PubMed and Cochrane databases up to and including October 2018. The following terms were used to search in both title and text: 'methylphenidate' combined with 'default mode network'. The search was limited to original research studies published in English in peer-reviewed journals. The titles and abstracts of the search results were then screened and the relevant papers identified.

Inclusion and exclusion criteria

Studies were included if they:
- They were human clinical trials that included randomized controlled trials, non-randomized trials, case studies and/or case series.
- They evaluated a direct effect of MPH administration on the DMN functioning.
- They were written in English.

Studies were excluded if:
- They did not present new or unique data (review articles, letters to the editor, duplicate articles).
- They did not present an outcome measure related to the effect on DMN.
- They did not use MPH to evaluate the outcomes.

In the first stage of the selection process, all papers whose title or abstract did not meet the inclusion criteria were excluded. From the initial 28 identified papers, we excluded 14. In the second stage of the selection process, the full text of remaining papers was read to exclude those not relevant to the review. At the end, two papers were excluded because they did not present a measure of DMN activity after MPH administration. The final review included 12 papers.

This systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search process is summarized in the figure.

Results

Characteristics of included studies

Twelve studies, involving 480 participants, were included, addressing the effects of MPH in DMN areas. The demographic and clinical features of the

samples were very heterogeneous and three studies did not refer the mean age of the samples. In the remaining studies, the mean age varied between 8.78 ± 0.85 and 39.9 ± 5.5 years old, with five studies using only pediatric samples. Five studies used only male subjects in their sample and all of the studies had a disproportionally predominance of males. The studies varied also in the clinical features of the sample. While the majority of studies tested the administration of MPH in ADHD patients (five MPH naïve, two MPH responsive patients and one previously MPH-treated patients washed-out), two studies administered MPH in healthy subjects, one used a sample of cocaine dependent patients and another tested MPH in patients seven months after TBI with diffuse axonal injury.

There was also a great variability in the methodologies and the brain regions analyzed across the different studies. Nine studies were controlled, while three lacked a control group. Five studies administered placebo in the experimental or in the control group. Oral administration of MPH was the most frequently used form of administration, with only one study preferring intravenous administration. Three of them tried to analyze the long-term effects of treatment with MPH, performing an evaluation after a period of more than one month of treatment.

Among the studies, ten evaluated DMN activity through fMRI scan, one used EEG and another used steady-state visual evoked potential. The majority of them evaluated the effects of MPH in DMN functioning during the performance of a neuropsychological task (requiring visual attention, inhibitory control or working memory), while two evaluated the effects of MPH in DMN functioning during resting-state only.

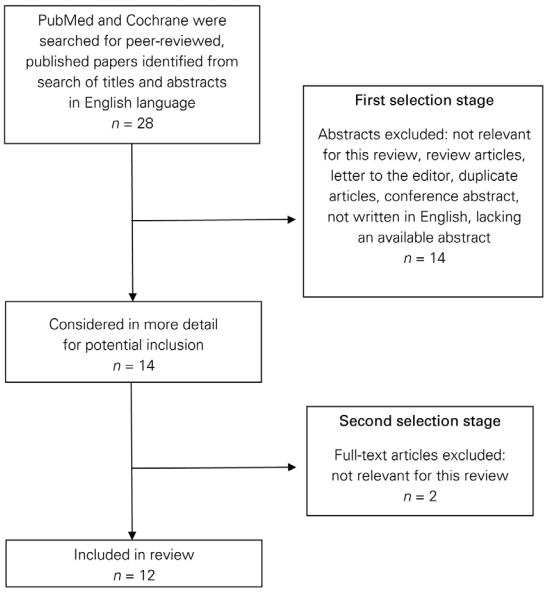
The complete characterization of the studies included is presented in the table.

Effects of methylphenidate on DMN activity

Eleven studies revealed an effect of MPH administration in the activity of brain areas related to DMN. Among those, ten revealed an increased deactivation of specific DMN areas after MPH administration [43-52]. The study which the sample included cocaine dependent patients showed that MPH increased the activation of the ventromedial prefrontal cortex and precuneus, before task errors, which translates a normalization of neural processes [53]. One study failed to show any DMN activity differences before and after MPH administration [54].

In the ten studies in which MPH produced DMN deactivation, different areas within DMN were observed to be affected: four studies, posterior cingulate cortex; two, prefrontal cortex; one, medial frontal cortex; one, insula; three, precuneus; one, ventral anterior cingulate cortex; one, temporal gyri; one, angular gyri; and one, frontoparietal regions and other areas involving occipital, temporal and cerebellar regions.

Figure. Flowchart of published studies examined for inclusion in the systematic review.



Discussion

In this systematic review, we identified 12 studies aiming to assess the effects of MPH administration on DMN functioning. Regarding subjects' disorders, eight studies included ADHD patients, one included patients with cocaine dependency, one included patients with TBI diagnosis and two studies included only healthy individuals. The diagnoses comprised in the studies, as well as its distribution, were not a surprise, since ADHD is the main targeted disorder for MPH administration and it is among the most well studied DMN dysfunction-related disorders. The hypothesis of intrusive DMN activity on ADHD was supported either by reported disrupted functional connectivity between DMN and other brain regions and reduced DMN homogeneity, both in ADHD child and adult patients [31,55,56]. A meta-analysis pointed DMN hyperac-

Table. Summary of studies discussed in the text.

	Subjects			
	Patients (MPH)	Controls	Intervention	Main findings on DMN activity after MPH administration
Tomasi et al [43]	16 healthy males (mean age: 33 ± 3 years)	16 healthy males (mean age: 36 ± 2 years)	Patients: oral administration of 20 mg MPH Controls: no pharmacological intervention	Deactivation
Liddle et al [44]	18 ADHD-C subtype MPH responsive (9-15 years)	18 typically developed (9-15 years)	Patients: regular oral MPH and 36 h after off-MPH, under different motivational conditions Controls: no pharmacological intervention	Deactivation
Marquand et al [45]	15 healthy (20-39 years)	–	Patients: oral administration of 30 mg MPH and placebo	Deactivation
Matuskey et al [53]	10 cocaine dependent (DSM-IV-R criteria) (8 male; mean age: 39.9 ± 5.5 years)	–	Patients: intravenous administration of MPH (0.5 mg/kg) and placebo	Increased activation: normalization of neural processes
Querne et al [46]	11 ADHD MPH-naïve (8-13 years; mean age: 9.8 ± 1.7 years)	11 typically developed (8-13 years; mean age: 10.8 ± 1.7 years)	Patients: performed twice, once before MPH and once after a month of continuous MPH (20 or 30 mg, extended release formulation) Controls: no pharmacological intervention	Deactivation
Cooper et al [47]	38 ADHD non-treated males and 17 on follow-up (on MPH) (18-58 years; mean age: 28.5 ± 9.5 years)	43 no-ADHD males and 34 on follow-up (19-65 years; mean age: 29.0 ± 10.4 years)	Patients: tested before the beginning of treatment with MPH and after a follow-up with MPH (mean follow-up: 9.4 months) Controls: no pharmacological intervention	Deactivation
Salavert et al [48]	41 ADHD patients: 26 under chronic MPH treatment and 15 treatment naive (28 males, 13 females)	41 healthy controls	Patients: Discontinued from medication at least four days prior to the fMRI Controls: no pharmacological intervention	Deactivation
Battel et al [54]	23 MPH-naïve ADHD boys (8-10 years; mean age: 8.78 ± 0.85 years); 21 at 6-months follow-up)	–	Patients: individual titrated MPH treatment (target dosage of 1 mg/kg/day)	No significant difference
Silk et al [49]	16 ADHD male: 10 MPH-naïve, 6 under 48 h MPH wash out (9-18 years; mean age: 13.4 ± 2.4 years)	15 typically developed male (mean age: 14.4 ± 2.5 years)	Patients: 20 mg MPH single dose administration and placebo (two weeks or more of interval) Controls: placebo	Deactivation
Moreno-López et al [50]	14 with > 7 months TBI patients with diffuse axonal injury: 10 male, 4 female (mean age: 36.86 ± 14.17 years)	20 healthy: 12 male, 8 female (mean age: 34.15 ± 11.12 years)	Patients: 30 mg oral MPH and placebo Controls: no pharmacological intervention	Deactivation
Silberstein et al [51]	42 ADHD treatment naïve boys (mean age: 10.04 years ± 2.00 years)	25 healthy boys (mean age: 10.83 ± 1.74 years)	Patients: 0.3 mg/kg of MPH Controls: no pharmacological intervention	Deactivation
Mowinckel et al [52]	20 ADHD adults under MPH treatment: 7 male, 13 female (mean age: 29.90 ± 1.41 years)	27 healthy adults: 8 male, 19 female (mean age: 27.42 ± 1.23 years)	Patients: MPH and placebo administration in randomized order Controls: no pharmacological intervention	Deactivation

ADHD: attention deficit/hyperactivity disorder; DMN: default mode network; fMRI: functional magnetic resonance imaging; MPH: methylphenidate.

tivity among the main findings in ADHD groups compared to controls [57]. In youths with ADHD, the DMN task-related deactivation was found to be attenuated during an inhibitory control task [41]. For TBI populations, abnormally increased DMN connectivity and reduced connectivity between salience and DMN during the execution of response inhibition tasks were reported [58-60]. DMN dysfunction was also associated with slower response inhibition in TBI patients [61].

DMN was found to be a brain network in which its activity is higher at the resting-state and that deactivates when an external task is performed [24]. Those individuals presenting a failure on attenuating DMN activity, during external tasks, had weaker performance on those tasks [37]. For example, the decreased deactivation of DMN was associated with errors in an inhibitory control task [62]. Moreover, intra-individual response time variability during a task was also associated with DMN activation [63]. In this review, nine out of the ten studies that included non-healthy individuals showed restoration of DMN activity after MPH administration. From those, the restoration was reflected by DMN deactivation in eight studies. Interestingly, the same pattern of functional activity was achieved in those two studies including healthy individuals only. When specific deactivated DMN areas were described, posterior cingulate cortex was the most often deactivated region. Indeed, posterior cingulate cortex integrates the core DMN, a subset that deactivates independently of the task [64]. prefrontal cortex, medial frontal cortex, precuneus, ventral anterior cingulate cortex, temporal gyri and angular gyri also showed MPH induced deactivation. Querne et al conducted an evaluation on DMN activity before and one month after initiating MPH treatment, while the subjects were performing a flanker task [46]. Their results showed a progression from no anticorrelation between DMN and TPN activities to an anticorrelation between those networks, one month after MPH treatment, similar to what was observed in the control group. In fact, TPN regions are activated under purposeful attention [65,66]. Since DMN and TPN anticorrelation is needed for efficient external tasks performance, induced DMN deactivation through MPH administration seems to normalize TPN functioning.

The study that included cocaine dependent patients, despite showing increased DMN activation with MPH, reflected normalization of neural processes with restoration of DMN normal activity [53]. The authors found an increased DMN activity preceding stop errors of a stop-signal task, under MPH. This is accordingly to the literature, as performance errors prediction by DMN activation, in healthy individuals, was suggested from the increased activity in key DMN structures during stop signal errors, as compared to the activity during stop signal successes [62]. Also, intravenous administration of MPH improved inhibitory control in non-treatment seeking cocaine using individuals [67]. Taken together, these findings provide support for the efficacy of psychostimulants in remediating self-control in cocaine addicts [68-70].

Only one study failed to show a MPH-induced normalization of DMN activity [54]. However, this was the only study that neither included a control group, placebo administration to the patients group or the performance of a task.

Silk et al, despite conducting the study in a resting-state condition, found reduced DMN activity under MPH, compared to the placebo condition [49]. Previous data demonstrated MPH evident alterations in the resting-state, and such effects were presumably related to a differentiation of signal from noise and restoration of attention focus [71-73]. Two studies included healthy subjects only and their results matched the expected MPH effects on DMN activity [43,45]. Actually, MPH previously demonstrated evidence in response inhibition paradigms both in psychiatric and healthy populations [74,75].

Limitations

This review should be considered in the light of some limitations that should be taken into account when interpreting the results. Firstly, the review is constrained by limitations at study level, due to the quality and methodological differences of the included studies. Scientific literature is still lacking significant studies and data on the specific effects of MPH in DMN and other brain regions. In what concerns to the type of studies included, initially we searched specifically for randomized controlled trials. However, because of the scarcity of randomized controlled trials, we had to reconsider our inclusion criteria and include different study designs, some of them lacking control groups, placebo testing and double-blinded measurements.

Also, the analysis of available data is difficult due to heterogeneity of studied populations. While the majority of studies selected exclusively patients with ADHD, comparing them with typically developing samples, some evaluated the effect of MPH in heterogeneous populations including cocaine dependent individuals or patients after TBI. Even between those that used samples of ADHD patients, the samples were significantly heterogeneous. Some studies started the administration of MPH in MPH-naïve patients, while others preferred patients with ADHD already treated and that showed to be responsive to MPH, and some also mixed these two groups in their samples. The heterogeneity of samples is also relevant with regard to age, showing a markedly broad age range across the studies.

Furthermore, the majority of studies used a predominance of male samples, which lead to caution when generalizing these results to the female population.

Comparison across studies was further hindered by heterogeneity in the methodologies used for the analysis of effects of MPH in the DMN activity, the instruments and measuring techniques, units and statistical procedures employed. The majority of studies tested the effect of MPH in DMN during the performance of a neurocognitive task. However, some studies tested the MPH effect during resting-state, which could minimize their results, because they did not allow observing the deactivation of DMN during a task requiring external attention.

Finally, regarding limitations at review-level, by including only publications written in English, we may have inadvertently excluded relevant publications, even though the literature search was comprehensive and systematic.

Conclusions

In this systematic review, we found favorable evidence for the effect of MPH in different areas related to DMN, in multiple clinical populations, which supports the previous literature in the field. Mostly, MPH was able to normalize the DMN and TPN anticorrelation, which is needed for efficient external tasks performance.

Data is still limited in terms of quality and quantity of studies. Further well designed, larger controlled trials, testing against placebos and analyzing the effects of MPH on DMN during the performance of a homogenous attention-task, are needed to offer evidence of sufficient quality for supporting these results and a posterior meta-analysis.

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¿Cómo afecta el metilfenidato al circuito de activación por defecto? Revisión sistemática

Introducción. El metilfenidato es un fármaco ampliamente usado como tratamiento del trastorno por déficit de atención/hiperactividad (TDAH) y otros trastornos neuropsiquiátricos. La dificultad para mantener la atención de forma prolongada y la deficiente ejecución de tareas que caracterizan a tales trastornos se han vinculado a la disfunción del circuito de activación por defecto –*default mode network* (DMN)–, revelado en estudios de resonancia magnética funcional. En los individuos sanos, el DMN y la red orientada a tareas (*task-positive network*) presentan una relación inversa. Se ha planteado que el metilfenidato revertiría la escasa desactivación del DMN durante la ejecución de tareas que caracteriza a los trastornos de la atención y del control inhibitorio, normalización que a su vez mejoraría la ejecución de las tareas.

Pacientes y métodos. Con objeto de examinar la hipótesis de que este fármaco propicia tal desactivación, se llevó a cabo una revisión sistemática de la bibliografía.

Resultados. Doce estudios se incluyeron finalmente en la revisión. Para ello, debían haber medido los efectos de la administración del metilfenidato sobre la actividad del DMN. Once estudios mostraron indicios de mejora atribuible al metilfenidato en áreas cerebrales vinculadas a dicho circuito. Los resultados indican la normalización de los circuitos cerebrales en los pacientes con disfunción del DMN.

Conclusiones. Los hallazgos preliminares ofrecen indicios sólidos de que el metilfenidato mejora la disfunción del DMN presente en el TDAH y otros trastornos neuropsiquiátricos. Se precisan nuevos estudios que diluciden los pormenores de este efecto y mejoren la comprensión sobre los mecanismos de acción del metilfenidato.

Palabras clave. Circuito de activación por defecto. DMN. Estado de reposo. Metilfenidato. Neurociencia. Psicofarmacología. TDAH. Trastorno por déficit de atención/hiperactividad.