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Two-month administration of methylphenidate improves olfactory sensitivity and suppresses appetite in individuals with obesity

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Abstract: Olfaction contributes to feeding behaviour and is modulated by changes in dopamine levels. Methylphenidate (MPH) increases brain dopamine levels and has been shown to reduce appetite and promote weight loss in patients with attention deficit hyperactivity disorder. The objectives of this study were to test the effect of MPH on olfaction, appetite, energy intake, and body weight (BW) on individuals with obesity. In a randomized, double-blind study, 12 participants (age 28.9 ± 6.7 years) with a body mass index (BMI) of 36.1 ± 4.5 kg/m^2 were assigned to MPH (0.5 mg/kg) (n = 5) or placebo (n = 7) twice daily for 2 months. Appetite (visual analog scale), odour threshold (Sniffin' Sticks®), energy intake (food menu), and BW (DEXA scan) were measured at day 1 and day 60. MPH intake significantly increased odour threshold scores (6.3 ± 1.4 vs. 9.4 ± 2.1 and 7.9 ± 2.3 vs. 7.8 ± 1.9, respectively; p = 0.029) versus placebo. There was a significantly greater suppression of appetite sensations (desire to eat (p = 0.001), hunger (p = 0.008), prospective food consumption (p = 0.003)) and an increase in fullness (p = 0.028) over time in the MPH versus placebo. MPH suppressed appetite and improved olfactory sensitivity in individuals with obesity. These data provide novel findings on the favourable effects of MPH on appetite and weight regulation in individuals living with obesity.

Key words: methylphenidate, olfaction, appetite, weight loss, energy intake, obesity.

Résumé : L'olfaction participe aux comportements alimentaires et se module par des variations des taux de dopamine. Le méthylphénidate (MPH) entraîne une augmentation des taux de dopamine dans le cerveau et on a montré qu'il entraîne une diminution de l'appétit et qu'il favorise la perte de poids chez les patients présentant un trouble de déficit de l'attention avec hyperactivité. Cette étude avait pour objectif d'évaluer l'effet du MPH sur l'olfaction, l'appétit, l'apport énergétique et la masse corporelle (MC) chez les personnes obèses. Dans le cadre d'une étude à double insu nous avons réparti aléatoirement 12 participants (âgés de 28,9 ± 6,7 ans) avec un indice de MC élevé (IMC de 36,1 ± 4,5 kg/m^2) dans un groupe MPH (0,5 mg/kg) (n = 5) ou placebo (n = 7) deux fois par jour pendant 2 mois. Nous avons mesuré l'appétit (échelle visuelle analogue), les seuils d'odeur (Sniffin' Sticks®), l'apport alimentaire (menu) et la MC (scan DEXA) aux jours 1 et 60. Les résultats ont montré que l'absorption de MPH entraîne une augmentation plus marquée des scores de seuils d'odeur (6,3 ± 1,4 *vs* 9,4 ± 2,1 et 7,9 ± 2,3 *vs* 7,8 ± 1,9, respectivement; p = 0,029) qu'avec le placebo. Nous avons observé une inhibition nettement plus élevée des sensations d'appétit (désir de s'alimenter (p = 0,001), faim (p = 0,008), consommation d'aliments prospective (p = 0,003)) et de la sensation de satiété (p = 0,028) en fonction du temps dans le groupe MPH qu'avec le placebo. En conclusion, le MPH entraînait une inhibition de l'appétit et permettait d'améliorer la sensibilité olfactive chez les personnes obèses. Ces données apportent de nouveaux résultats quant aux effets favorables du MPH sur l'appétit et la régulation du poids chez les personnes aux prises avec l'obésité. [Traduit par la Rédaction]

Mots-clés : méthylphénidate, olfaction, appétit, perte de poids, apport énergétique, obésité.

1. Introduction

Olfaction is an important food cue that enhances motivation to seek food and contributes to feeding by influencing taste and food palatability (Blundell et al. 2010; Rolls 2005; Yeomans et al. 2004). Although we do not yet understand the mechanisms by which periods of energy deprivation may alter our sensation of smell, energy deprivation is indeed linked to changes in olfactory bulb activity (Apelbaum et al. 2005) and to changes in olfactory sensitivity in rats (Aime et al. 2007). Previous research on human participants found that olfactory acuity to a neutral odour increased in the high versus low hunger state (Stafford and Welbeck 2011). Acute food deprivation, in the form of a 24-h complete fast from feeding, resulted in heightened olfactory performance in males and females living with overweight and obesity, and this improved smell function related to increased palatability ratings in females (Cameron et al. 2012). Similarly, when overweight men were exposed to a 25% acute energy deprivation for

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4 days it was shown that this daily energy deprivation of approximately 700 kcal per day resulted in increased olfactory sensitivity as measured by the Sniffin' Sticks® olfactory testing battery (Cameron et al. 2016). Indeed, initial body weight (BW) has been reported to predict changes in olfactory sensitivity (Cameron et al. 2012; Richardson et al. 2004; Stafford and Welbeck 2011) and olfactory performance is negatively correlated with BW (Peng et al. 2019); however, changes in olfactory function in the context of sustained energy deprivation such as weight loss interventions remain to be thoroughly investigated.

The early stages of olfactory perception are mediated by dopaminergic neurons in the olfactory bulb where they play an inhibitory role to olfactory transmission (Hsia et al. 1999; Pignatelli and Belluzzi 2017). The age-related loss of olfactory sensitivity has been linked to reduced activity of brain dopamine transporters (Larsson et al. 2009). Also, impaired olfactory function is found in many neurodegenerative diseases that are characterized by the loss of striatal dopaminergic tone such as Parkinson's disease (Ansari and Johnson 1975; Berendse et al. 2001; Doty 2012; Morley et al. 2018). In Parkinson's disease, the number of dopaminergic neurons in the olfactory bulb, as measured by immunohistochemistry, was found to be double the number in healthy counterparts (Huisman et al. 2004). Research suggests that the decrease in brain dopamine activity is accompanied by a compensatory increase in the neurogenesis of inhibitory dopamine cells in the olfactory bulb (Winner et al. 2006). This increase in bulbar dopaminergic neurons is thought to be one of the reasons behind hyposomia, the deterioration in smell function, in patients with Parkinson's disease (Berendse et al. 2001) which is present 90% of the patients (Millar Vernetti et al. 2016). Because hyposomia onset in Parkinson's disease might precede motor impairment, olfactory testing using Sniffin' Sticks® (Hummel et al. 2007) is investigated as a clinical diagnostic tool of Parkinson's disease to allow for earlier intervention plans (Antsov et al. 2014; Daum et al. 2000, Millar Vernetti et al. 2016; Pinkhardt et al. 2019; Santin et al. 2010).

Brain dopamine activity modulates appetitive behaviours in response to food cues including olfactory food cues (Alcaro et al. 2007; Epstein et al. 2009; Schultz 2010; Volkow et al. 2008). Literature suggests that blunted brain dopamine activity, caused by rapid dopamine reuptake or low dopamine signaling, is linked to increased food intake and the development of obesity (Noble et al. 1994; Volkow et al. 2017; Wang et al. 2001). Recent systematic reviews have found that attention deficit hyperactivity disorder (ADHD), a syndrome that is characterized by low brain dopamine activity, is strongly associated with obesity (Cortese et al. 2008, 2016). Though the factors underlying this association are still unclear, reduced brain dopamine activity is implicated as a common pathological pathway (Cortese and Morcillo-Peñalver 2010; Liu et al. 2008; Seymour et al. 2015). In fact, non-medicated individuals with ADHD have higher obesity rates compared with medicated individuals (Cortese et al. 2008, 2016). Indeed, the administration of methylphenidate (MPH), a brain dopamine transporter inhibitor (Kuczenski and Segal 2001) that is used to treat individuals with ADHD (McGough et al. 2006; Schachter et al. 2001), leads to reduced appetite and weight loss as a side effect (Cortese et al. 2018; Efron et al. 1997; Gurbuz et al. 2016). Additionally, MPH has been shown to suppress appetite and reduce food intake when given acutely to healthy individuals with obesity (Davis et al. 2012; Leddy et al. 2004) and without obesity (Goldfield et al. 2007, 2011). It is unclear, however, whether the sustained intake of MPH for a longer duration would affect olfactory sensitivity in individuals with obesity and whether the postulated changes in olfactory sensitivity would be related to changes in appetite and energy intake.

The aim of this study was to examine the effects of the administration of a moderate dose (0.5 mg/kg) of short-acting MPH for 2 months on appetite sensations, olfactory threshold, energy intake, and BW in individuals living with obesity in a randomized double-blind, placebo-controlled parallel arm pilot trial. We hypothesized that hunger, odour threshold, energy intake, and BW would decrease in the MPH group compared with the placebo group. A secondary objective was to evaluate whether changes in BW, energy intake, and appetite from MPH were associated with changes in olfactory sensitivity in individuals with obesity.

2. Methods

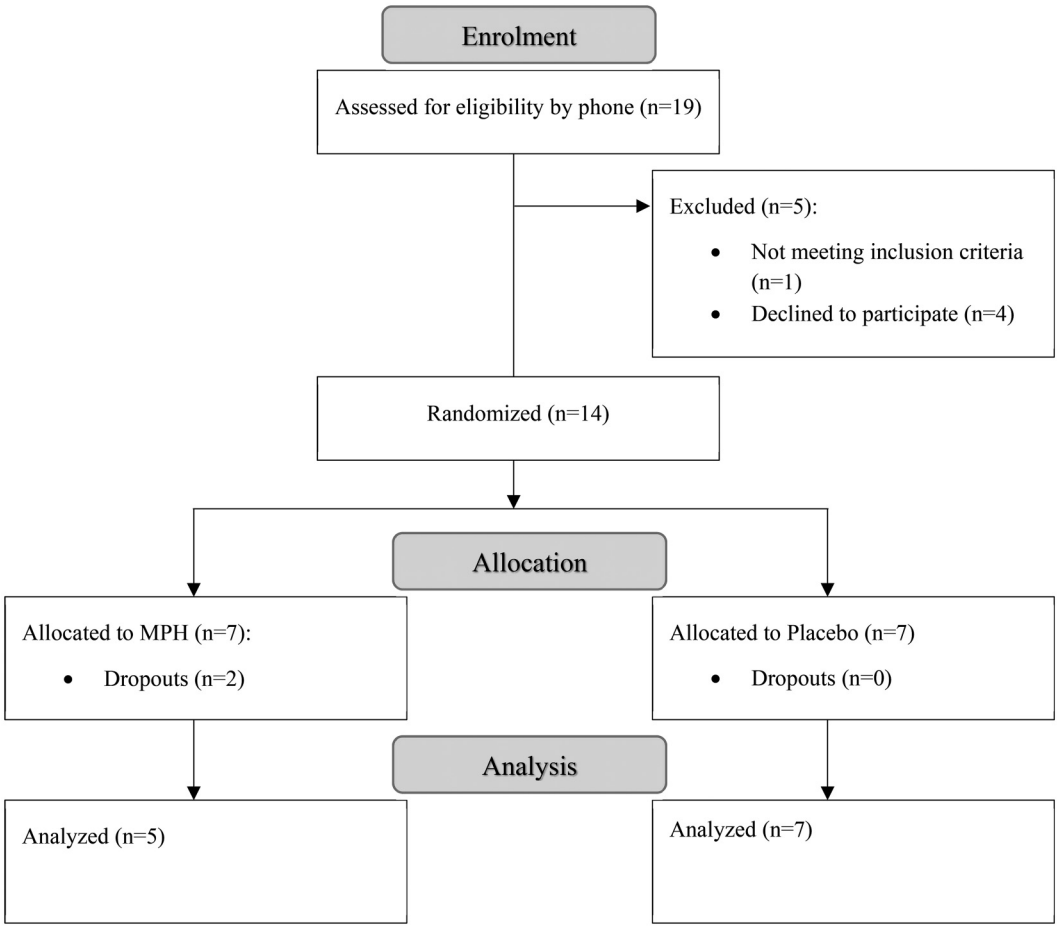
2.1. Participants

Participants were recruited through posting flyers at community centers, local universities, and buses, as well as social media (Facebook) and referrals from other participants. One hundred and three participants contacted us to inquire about the study. Nineteen were screened, 14 were randomized to the placebo (n = 7; 3 males and 4 females) or MPH (n = 7; 2 males and 5 females) groups. The final study sample contained 12 participants randomized to placebo (n = 7; 3 males, 4 females) and MPH group (n = 5; 2 males, 3 females). Two female participants from the MPH group fail to show at the appointments and did not complete the study. The subjects were healthy individuals who met the following inclusion criteria: males and females 18 to 40 years old; body mass index (BMI) in the obese category ($>$29.9 kg/m^2); with BW $<$ 200 kg so as not to exceed the maximum allowed dose of MPH of 100 mg/day as per the National Institute of Health and Clinical Excellence (NICE) (2018); weight stable for the last six months; able and willing to comply with the scheduled appointments and experimental protocol; non-smokers; no known food allergies; no history or current use of MPH; no history of ADHD or current diagnosis of an axis one psychiatric disorder (for example, depression, panic disorder, schizophrenia) as measured by clinical interview and self-report questionnaires (Wender-Utah rating scale, the Beck depression inventory (Beck et al. 1996); not taking antidepressants, thyroid medication, or any medication that could affect appetite; no excessive use of alcohol or alcoholism, or current addictions to opiates, cocaine or stimulants as measured by the drug abuse screening test; not currently taking monoamine oxidase inhibitors, pressor agents, Coumadin, anticonvulsants, or tricyclic antidepressants; and no personal or family history of motor tics or Tourette syndrome. Participants were free from any chronic illness like diabetes, hypertension or any cardiovascular condition, and female participants were not pregnant or lactating at the time of intervention. This study received approval from the Research Ethics Boards at the University of Ottawa and Children Hospital of Eastern Ontario (CHEO, ON, Canada). Written informed consent was obtained from all participants and the study was conducted according to the guidelines laid down in the Declaration of Helsinki (World Medical Association 2013).

2.2. Design and experimental procedure

We employed a randomized, double-blind, placebo-controlled, parallel arm, clinical trial to test the effects of a 2 month MPH administration on appetite sensations and olfaction in individuals with obesity (ClinicalTrials.gov Identifier: NCT02754258). The study recruitment and conduct were per the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz et al. 2010) as illustrated in Fig. 1. The initial contact with the participants was through email or by phone to briefly explain the layout of the experiment and to ensure that they were eligible for the clinical screening. After consenting to the study and the initial screening visit, the participants were randomized into the placebo or MPH group. Participants were prescribed either a placebo or short-acting MPH (0.5 mg/kg) twice daily, 1 h after lunch and dinner for two consecutive months. The CHEO pharmacy led the randomization process, which was blinded to the researchers and the participants. The randomization used a 1:1 ratio in blocks of two, stratified by sex. The study was conducted between October 2017 and August 2018 at the Behavioural and Metabolic Research Unit located at the

Fig. 1. CONSORT flow chart of study population from enrolment to data analysis.



University of Ottawa. Both the study medication and the placebo were manufactured by the CHEO pharmacy. The contents of capsules were MPH powder with lactose monohydrate powder as filler. Capsules were available as 5 mg and 20 mg of MPH. The placebos were capsules containing lactose monohydrate powder. Capsules were opaque gelatin capsule size No. 4 for all formulation. No marking was present on the capsules. Medication was labeled with drug name, strength, form, manufacturer, expiry date, quantity in bottle. The bottle was opaque and plastic. The expiry of all manufactured products was 6 months.

The study consisted of three visits to the laboratory, as follows: the initial screening visit (4 h), and two repeated measures test days (6 h each; baseline visit (day 1) and final visit (day 60). After phone screening, participants were asked to come to an initial screening visit to be assessed physically, psychologically, and nutritionally to check if they met the inclusion criteria. As soon as they arrived, the potential participants were introduced to the study goals and procedures and were asked to sign an informed consent form. Then, BW and height were measured to ensure that their BMI was >29.9 kg/m^2. The participant completed a number of questionnaires to evaluate exclusion criteria such as ADHD with Wender-Utah Rating Scale (Stein et al. 1995), depression with the Beck Depression Inventory II (Beck et al. 1996), as well restrained eating with the Three-Factor Eating Questionnaire (Stunkard and Messick 1985). Participants were also clinically examined by the study physician. Female participants were asked to take a pregnancy test to confirm that they were not pregnant at the time of experiment.

After clearance from the physician, participants were given a test dose of MPH (0.5 mg/kg BW) under the supervision of a research nurse to assess their tolerability to MPH. Drug side effects and vital signs (blood pressure and heart rate) were evaluated every hour for 3 h following the ingestion of the test dose. Electrocardiogram readings were also collected for 3 h and were evaluated by a cardiologist. Responses to MPH test dose that included systolic blood pressure exceeding baseline reading by 20 mm Hg, diastolic blood pressure exceeding the baseline reading by 10 mm Hg, blood pressure $>$ 160/100, or resting pulse increased by 20 beats/minute from the baseline, or those who reported severe side effects like severe headache, nervousness, and nausea were considered as exclusion criteria. No participants were excluded due to adverse drug reaction.

In this experiment, the drug was administered twice per day, and titrated gradually over 7 days until reaching the best tolerated dose (up to 0.5 mg/kg BW). The dose titration began at 0.25 mg/kg and increased by 15% daily increments for 7 days. All participants tolerated the maximal dose and therefore after the 7 day titration period, all participants in the MPH group were on a twice daily dose of 0.5 mg/kg of BW. Thus, this dose of MPH was administered for a total of 50 days out of the 60 day intervention. Participants were asked to rate their side effects online for the first 14 days of drug intake and were contacted promptly by the study coordinator if they checked any side effect as moderate or severe; however, no such incidence occurred. The dose was given twice per day and participants were asked to take each pill 1 h before their lunch and dinner meals. The pills were given to the participants by the study coordinator twice during the study:

once at day 1 and then renewed at day 30 in a calendar-style blister-card dispensary system (DISPILL; Grandby, Quebec). Participants were asked to return the empty blister packs of the study medication to monitor compliance and ensure that pills were taken as prescribed.

On the testing days, i.e., baseline and final visits, all participants who met the inclusion criteria and agreed to participate were instructed to arrive at the laboratory early in the morning ~0730 after a 12-h overnight fast and after having refrained from any vigorous physical activities for at least 48 h. In the day of the final visit, participants were asked to take their morning MPH or placebo dose as soon as they arrive to the laboratory at 0730. In both the baseline and final visits, the participants were asked questions about their level of physical activity during the last 3 days to ensure that they did not perform strenuous exercise in the past 48 h. Then measurements of BW and composition were done ~0740. Participants were also asked to rate their appetite on a 150 mm visual analog scale (VAS) with the assistance of our research staff. They continued to rate their appetite sensations throughout the morning at 60 min intervals (from 0800 until study completion). Between 0905 to 0920, a standardized breakfast (~400 Kcal, 70% carbohydrates, 20% fat, 10% protein) was served (white bread, butter, strawberry jam, and orange juice). Then, an hour later, the participants completed a 15 min smell test using Sniffin' Sticks®. At 1230, participants were provided with an ad libitum buffet (McNeil et al. 2012) and were given 30 min to finish, after which appetite sensations were assessed with VAS (Flint et al. 2000).

2.3. Measurements

2.3.1. Measures of appetite variables

Different sensations of appetite that are related to food wanting and motivation to eat (desire to eat and prospective food consumption (PFC)) along with sensations related to hunger and fullness were measured. The measurements were done using a 150 mm VAS in 1 h intervals during experimental sessions, as explained above. VAS has been previously validated in single meal studies (Flint et al. 2000). We assessed appetite sensations globally by calculating the area under the curve (AUC) of appetite ratings over 3 h using the trapezoid method (Doucet et al. 2003). AUC values have better reproducibility than single time point values (Kirkmeyer and Mattes 2000; Raben et al. 1995) and are better predictors of energy intake (Drapeau et al. 2005).

2.3.2. Olfaction (smell function)

Sniffin' Sticks® (Burghart Instruments, Wedel, Germany) that were validated (Hummel et al. 2007; Wolfensberger et al. 2000) were used to test the odour detection threshold. The test was carried out in a well-ventilated room with little or no odour, and participants were not allowed to eat, smoke, or chew gums for ~1 h before the test. The olfactory threshold test consisted of a set of three pens: two pens (one with a green and the other with a blue cap) contained an odourless solvent (propylene glycol), and a third pen (with red cap) contained a concentrated level of butanol. The concentration of butanol in red-capped pens decreased on a dilution scale from 1–16 points (1 is the strongest odour concentration/lowest dilution and 16 is the weakest odour concentration/strongest dilution). As each number corresponds with a concentration of the odourant that is lower than the number before, a high odour threshold score reflects a higher odour sensitivity compared with a lower score. The test started with familiarizing the participant with the test odour by allowing them to smell red-capped pen number 1. Then the participant was blindfolded and was presented with a weak concentration of butanol that corresponded to scale point 14. Triplets of pens were presented each time to the participant in 30 s intervals and with a different order of presentation. The participant was asked to point to the pen containing the odour (butanol). When the pen was correctly identified (twice in a row) the concentration was decreased (i.e., the triplet of pens with one-point higher dilution was presented) and increased when incorrectly identified once in a single up-down staircase procedure. The steps were repeated seven times, i.e., for seven turning points, and the threshold score was the mean of the last four turning points.

Table 1. Participants' characteristics at baseline.

Variable	Placebo ($n = 7$) Mean (SD)	MPH ($n = 5$) Mean (SD)	p
Age (yrs)	29.1 (7.2)	28.6 (6.7)	0.867
Sex (M/F)	3/4	2/3	0.881
Height (cm)	168.8 (9.4)	168.7 (11.6)	0.989
BW (kg)	104.9 (21.8)	102.4 (25.6)	0.857
FM (kg)	46.6 (13.3)	45.5 (10.2)	0.877
BMI (kg/m^2)	36.4 (3.8)	35.6 (5.8)	0.771

Note: MPH, methylphenidate; BW, body weight; FM, fat mass; BMI, body mass index.

2.3.3. BW, height, and body composition

BW was assessed using the Tanita scale to the nearest 0.1 kg. Height was measured by a SECA stadiometer. BMI (kg/m^2) was calculated, and body composition (% body fat, fat mass (FM), fat-free mass (FFM)) was measured using the dual-energy X-ray absorptiometry (DEXA method) as previously described (Hummel et al. 2007; Wolfensberger et al. 2000).

2.3.4. The measures of energy intake

In laboratory feeding (ILF) was assessed by asking the participant to choose their lunch meal from our previously validated lunch buffet (McNeil et al. 2012) during baseline and final repeated measures visits. Food was offered in large amounts, and the participants were instructed that they had 30 min to eat until satiation was achieved. All food was weighed to the nearest 0.1 g before and after ingestion.

2.4. Data analysis

Baseline characteristics for age, BW, and body composition (BMI, FM and FFM) for MPH and placebo groups were compared by independent t tests to ensure that there were no baseline differences between the groups and that the randomization was successful. A mixed two-way analysis of variance (ANOVA) with group as between-subject independent variable (MPH versus placebo) × time (baseline (day 1) versus final visit (day 60)) as the within-subject variable was performed to test the effect of MPH on odour threshold, AUC of appetite variables, as well as BW, body composition, and ILF. Statistical significance of results was set as $p < 0.05$, and effect sizes were reported as eta squared, η^2, to assess the magnitude of observed effects. The values of 0.009, 0.059, and 0.138 were considered cut-off points for small, medium, and large effect sizes, respectively (Richardson 2011). Pearson correlations were performed to evaluate the relationship between (pre-post) changes in odour threshold and (pre-post) changes in appetite variables, BW, body composition, and ILF in MPH and placebo groups. Significant correlations were reported when $p < 0.05$.

3. Results

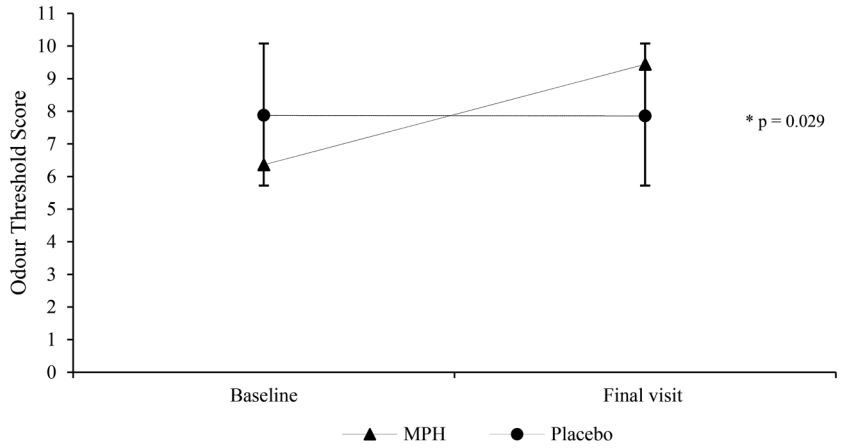
3.1. Participant characteristics

As shown in Table 1, baseline characteristics of participants in the placebo versus the MPH group showed that there were no statistically significant differences between the groups for age, height, baseline BW, FM, and BMI.

3.2. Effects of MPH on odour threshold

There was a statistically significant interaction between the intervention group (MPH versus placebo) and time for odour

Fig. 2. Effect of methylphenidate (MPH) on odour threshold scores in placebo vs. MPH from baseline to final visit. * significant group*time interaction. Mean (±standard deviation). Each number corresponds with a concentration of the odourant that is lower than the number before; a high odour threshold score reflects a higher odour sensitivity compared with a lower score.



threshold, ($F_{[1,10]}$ = 6.54, p = 0.029, η^2 = 0.4). MPH produced greater increases in odour threshold scores over time (M = −3.08, SE = 0.79, p = 0.017) whereas no significant changes were noted in the placebo group (M = 0.03, SE = 0.86, p = 0.974) (Fig. 2).

3.3. Effects of MPH on appetite variables

As shown in Fig. 3, MPH produced significant reductions in AUC values for desire to eat (p = 0.001) (Fig. 3A), hunger (p = 0.008) (Fig. 3B), and PFC (p = 0.003) (Fig. 3C), as well as an increase in AUC value for fullness (p = 0.028) (Fig. 3D) when compared with values from the placebo group.

3.4. Effects of MPH on BW and energy intake

The decrease in BW, BMI, and energy intake were significant over time (p = 0.005, p = 0.006, and p = 0.021, respectively) (Table 2). The decrease in BW was associated to a large effect size favouring greater weight loss in the MPH group (−2.66 kg vs. −1.16 kg; η^2 = 0.56); however, no significant group*time interactions were noted for any of these variables. Changes in FM and FFM were not significant for any of the groups.

3.5. Correlation between changes in olfaction threshold scores and changes in appetite variables AUC scores in MPH versus placebo groups

Pearson's correlation showed that changes in odour threshold were not statistically significantly correlated with changes in appetite sensations in the MPH or placebo groups (data not shown).

3.6. Correlation between changes in olfaction threshold scores and changes in anthropometric measurements and ILF in MPH versus placebo groups

No statistically significant correlations were found between changes in olfaction threshold and changes in BW, FM, FFM, or ILF (data not shown).

4. Discussion

The results from this study showed that the administration of short-acting MPH, a drug that increases brain synaptic dopamine levels, improved olfactory sensitivity and suppressed appetite compared with placebo in individuals with obesity. Changes in olfactory sensitivity, however, were not correlated with changes in appetite sensations or changes in BW and body composition in the MPH group. Additionally, we observed that BW and energy intake significantly decreased over time, and although these reductions were in the hypothesized direction, the differences between MPH and placebo groups did not reach significance despite moderate to large effect sizes.

Our study is the first to indicate that a 2 month intake of MPH is associated with a higher mean odour threshold score in individuals with obesity, compared with placebo, which was contrary to our hypothesis. Our results are inconsistent with the results of other studies that have examined the effects of MPH intake on the smell function in patients with ADHD. Non-medicated children with ADHD have heightened odour sensitivity (assessed by high odour threshold scores) compared with healthy controls, while children living with ADHD on chronic MPH treatment (0.5–1.0 mg/kg of MPH intake >2 months) had lower odour threshold scores that are comparable to healthy controls (Romanos et al. 2008). Another study has shown that acute cessation of MPH treatment for 2 weeks resulted in increased odour discrimination and reduced brain activity in olfactory-processing regions in the orbitofrontal cortex (Schecklmann et al. 2011). Differences in methodology including the type of odourant used butanol versus phenylethanol (Romanos et al. 2008; Schecklmann et al. 2011), as well as study population characteristics (individuals with obesity herein versus children with ADHD) (Romanos et al. 2008; Schecklmann et al. 2011), are likely to partly explain discrepancies in study outcomes.

The improved smell function in our sample might be better explained in the context of MPH-induced amplification of dopamine activity in the brain. In patients with Parkinson's disease, the loss of striatal dopaminergic tone leads to increased expression of inhibitory dopaminergic cells in the olfactory bulb and hyposomia (Oppo et al. 2020). As proposed by the Reward Deficiency Syndrome model of feeding behaviour, individuals with obesity may have low brain dopaminergic tone (Blum et al. 1996), and they exhibit a lower than normal olfactory performance (Peng et al. 2019). Thus, it can be speculated that correcting dopamine activity with MPH might lead to an increase in olfactory function as noted in our sample by modulating dopamine neurons in the olfactory bulb. Enhancing smell function might seem counter-effective to weight loss efforts as heightened olfactory sensitivity that follows energy restriction is thought to contribute to increased appetite and weight regain (Cameron et al. 2012, 2014; Stafford and Welbeck 2011). Yet, eliminating oro-sensory stimulation of food by gastric feeding resulted in increased hunger and decreased fullness ratings compared to oral feeding (French and Cecil 2001). Also, studies reported that inhalation of pleasant odours before food intake suppresses appetite and might contribute to long-term weight loss (Hirsch and Gomez 1995; Mayer et al. 1999; Sorensen et al. 2003; Warwick et al. 1993).

Fig. 3. Appetite area under the curve (AUC) scores for (A) desire to eat, (B) hunger, (C) prospective food consumption (PFC), and (D) fullness in MPH vs. placebo. *significant group*time interaction. Mean (±standard deviation).

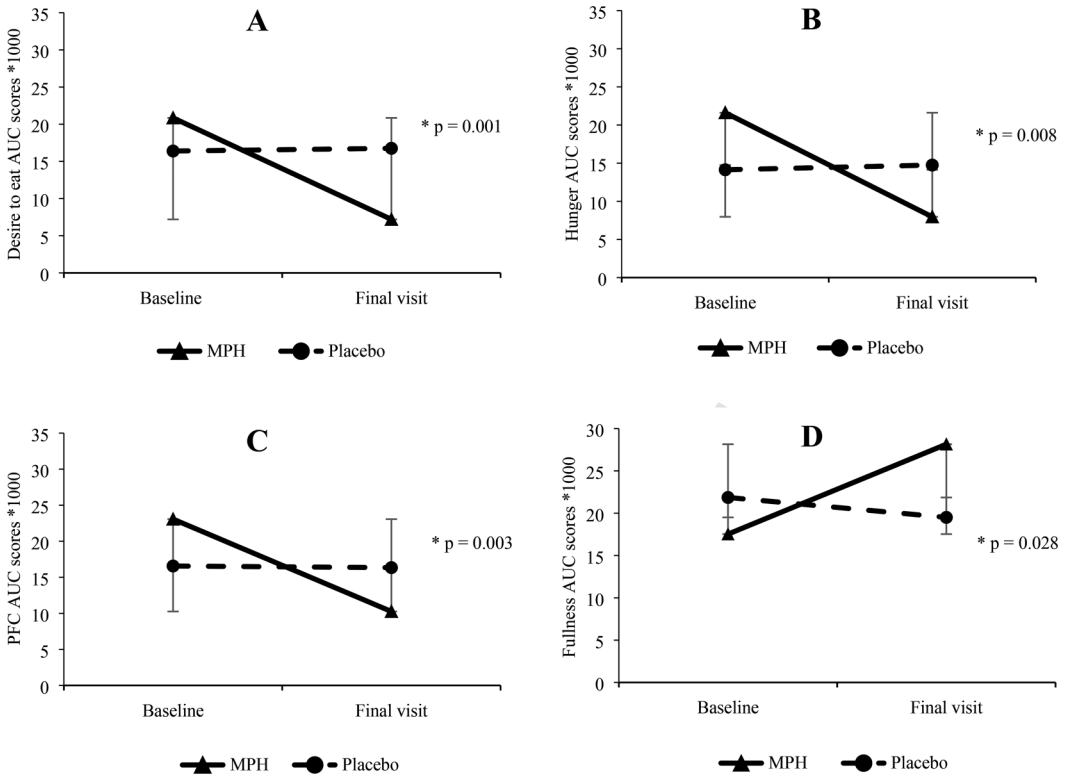


Table 2. Changes in BW and ILF in MPH vs. placebo group.

	Baseline 1		Final Visit		Time	Group*time
Variables	Placebo	MPH	Placebo	MPH	*p*	*p*
BW (Kg)	104.9 (21.8)	102.4 (25.6)	103.6 (25.6)	99.7 (26.9)	0.005*	0.225
FM (Kg)	46.6 (13.3)	45.5 (10.2)	46.2 (11.6)	43.3 (11.0)	0.116	0.177
FFM (Kg)	53.7 (11.7)	53.4 (15.9)	53.1 (10.1)	52.9 (16.6)	0.462	0.985
BMI (kg/m^2)	36.4 (3.8)	35.6 (5.8)	36.0 (3.6)	34.7 (6.3)	0.006*	0.195
ILF (Kcal)	1559.9 (512.9)	1587.9 (546.3)	1402.2 (369.7)	1347.4 (455.8)	0.021*	0.582

Note: Placebo (n = 7; 4 M, 3 F), MPH (n = 5; 2 M, 3 F). Mean (±standard deviation). *$p < 0.05$. MPH, methylphenidate; BW, body weight; FM, fat mass; FFM, fat-free mass; BMI, body mass index; ILF, in laboratory feeding.

These findings suggest that smell function contributes to the sensory stimulation of food (Mattes 1997) and that improving basic olfactory acuity in individuals with obesity might potentially modulate satiety and help to regulate BW (Miras and le Roux 2010).

As expected, MPH suppressed appetite when prescribed for 2 months. Our findings are consistent with the reported acute effects of a single dose of MPH on appetite sensations in healthy individuals without ADHD. The increase in pre-meal hunger scores were smaller with MPH than with placebo in healthy normal-weight individuals following the administration of a single dose of 0.5 mg/kg MPH (Miras and le Roux 2010). It was also reported that energy intake was 34% lower with MPH compared with placebo in individuals with obesity (Goldfield et al. 2007). What is more, women with obesity had reduced post-prandial appetite sensations in response to a single dose of MPH (Davis et al. 2012); however, our study is the first to document a sustained reduction of appetite in response to chronic MPH administration in individuals with obesity who do not have ADHD. In fact, we show that MPH produced a 55%–65% reduction from baseline in appetite scores, an effect sufficiently robust to trigger subsequent reductions in energy intake (Sadoul et al. 2014).

Interestingly, the MPH-induced appetite suppression persisted for 2 months despite ~3 kg weight loss in the MPH group. In a weight loss state, appetite sensations related to desire to eat, hunger and PFC are stimulated, whereas satiety (fullness) is inhibited (Doucet et al. 2000; Drapeau et al. 2005; Maclean et al. 2011). In an attempt to quantify the changes in appetite sensations relative to weight loss, it was noted that for each 1 kg of fat loss, there is a delta increase in fasting desire to eat of 5.8 mm and a 3.6 mm decrease in fasting fullness in their rating on 150 mm VAS (Gilbert et al. 2009). Concurrent with these findings, our placebo group demonstrated non-significant heightened appetite sensations and depressed fullness scores following a modest weight loss. MPH administration, however, seemed to curb the weight loss-induced appetite stimulation, highlighting its potent appetite suppressing effects even in the presence of depleted energy stores.

Based on its appetite suppressing effects (Cortese et al. 2018; Efron et al. 1997; Gurbuz et al. 2016), we hypothesized that MPH would produce a greater reduction energy intake. Our data showed

that energy intake decreased significantly overtime in both MPH and placebo groups, and although the MPH group showed a 50% larger decrease in energy intake relative to placebo, these differences did not reach statistical significance despite large effect size.

Our results showed that the change in BW from baseline to final visit was not statistically significantly different between groups; however, there was large effect size of greater weight loss with MPH (2.6% weight loss) than with placebo (1.3% weight loss), and this occurred in the absence of a prescribed diet, which is in line with our hypothesis. Unintentional weight loss as a side effect of MPH treatment has been reported in patients with ADHD (Mattes and Gittelman 1983; Poulton et al. 2012; Schertz et al. 1996). Furthermore, adults with ADHD and refractory obesity lost 18 kg in ∼16 months when they were treated with MPH compared with the untreated group (Levy et al. 2009). Thus, our findings along with the previously documented impact of MPH on weight loss warrant further investigation in future studies.

Although we employed a double-blind, placebo-controlled, randomized clinical trial which is a gold standard in clinical testing (Hariton and Locascio 2018), we acknowledge that our results are preliminary and that the power of the study was limited by the small sample size. It is likely that with a larger sample, the effects of MPH on weight loss (large effect size) would have reached statistical significance. Of note, our study was not designed to address possible sex differences in the response to MPH. Some laboratory studies have reported sex differences related to appetite and energy intake in response to a single dose of MPH, but results were contradictory (Davis et al. 2012; Goldfield et al. 2011).

In conclusion, our data show for the first time that the MPH intake for 2 months was effective in suppressing appetite and in improving olfactory sensitivity in individuals with obesity despite the potential to induce greater weight loss compared with placebo. As changes in appetite sensations and olfaction are implicated in obesity and weight relapse, our study provided a novel insight into the possible mechanisms by which MPH might exert its weight loss effects.

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Contributor statement

Conceptualization (ED, GSG, PR, JC, RV), methodology (ED, GSG, PR, JC, RV), formal analysis (ED, GSG, JC, FE), investigation (PR, JC, FE, KH, SB), resources (JC, FE, KH, SB), data curation (ED, GSG, JC, FE), writing-original (FE, ED, GSG, JC), writing-review (ALL), supervision (ED, GSG, JC), administration (ED, GSG, JC), and funding (ED, GSG, RV).

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