THE EFFECT OF TWO-MONTH ADMINISTRATION OF METHYLPHENIDATE ON APPETITE, OLFACTION AND ENERGY INTAKE IN INDIVIDUALS WITH OBESITY

THESIS

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Abstract

Background: Dopamine levels has been implicated in obesity, feeding behaviour, and hedonic control of appetite like olfactory cues and food palatability. Methylphenidate (MPH) is a dopamine reuptake inhibitor that increases brain dopamine levels and has been shown to reduce appetite and promote weight loss in patients with attention deficit hyperactivity disorder (ADHD). As such, the objectives of this study were to test the possible effect of MPH on appetite, olfaction, and food palatability as well as its effects on energy intake and body weight of healthy individuals with obesity.

Methods: In a randomized, double-blind study, 12 participants (age 28.9±6.7 yrs) (BMI 36.1±4.5 kg/m^2) were assigned to receive MPH (0.5mg/kg) (n=5) or placebo (n=7) twice daily for two months. Appetite and palatability (Visual Analog Scale (VAS)), odour threshold (Sniffin' Sticks®), in-lab energy intake (*ad libitum* buffet), free-living energy intake (3-day food boxes) and body weight (DEXA scan) were measured at baseline (day 1) and final visit (day 60).

Results: MPH intake caused significantly greater suppression of appetite sensations (desire to eat (p=0.001), hunger (p=0.008), and prospective food consumption (p=0.003)) and increase in fullness (p=0.028) over time compared to placebo. There was a significant increase in odour threshold scores in the MPH group (6.3±1.4 vs. 9.4±2.1) compared to placebo (7.9±2.3 vs. 7.8±1.9) (p=0.029). Both placebo and MPH groups showed decreases in their energy intake (p=0.021) and body weight (p=0.005) over time but with large effect sizes favouring greater reduction in the MPH group compared to placebo.

Conclusions: Compared to placebo, MPH intake over 60 days suppressed appetite and improved olfactory sensitivity in individuals with obesity. These data provide novel findings into the possible efficacy of MPH to favourably impact appetite and therefore promoting weight loss in individuals living with obesity.

Key words: Methylphenidate; dopamine; food reward; feeding behaviour; appetite; olfaction; food palatability; weight loss; obesity pharmacotherapy.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ARC	Arcuate Nucleus
ANOVA	Analysis of Variance
AUC	Area Under Curve
BED	Binge Eating Disorder
BMI	Body Mass Index
BMRU	Behavioural and Metabolic Research Unit
CHEO	Children's Hospital of Eastern Ontario
CCK	Cholecystokinin
DAT	Dopamine transporter
DEXA	Dual X-ray Absorptiometry
ECG	Electrocardiogram
FM	Fat Mass
GLP-1	Glucagon Like Peptide 1
EI	Energy Intake
ILF	In Lab Feeding
MPH	Methylphenidate
NAc	Nucleus Accumbens
NHANES	National Health and Nutrition Examination Survey
NICE	National Institutes for Health and Care Excellence
OOLF	Out of Lab Feeding
PYY	Peptide Tyrosine Tyrosine
PFC	Prospective Food Consumption
TDI score	Odour Threshold, Discrimination and Identification score
VAS	Visual Analog Scale
VTA	Ventral Tagmental Area

1 Introduction:

1.1 Background

Obesity (defined as having body mass index (BMI) $\geq$ 30 kg/m^2), is a growing health problem in Canada and worldwide. Obesity prevalence rates have doubled between 1978 and 2015 from 6.3% to 14.3% in Canadian adolescents and from 13.8% to 26.4% in Canadian adults (Bancej et al., 2015) with predictions that obesity rates will continue to increase for the next two decades (Twells, Gregory, Reddigan, & Midodzi, 2014). It is well established that obesity is associated with several comorbidities such as type 2 diabetes, hypertension, metabolic syndrome, certain types of cancer, dyslipidemia, sleep apnea and arthritis (Pi-Sunyer, 2009) as well as increased premature mortality (Flegal, Graubard, Williamson, & Gail, 2005). Recently, the Canadian Medical Association and Obesity Canada have recognized obesity as a chronic disease that requires preventive measures and appropriate treatment (Canadian Medical Association, 2015). Knowing that 80% of obese adolescents become obese adults (Freedman et al., 2005), adolescence becomes a critical period for treating obesity early on to improve body weight management and obesity-related co-morbidities.

The current treatment options for obesity include nutritional and behavioural modifications which are the cornerstone in the management of obesity (Lau, Douketis, Morrison, Hramiak, & Sharma, 2007). Other treatment options are weight loss surgeries (Park & Torquati, 2011), and obesity pharmacotherapy (Pilitsi et al., 2019). Despite the abundance of behavioural and dietary interventions for obesity treatment (Santos, Sniehotta, Marques, Carraça, & Teixeira, 2017), the long-term effectiveness of these methods is questionable. In adolescent population, the current behavioural interventions have shown limited efficacy (Epstein, Myers, Raynor, & Saelens, 1998). Likewise, in adults, body weight data from ~ 14000 participants (age 20–84 years) in the

1999–2006 National Health and Nutrition Examination Survey (NHANES), found that only 17% of individuals with obesity were able to maintain a 10% weight loss for at least one year following diet-induced weight loss (Kraschnewski et al., 2010). Also, meta-analyses of weight loss studies, which included diet or exercise or a combination of both, reported that weight loss plateaus after the first six months of a weight loss regime (Franz et al., 2007; Headland, Clifton, Carter, & Keogh, 2016; Johnston et al., 2014) and that only 3-6 kg of the weight loss is maintained after one (Johnston et al., 2014) or two years of initial weight loss (Franz et al., 2007) following the intervention. Moreover, Curioni & Lourenço (2005) conducted a systematic review of 33 clinical trials looking at long-term weight loss outcomes and found that, in both diet alone and diet-exercise combination plans, almost half of the lost weight was regained after one year (Curioni & Lourenço, 2005). Indeed, the challenges of traditional weight-loss interventions and the difficulty in maintaining the lost weight attest to the complexity of the obesity problem and necessitate the development of alternative or complementary approaches to treat obesity.

Weight loss (bariatric) surgeries are currently considered to be the most effective treatment choice for obesity (Park & Torquati, 2011). Yet, due to its invasive nature and risk of surgical complications (Finks et al., 2011; Morino et al., 2007), bariatric surgery is reserved for patients with morbid obesity (BMI > 40kg/m^2) or patients with obesity and associated comorbidities (Lau et al., 2007; Pories, 2008). Besides surgical intervention, the development of pharmaceutical agents that can reduce body weight by reducing food intake or increasing energy expenditure or both is another possible therapeutic option. The currently approved anti-obesity drugs show better efficacy than diet and exercise alone for promoting weight loss and maintenance, where the drug-induced weight loss outcome is 3-7 kg higher than the placebo-induced weight loss after one year of intervention (Khera et al., 2016). Unfortunately, the serious side effects (Colman,

2005) and issues of tolerability leading to high attrition (Day, 2018; Khera et al., 2016), are limiting the appeal of obesity pharmacotherapy (Wharton, Lee, & Christensen, 2017). Nevertheless, with the recent advances in understanding the physiological processes that control appetite and feeding behaviour and their impact on weight loss and weight relapse (Halford, Boyland, Blundell, Kirkham, & Harrold, 2010; Pilitsi et al., 2019), new pathways can be explored as targets for anti-obesity drugs (Dietrich & Horvath, 2012; Halford et al., 2010).

Research in the field of feeding behaviour has shown that feeding is under the influence of homeostatic control of peripheral energy signals, (Doucet & Cameron, 2007; Lam, 2010; Murphy & Bloom, 2006) as well as the non-homeostatic or hedonic factors that modulate food reward circuitry in the brain, (Alonso-Alonso et al., 2015; Begg & Woods, 2013; Berthoud, 2011; Cameron & Doucet, 2007). In other words, food intake is not only driven by metabolic hunger but also by the reward value of food, that interacts with the fed state of individuals to preserve long-term energy stores. The mechanisms that regulate food reward in the brain are multifaceted with elements of liking, wanting, and learning (Berridge, 1996). Food liking, or the hedonics of food, is a major constituent of the food reward circuitry and it might modulate appetite and energy intake in response to physiological need (Cameron & Doucet, 2011) and in response to food cues (Denis et al., 2015; Mccrickerd & Forde, 2016), like sight, smell or taste of food. Individuals with obesity are thought to find energy-dense food more palatable than their normal-weight counterparts, which might lead to overconsumption of energy-dense food and weight gain (Blundell & Rogers, 1991; Johnson & Wardle, 2014).

Additionally, caloric restriction has been shown to increase the rating of food palatability (Cabanac, 1971; Cameron, Goldfield, Cyr, & Doucet, 2008) indicating that caloric restriction, as a means to promote weight loss, might increase food hedonics which could stimulate appetite

and possibly lead to weight relapse (Yeomans, Blundell, & Leshem, 2004). Food hedonics can also be affected by food cues, such as the smell of food (olfaction). Olfactory food cues have been shown to contribute to food palatability and flavour, as well, alterations in olfactory function are implicated in changes in food intake (Cameron, Goldfield, Finlayson, Blundell, & Doucet, 2014; Rolls, 2005). For example, the loss of olfactory function in senior adults (Morley, 2001) or patients with Parkinson's disease (Huisman, Uylings, & Hoogland, 2004) is reportedly linked with reduced food intake. Also, people with obesity were found to exhibit reduced olfactory function compared to normal-weight individuals, which might contribute to changes in food palatability and food intake (Rolls, 2011; Soria-Gomez, Bellocchio, & Marsicano, 2014; Yin, Hewson, Linforth, Taylor, & Fisk, 2017). On the other hand, heightened olfactory sensitivity following caloric restriction correlated with increased food palatability and subsequent energy intake (Cameron, Goldfield, & Doucet, 2012). In short, changes in feeding behaviour that are related to alterations in food hedonics and olfactory function can be noted in obesity and under caloric restriction conditions. Such changes might stimulate appetite and lead to increased food intake, which is thought to exacerbate the obesity problem (Volkow & Wise, 2005; Wang et al., 2001) and undermine the individual's efforts to lose weight (Sharma, Fernandes, & Fulton, 2013; Shizgal, Fulton, & Woodside, 2001).

An intricate network of brain substrates such as dopamine, opioids, and endocannabinoids are involved in regulating food reward circuitry and modulating food hedonics (Berridge, Ho, Richard, & Difeliceantonio, 2010). Dopamine has been shown to play an essential role in motivating individuals to eat highly palatable food (Berridge, 1996) in response to olfactory food cues (Alcaro, Huber, & Panksepp, 2007; Epstein, Temple, Roemmich, & Bouton, 2009; Schultz et al., 2010; Volkow, Wang, Fowler, & Telang, 2008) and to physiological needs (S. Liu &

Borgland, 2015). Additionally, early stages of olfactory perception are modulated by dopaminergic neurons in the olfactory bulb (Hsia, Vincent, & Lledo, 2017). It is hypothesized that alterations in the dopaminergic tone in the brain may result in an increased intake of palatable food and obesity (Blum et al., 2015; Cameron, Chaput, Sjödin, & Goldfield, 2017; Davis & Fox, 2008). Therefore, targeting brain dopamine pathways might be a useful tool to curb the potential changes in food hedonics and olfaction in individuals with obesity, which can help to improve the outcome of dietary interventions (Khorassani, Misher, & Garris, 2015). It was demonstrated that the intake of dopamine transporter (DAT) inhibitors, like Methylphenidate (MPH), resulted in reduced body weight and suppressed appetite in patients with Attention Deficit Hyperactivity Disorder (ADHD) (Cortese et al., 2016; Efron, Jarman, & Barker, 1997; Gurbuz et al., 2016). Also, studies on healthy adults who do not have ADHD indicated that the acute (laboratory) administration of MPH caused an immediate reduction of energy intake, as well as reduced reinforcement of food but not reduced hunger (Goldfield, Lorello, & Doucet, 2007; Leddy et al., 2004). However, whether the appetite reducing effects of MPH are sustained for a longer duration in individuals with obesity and whether they are related to alterations in food palatability and olfaction is not known.

1.2 Rationale and Research Problem:

Despite persistent efforts to address the problem of obesity, it is still a global health issue , and it has recently been recognized as a disease by leading health organizations worldwide and in Canada (Canadian Medical Association, 2015; Kyle, Dhurandhar, & Allison, 2016; Lancet Diabetes, 2017; Mechanick, Hurley, & Garvey, 2017; Wharton et al., 2017). There is mounting evidence of the contribution of behavioural and motivational aspects of feeding to the

development of obesity and weight regain, which likely renders most traditional behavioural weight loss programs ineffective in the long term. Changes in food hedonics and olfactory function in individuals with obesity and after diet-induced weight loss have been proposed to be amongst the contributing factors to appetite stimulation and increased energy intake. Dopamine is a brain neurotransmitter that is involved in olfaction, food reward (including food hedonics), and energy intake. Changes in brain dopamine activity are thought to cause weight gain and obesity, while enhancing brain dopamine levels by administering acute doses of MPH, a DAT inhibitor, was shown to suppress appetite and reduce energy intake in healthy individuals with obesity (Davis et al., 2012; Goldfield et al., 2007; Leddy et al., 2004). Nevertheless, there appears to be a gap in the literature as to whether the appetite suppressing effects of MPH can be sustained for a longer duration and whether MPH intake can modulate olfactory function and reduce food palatability in individuals living with obesity. Thus, we performed a study to test the effects of a two-month administration of MPH on olfaction, food palatability, and appetite in persons with obesity. A secondary aim of this study was to assess the effects of MPH on energy intake and body weight of individuals with obesity.

2 Literature Review

This section will present an overview of the control of feeding behaviour, and the role of dopamine in modulating feeding behaviour, food hedonics, and olfaction as well as its interaction with peripheral energy signals to regulate appetite and energy intake. The effects of MPH on appetite, food palatability, and olfaction will be discussed as will the current status of anti-obesity drugs in the context of their weight loss outcomes.

2.1 Overview of The Control of Feeding

Feeding behaviour is co-determined by homeostatic (metabolic driven), and non-homeostatic (pleasure-driven) neural circuits (C. M. Liu & Kanoski, 2018) **(Figure 1)**. These factors regulate energy intake and energy expenditure to prevent changes in the long-term energy stores despite the day to day fluctuations in energy input and output (Rosenbaum, Kissileff, Mayer, Hirsch, & Leibel, 2010).

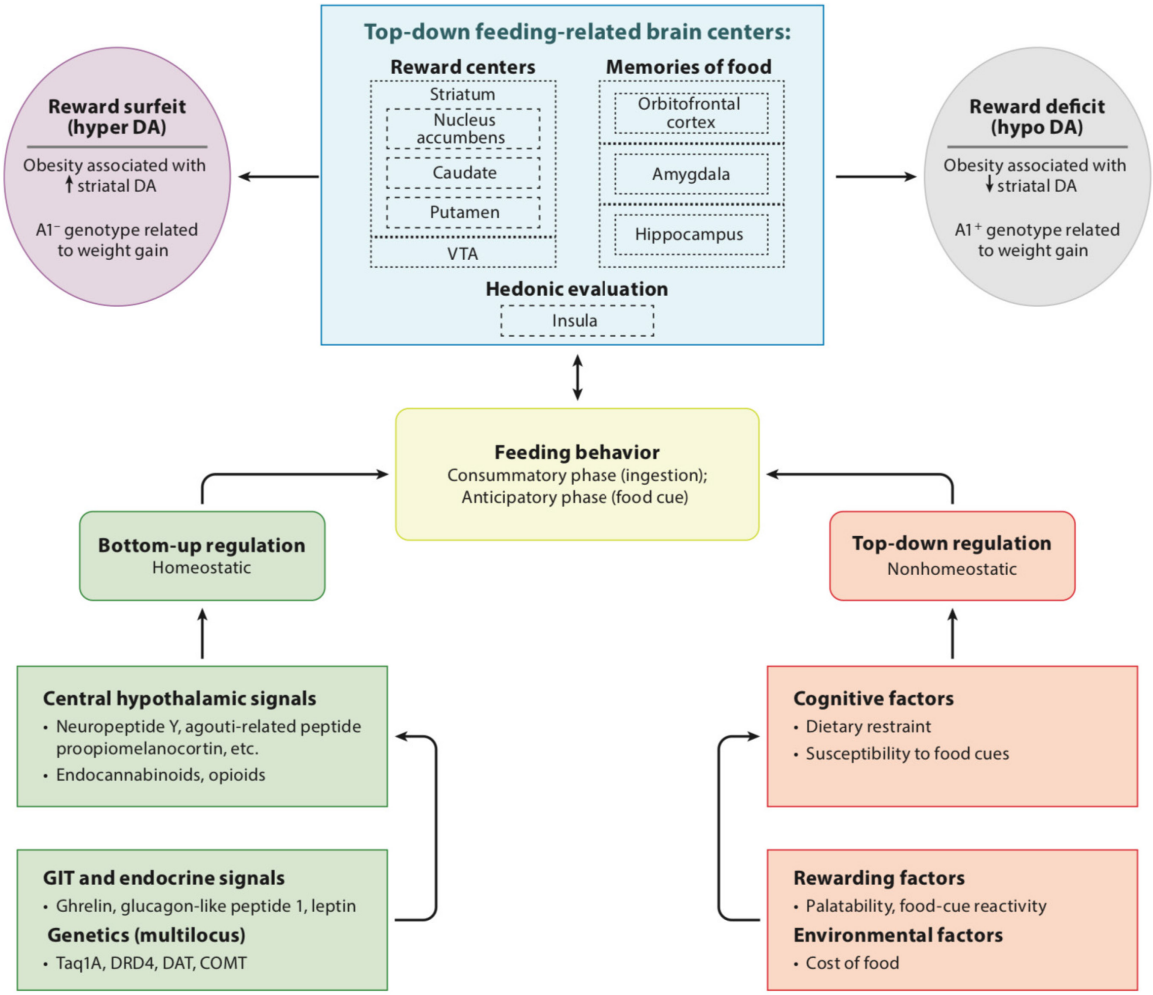

Figure 1: a schematic diagram representing the homeostatic and non-homeostatic players in feeding behaviour, adapted from (Cameron, *et al.* 2017)

A well-characterized network of peripheral energy signals conveys information pertaining to long term energy stores (*i.e.,* leptin in the adipose tissue and insulin in the pancreas) (Friedman, 2011) and short-term nutrient availability (such as appetite hormones in the gut) (F. Greenway, 2015) to the arcuate nucleus (ARC) in the hypothalamus. Briefly, both leptin, an adipocyte-derived hormone, and insulin, a hormone that is mainly involved in glucose regulation, reflect the overall nutritional status of the body and are involved in modulating long-term energy intake (Havel, 2001). On the other hand, the digestive tract secretes several peptides (appetite

hormones), in response to nutrient intake, that control appetite, and meal-to-meal satiety. These gut hormones include ghrelin, peptide tyrosine tyrosine (PYY), cholecystokinin (CCK), and glucagon-like peptide-1 (GLP-1), amongst many others (Guyenet & Schwartz, 2012). Except for ghrelin, which is the only known hunger-signalling hormone, all other appetite hormones act as satiety signals and are released in response to nutrient intake. After the binding of these peptides to their receptors in the brain stem and the ARC, ARC then integrates these signals and activates downstream orexigenic or anorexigenic peptide pathways (Blundell, Halford, King, & Finlayson, 2000; Timper & Brüning, 2017). In general, this system acts as a negative feedback loop that suppresses appetite and inhibits food intake in response to internal physiological cues (Berthoud, 2013; Schwartz et al., 2003).

In contrast, the neural circuits that operate in the cortico-limbic areas of the brain process appetitive and rewarding aspects of feeding (Zheng, Lenard, Shin, & Berthoud, 2009). Pleasure-driven feeding behaviour is influenced by "wanting" and "liking" of food. Food hedonics is a component related to food palatability or the "pleasure," which corresponds to the "liking" component of reward stimuli (T. E. Robinson & Berridge, 2000) while the reinforcing value of food has a motivational element that is associated with desire and the "wanting" part of the reward stimuli (Berridge, 1996; Berridge & Robinson, 1998; Wyvell & Berridge, 2000).

The non-homeostatic regulatory pathways are mediated by a number of neurotransmitters (Berridge, 2009), including dopamine (Volkow et al., 2008), opioids (Yeomans & Gray, 1996) and endocannabinoids (Cooper, 2004). The activation of these pathways usually elicits a feed-forward signal that induces appetite and increases energy intake in response to external food-related cues (Berthoud, 2013; Finlayson, King, & Blundell, 2007). Under normal conditions, a number of homeostatic regulators like leptin, insulin, and appetite hormones such as ghrelin and

GLP-1 (Atkinson, 2008; Rosenbaum, Sy, Pavlovich, & Leibel, 2008; Skibicka, 2013) have been shown to interact with non-homeostatic regulatory neural circuits in order to maintain energy balance and body weight (Berthoud, 2007; Figlewicz, Naleid, & Sipols, 2007).

However, there is substantial evidence that, in the world of abundance, obesity might be caused by overconsumption of palatable (pleasant) food; which is driven by specific changes in the feeding behaviour of genetically predisposed individuals (Cecil, Tavendale, Watt, Hetherington, & Palmer, 2008; Drapeau et al., 2005; Wardle et al., 2008). These changes are characterized by heightened motivation to eat in response to food cues (food wanting) and increased pleasure derived from eating (food liking) (Berthoud, 2006; Finlayson et al., 2007; Mela, 2006). The changes in food wanting and liking would mean that food intake can occur even in the presence of homeostatic signals of satiety (Erlanson-Albertsson, 2005; Zheng et al., 2009), which is speculated to cause positive energy balance and weight gain or weight relapse (Berridge, 2009).

2.2 Role of Dopamine in Feeding behaviour

As stated earlier, both non-homeostatic neurotransmitters and homeostatic regulators are implicated in the regulation of food reward circuitry. Dopaminergic neuronal pathways have been among the most extensively studied and are the best described (Di Chiara, 1995; Fibiger & Phillips, 1988; Martel & Fantino, 1996; Pierce & Kumaresan, 2006; Spyraki, Fibiger, & Phillips, 1983; Stevens & Livermore, 1978; Volkow, Wise, & Baler, 2017; Wise & Bozarth, 1984). Dopamine plays a key role in modulating reward through its mesolimbic pathway (Alcaro et al., 2007). The mesolimbic dopaminergic neurons project from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAc) (Stott & Ang, 2013) and the activation of (VTA-NAc) circuitry occurs in response to a rewarding stimulus (Martel & Fantino, 1996). Under

normal conditions, the circuit regulates an individual's responses to natural reinforcers, such as food, and is, therefore, a principal determinant of motivation, *i.e.*, "wanting" (Berridge & Kringelbach, 2015; Ikemoto & Panksepp, 1999; Le Moal & Simon, 1991; Salamone, 1994). Dopamine neurons also project into the dorsal striatum, which is involved in food liking and conditioning of reward cues. Research has shown that dopamine release from the dorsal striatum in the brain correlated positively with the pleasure of the eating experience, which implicates its function in the liking component of reward and in food palatability (Small, Jones-Gotman, & Dagher, 2003). Nevertheless, dopamine plays a more complex role than merely encoding for the hedonic value of food. During the first exposure to the reward, striatal dopamine level increases as the pleasure increases (Norgren, Hajnal, & Mungarndee, 2006) but with repeated exposure, dopamine concentration habituates and is transferred to cues associated with the reward, such as the smell of food, so that dopamine becomes linked to the predictor of the reward, *i.e.* "the food cues", rather than the pleasure from consuming the food reward, *i.e.* "liking" (Epstein et al., 2009; Schultz et al., 2010; Volkow et al., 2008). Besides its role in food wanting, liking and in food cues, dopamine neurons also project into other brain reward areas including cortical areas, which are implicated in inhibitory control, and limbic regions like hippocampus and amygdala that are mainly associated with memory and learning (Setlow, 1997; Wise, 2004).

Both hyperdopaminergic, *i.e.*, heightened sensitivity to reward, (Stice & Yokum, 2016; Yokum, Marti, Smolen, & Stice, 2015) and hypodopaminergic, *i.e.*, reward deficit, (Blum, Gardner, Oscar-Berman, & Gold, 2012; Davis & Fox, 2008; Stice, Spoor, Bohon, & Small, 2008; Wang et al., 2001) response to food reward has been hypothesized in increasing the risk of weight gain. Research has shown that changes in the genes associated with dopamine signalling might

moderate the reward response of individuals at risk of weight gain with either high or low dopamine levels in these individuals (Stice, Burger, & Yokum, 2015; Yokum et al., 2015).

In their research paper, Wang *et al.* (2001) found that the availability of the dopamine receptor (DRD2) was decreased in individuals with obesity in proportion to their BMI (Wang et al., 2001). As such, they concluded that some individuals living with obesity might have lower than normal response to food reward, and that puts them at higher risk of overindulgence and weight gain (Wang, Volkow, Thanos, & Fowler, 2004). Another brain imaging study has also found that reward-related signalling in striatum and NAc is inversely related to BMI (Born et al., 2011).

Blum *et al.* (1996) have defined the blunted dopamine signalling as the reward deficiency syndrome (RDS) (Blum, Cull, Braverman, & Comings, 1996). RDS is an umbrella term that is used to describe genetic and epigenetic mutations in neurotransmitter signalling pathways in the brain that leads to impulsive/addictive behaviours to compensate for low dopamine activity (Blum et al., 2012; Noble et al., 1994; Stice, Yokum, Zald, & Dagher, 2010). Studies have shown that carriers of the *Taq1 A1* allele, which is located downstream of the DRD2, gene exhibit 30-40% decrease in their dopamine receptor sites that result in response attenuation in the dopamine target regions of the reward center in the brain, thus curbing dopamine activity (Blum, Thanos, & Gold, 2014; Delis et al., 2013; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991). Moreover, carriers of the *Taq1 A1* allele with BMI >30 kg/m^2 lost less body and fat mass compared to their counterparts who do not have this genotype when both groups followed the same diet and resistance training program for six months. The researchers also noted that carriers of *Taq1 A1* allele had higher carbohydrate intake, which might be related to greater reinforcing value of food and motivation to eat (Cameron et al., 2013). Thus, according

to the RDS model of feeding, it is argued that low brain dopaminergic tone might put individuals at higher risk of weight gain, as it might blunt their response to diet-induced weight loss plans. Altogether, these findings provide evidence of the complex role of dopamine in feeding behaviour and body weight regulation. The activity of dopaminergic pathways in the brain are also implicated in appetite and short-term food intake, as will be discussed below.

2.2.1 Appetite, Energy Intake and The Role of Dopamine

Appetite is defined as the desire to eat, which might be stimulated by physiological need, *i.e.*, hunger, or by other psychological stimuli like the rewarding value of food (Blundell et al., 2010). Increased appetite as assessed by changes in appetite sensations, like hunger, desire to eat, prospective food consumption (PFC) and fullness were observed following weight loss (Doucet et al., 2000; Doucet, St-Pierre, Alméras, & Tremblay, 2003; Drapeau et al., 2007). Furthermore, elevated appetite sensations were found to persist even during partial weight regain a year after initial loss (Sumithran et al., 2011), and some studies have found that heightened appetite sensations predict weight regain after long-term weight maintenance (McGuire, Wing, Klem, Lang, & Hill, 1999; Pasman, Saris, & Westerterp-Plantenga, 1999). The changes in appetite affect short-term food intake and are partly modulated by peripheral energy signals (Delzenne et al., 2010). Both long-term (leptin and insulin) and short-term (GLP-1, ghrelin) peripheral energy signals have been shown to exert some of their effects on appetite and energy intake by modulating motivation to eat via dopaminergic reward pathways as noted in animal studies (Abizaid et al., 2006; Dickson et al., 2012; Hommel et al., 2006; Mebel, Wong, Dong, & Borgland, 2012; Naleid, Grace, Cummings, & Levine, 2005; Speed et al., 2011). In humans, brain imaging studies have provided some evidence that the binding of leptin (Hinkle, Cordell,

Leibel, Rosenbaum, & Hirsch, 2013; Rosenbaum et al., 2008), insulin (Guthoff et al., 2010) and GLP-1 (Batterham et al., 2007) to their receptors in limbic and cortical brain regions might be correlated with the appetite and energy intake suppressing effects of these hormones.

Alternatively, appetite and energy intake might increase in response to non-homeostatic factors like the palatability of food, or food cues, such as the smell of food (Berridge, 2009; Rolls, 2005). The activation of the non-homeostatic food reward circuitry contributes to appetite stimulation, at least in part, via the dopaminergic mesolimbic pathways (Davis et al., 2009). In other words, highly palatable food could enhance appetite and promote food intake by increasing dopamine-regulated motivation to eat.

2.2.2 Food Liking/Palatability and The Role of Dopamine

Food liking or pleasure of consuming food is a distinctive aspect of feeding behaviour (Finlayson et al., 2007) and is related to food palatability. Food palatability refers to the hedonic evaluation of food under specific circumstances, and it is usually used as a proxy of food liking (Ramirez, 1990; Yeomans, 1998). Both opioid (Barbano & Cador, 2007; Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1992; Mucha & Herz, 1985; Yeomans & Wright, 1991) and endocannabinoids (Colombo et al., 1998; Cooper, 2004; Kirkham & Williams, 2001; Mahler, Smith, & Berridge, 2007) signalling in brain areas like NAc shell and orbitofrontal cortex (Berridge & Kringelbach, 2015) have been implicated in stimulating appetite by enhancing the hedonic "liking" value of food. Studies have shown that μ-opioid receptor agonists increase the activity of dopaminergic neurons in the VTA (Latimer, Duffy, & Kalivas, 1987; Leone, Pocock, & Wise, 1991; Spanagel, Herz, & Shippenberg, 1992; Tanda & Di Chiara, 1998). Similarly, there is growing evidence that endocannabinoid signalling promotes dopamine release in the VTA (Cheer, Wassum, Heien,

Phillips, & Wightman, 2004; Gardner, 2005; Tanda, Pontieri, & Di Chiara, 1997). When dopamine is released in the VTA, the VTA-NAc circuitry is activated, and it leads to reinforcement of behaviours that are driven by pleasure or expectation of reward (M. J. F. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2015; Stewart, de Wit, & Eikelboom, 1984). As such, the reinforcement of palatable food consumption increases, which could lead to overeating and weight gain (Geiger et al., 2009; Wiss, Avena, & Rada, 2018).

The link between food palatability and higher food intake is reported in a number of studies in human subjects (Bellisle, Lucas, Amrani, & Le Magnen, 1984; Bobroff & Kissileff, 1986; de Castro, Bellisle, & Dalix, 2000; de Castro, Bellisle, Dalix, & Pearcey, 2000; De Graaf, De Jong, & Lambers, 1999; Spiegel, Shrager, & Stellar, 1989; Tuorila', Iiyvonen, & Vain10, 1994; Yeomans, 1996; Yeomans & Gray, 1997). Also, several reviews have noted that individuals living with obesity have a higher preference of highly palatable food that is usually energy-dense (Berthoud & Zheng, 2012; Drewnowski, Saari, Kurth, & Holden-Wiltse, 1992; Finlayson & Dalton, 2012; Johnson & Wardle, 2014; Mela, 2001). Additionally, acute caloric restriction, induced by a 4-hour fast, was found to increase the hedonic rating of food (Epstein, Truesdale, Wojcik, Paluch, & Raynor, 2003; Raynor & Epstein, 2003). Likewise, chronic caloric restriction has been shown to lead to an increase in the liking component of the food reward (Cameron et al., 2008; Esses & Herman, 1984; Frankham, Gosselin, & Cabanac, 2005; Nisbett et al., 1973).

Brain imaging studies have provided some insight into plausible alterations in the activity of the brain regions that process food palatability and in dopamine activity in individuals living with obesity. Wang *et al.* (2002) found that brain activity in the regions that are related to food palatability is more enhanced in subjects living with obesity compared to lean subjects. Researchers concluded that individuals with obesity might be more vulnerable to the rewarding

properties of food related to palatability, and that could be one of the factors leading to their food overconsumption (Wang et al., 2002). Likewise, adolescent girls with obesity as compared to normal-weight counterparts exhibited greater activation of brain areas that process food hedonics and palatability while also presented lesser activation of dopamine-releasing areas after actual food intake (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008). Thus, some individuals living with obesity would find food more palatable than their lean peers, an effect that is accompanied by decreased dopamine availability in the brain, which promotes food overconsumption as a compensation mechanism for dopamine deficiency (Stice, Spoor, Bohon, Veldhuizen, et al., 2008).

Together, these findings indicate that both obesity and dietary restriction might increase food hedonics. The blunted dopaminergic response to food reward might be implicated in such effects leading to increased energy intake and weight gain in vulnerable individuals. In addition to its role in food palatability, dopamine also mediates olfactory cues that enhance food palatability, as will be discussed in the below section.

2.2.3 Olfaction and The Role of Dopamine

Dopamine is involved in cues related to food reward prediction (Alcaro et al., 2007; Epstein et al., 2009; Schultz et al., 2010; Volkow et al., 2008). Olfaction, or the smell of food, is one of the important prediction cues; throughout evolution, olfaction played a crucial role in locating food sources and in determining which food items were acceptable to consume (Stevenson, 2010). Besides its role as a food reward cue, olfaction is linked to feeding behaviour as it contributes largely to the taste of food and its palatability (Rolls, 2005; Yeomans et al., 2004). Enhancing food palatability by adding strawberry aroma has been shown to stimulate appetite and increase

subsequent food intake in healthy participants (Yin et al., 2017). Additionally, the loss of olfactory function with old age is thought to play a role in the loss of appetite and reduced food intake (Morley, 2001), whereas enriching the diet with food-related odours was shown to increase food liking and consumption in a group of senior participants (Schiffman & Warwick, 1993).

The relationship between olfactory function and obesity has been evaluated in a recent meta-analysis of 10 studies (Peng, Coutts, Wang, & Cakmak, 2019). Researchers reported that olfactory performance is negatively correlated with body weight and that individuals with obesity exhibited reduced olfactory function compared to normal-weight individuals (Peng et al., 2019).

Food deprivation, a common method to promote weight loss, is not only associated with increased motivation to eat but also to enhanced olfactory performance, which is related to increases in food palatability and could result in higher *ad libitum* energy intake (Cameron et al., 2012). Changes in olfactory sensitivity in acute hunger state were also observed in other studies (Albrecht et al., 2009; Stafford & Welbeck, 2011; Trellakis et al., 2011), and following intravenous ghrelin administration in a group of human participants (Tong et al., 2011). The increase in the olfactory threshold, which corresponds to higher sensitivity to smell, was also detected when putting rats under strictly controlled energy intake conditions (Aimé et al., 2007; Pager, Giachetti, Holley, & Le Magnen, 1972). So, heightened olfaction sensitivity in the case of acute or prolonged caloric deficit may play a role in increasing food palatability and in promoting positive energy balance.

Besides its potential role in modulating olfactory cues, dopaminergic signalling is also involved in the early stages of olfactory perception. The olfactory input is first received by the olfactory

bulb, which is a neural structure located in the human forebrain, then, it is transferred to the amygdala and the orbitofrontal cortex to be further processed resulting in the sense of smell (Spors et al., 2012) **(Figure 2)**.

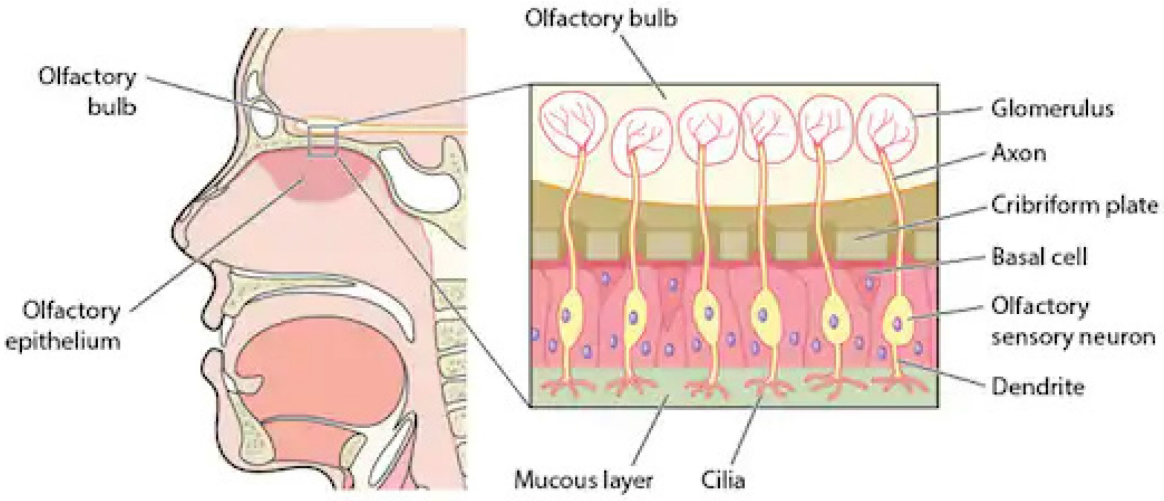

Figure 2: Anatomy of the olfactory bulb. Dopaminergic neurons are extensively located in the glomerulus

The olfactory bulb hosts the highest number dopaminergic neurons in the central nervous system; these neurons are located almost exclusively in the external layer of the olfactory bulb known as the glomerular layer (Pignatelli & Belluzzi, 2017). The dopaminergic neurons in the olfactory bulb have an inhibitory role on olfaction (Hsia et al., 2017). Also, research has shown that the loss of striatal dopaminergic neurons in Parkinson's disease patients is accompanied by a compensatory increase in the neurogenesis of the inhibitory dopaminergic neurons in the olfactory bulb (Huisman et al., 2004). This increase in bulbar dopaminergic neurons has been speculated as one of the reasons behind the deterioration in smell function in patients with Parkinson's disease (Berendse et al., 2001). The age-related loss of olfactory sensitivity has also been linked to reduced activity of brain dopamine transporters (Larsson et al., 2009). Together,

these findings support the hypothesis that olfactory perception is related to brain dopamine activity. In addition, olfaction is an important determinant of food palatability and energy intake. However, it is yet to be determined whether the alterations in olfactory function in obesity are linked with changes in dopamine activity.

Collectively, brain dopaminergic pathways are integral to reward-induced feeding by contributing to food liking and olfactory food cues. Enhancing brain dopamine activity might be a means to curb food reward changes in obesity and weight loss. One way to stimulate brain dopamine activity is to use dopamine reuptake inhibitors such as Methylphenidate (MPH), which is primarily used to treat patients with attention deficit hyperactivity disorder (ADHD), but has been shown to have appetite suppressant effects as well as weight loss effects.

2.3 Methylphenidate

2.3.1 Overview

MPH, is a DAT inhibitor that is used to treat youth and adults with ADHD (McGough et al., 2006; Schachter et al., 2001). MPH is prescribed orally in the form of short-acting or extended-release tablets that are administered twice or once daily, respectively. In the paediatric population, MPH is titrated up to a maximum dose of 60 mg MPH daily and to a dose of 72 mg in adolescents and adults. Since there are marked individual differences in MPH metabolism (Lyauk et al., 2016), most clinicians start with the lowest possible dose and then adjust the dose based on the patient's clinical response rather than based on their age or weight (Pedro & Ortiz, 2018; Rapport & Denney, 1997). MPH is usually well tolerated, with the most commonly reported side effects being nausea, abdominal pain, insomnia, as well as appetite suppression,

and weight loss (Godfrey J., 2009). The discontinuation rates of MPH because of its side effects are between 8-25% in children (Clavenna & Bonati, 2014) and adults (Cortese et al., 2018).

Research has shown that MPH concentration peaks in the brain 60-90 minutes after its administration (Volkow, Fowler, Wang, Ding, & Gatley, 2002) and that it acts by binding and blocking more than 50% of DAT in mesolimbic and cortical areas in the brain (Kuczenski & Segal, 2001; Seeman & Madras, 1998). Thus, MPH mainly acts by increasing brain dopamine availability in the synaptic cleft and amplifying its activity in brain regions that are involved in motivation and reward (Volkow, Wang, Fowler, & Ding, 2005; Volkow et al., 2004), which might affect food consumption. As noted earlier, changes in food reward circuitry could play a role in developing obesity by promoting palatable food overconsumption to compensate for reduced brain dopamine response. Thus, MPH could be a practical pharmacological agent to improve the outcome of weight management in light of its anorexic and weight loss effects. As well, it might provide a safe adjunctive therapy to lifestyle modifications in adolescent populations with obesity given its long-term use and safety profile in paediatric population.

2.3.2 MPH and weight loss

The weight loss effects of MPH were first noted as a side effect in individuals with ADHD (Cortese & Morcillo Peñalver, 2010; Cortese et al., 2016). In a case-control study, a two-month MPH administration to children with ADHD resulted in ~ 1 kg of weight loss in 70% of the subjects (Sahin et al., 2014). Similarly, treating children with MPH for six months resulted in a 1.4 kg loss of total fat mass (Poulton et al., 2012). Also, the treatment of adults with obesity and ADHD resulted in ~18 kg weight loss in the MPH group compared to a non-medicated control group over 466 days (Levy, Fleming, & Klar, 2009). These findings show that individuals with

ADHD experience weight loss with MPH treatment. Nevertheless, the weight loss effects of MPH in individuals with obesity but without ADHD have not been tested before.

2.3.3 MPH intake, appetite suppression and energy intake:

MPH intake has been shown to result in varying degrees of appetite suppression among individuals. Appetite reduction ranges from 8-57% (Didoni, Sequi, Panei, & Bonati, 2011; Findling et al., 2009; Gurbuz et al., 2016; Lee et al., 2011; McGough et al., 2006) in patients with ADHD as a response to MPH treatment. This variability in reported appetite reduction may be due to the differences in the length of experiments as well as the variability in the methods employed to assess appetite suppression. Such methods include parents reporting the decreased appetite of their ADHD children (Lee et al., 2011), a clinical assessment done by a trained paediatrician (Findling et al., 2009) and self-reporting (Didoni et al., 2011; McGough et al., 2006)

In a pilot study examining the effects of MPH on appetite and energy intake of individuals without ADHD, Goldfield *et al.,* (2011) showed in that men were more responsive than women to a single dose of 0.5 mg/kg body weight of MPH (Goldfield, Lorello, Cameron, & Chaput, 2011). That is, men showed a significantly greater reduction in energy intake compared to women. In a different manner, Davis *et al.* (2012) found that although normal-weight men and women responded similarly to acute MPH treatment when appetite sensations were measured, women living with obesity showed higher appetite suppression than men living with obesity (Davis et al., 2012). Moreover, the decrease in measured appetite sensations in people suffering from Binge Eating Disorder (BED) was higher than that noted in their healthy counterparts in a double-blind crossover study of the effects of MPH on appetite (Davis et al., 2007).

The acute effects of administering MPH on energy intake in healthy individuals who do not have ADHD were also studied. Leddy *et al.* (2004) tested the effects of MPH on men living with obesity aged 18-40 years old in a double-blind placebo-controlled crossover study and assessed their consumption of pizza one hour after the intake of a single dose of MPH. This study showed a 23% reduction in energy intake after ingesting MPH (Leddy et al., 2004). Similarly, Goldfield *et al.* (2007) found that healthy normal-weight individuals who took a single dose of MPH had reduced energy intake of 11% in an *ad libitum* meal (Goldfield et al., 2007). Both of these studies noted that MPH intake reduced the reinforcing value of food, *i.e.,* reduced motivation to eat but did not decrease hunger (Goldfield et al., 2007; Leddy et al., 2004)

It is worth noting that all the studies that employed individuals without ADHD tested appetite variables and energy intake following a single dose of MPH. However, to assess the feasibility of using MPH as part of more comprehensive obesity treatment, there is a need to study the effects of MPH intake for a longer duration in individuals living with obesity. To our knowledge, the effects of long-term administration of MPH on the appetite sensations and feeding behaviour of individuals living with obesity who are otherwise healthy have not yet been investigated.

2.3.4 MPH and Changes in Food Palatability

Opioid and endocannabinoid signalling in brain reward regions, particularly in the NAc shell and dorsal striatum, is implicated in food liking (Barbano & Cador, 2007; Mahler et al., 2007). Whether enhancing dopamine levels modulates opioid and endocannabinoid signalling and affects food palatability is yet to be elucidated. However, animal studies have shown that increasing dopamine release in the NAc by injecting a DAT inhibitor in mice resulted in reducing opioid-induced intake of palatable food (MacDonald, Billington, & Levine, 2004;

Ragnauth, Znamensky, Moroz, & Bodnar, 2000). Similarly, the sucrose intake of MPH-treated rats was reduced compared to a placebo group (Bello & Hajnal, 2006). Also, increasing synaptic dopamine concentrations with MPH significantly and dose-dependently decreased endocannabinoid signalling in limbic regions of rodents brain (Patel, Rademacher, & Hillard, 2003). In humans, acute studies have shown that a single dose of MPH resulted in reduced intake of a palatable meal (pizza) (Leddy et al., 2004) or a favourite snack food (Davis et al., 2012) in individuals with obesity. Whether the reported reductions of palatable food intake in humans were a function of reduced liking of these foods was not documented. These findings provide preliminary evidence of the possible effects of MPH intake on food liking signalling in the brain and the possible subsequent reduction in the intake of palatable food. However, the effects of MPH intake on food liking and food consumption in humans need further investigation.

2.3.5 MPH and Changes in Olfaction

Few studies have examined the effects of MPH administration on the olfactory function. Patients with ADHD show a heightened olfactory sensitivity (Fuermaier et al., 2018; Lorenzen et al., 2016), which is linked to dysfunctional dopaminergic signalling in ADHD. However, patients with ADHD who were treated with MPH medication for a long time have exhibited normalized odour discrimination scores (Romanos et al., 2008), and reduced odour threshold values (Schecklmann et al., 2011) that are comparable to healthy controls. The impact of MPH in curbing olfactory sensitivity might be related to its effects on reducing dopamine reuptake in the olfactory bulb and prolonging the inhibitory function of bulbar dopaminergic neurons (Gatley et al., 1999). To our knowledge, the outcomes of MPH intake on the olfactory sensitivity of healthy individuals with obesity have never been examined.

Collectively, MPH is a known appetite suppressant, and potential modulator of dopamine-related reward aspects like food liking, and olfaction. Its long-term use in the paediatric population and good tolerability suggest that it might be a useful adjunct therapy to obesity in comparison to the currently available weight loss medications.

2.4 Weight loss medications: Current Status

The currently approved weight loss medications in Canada are Orlistat®, Liraglutide®, Lorcaserin®, and Contrave®. None of these drugs are indicated for use in the adolescents with obesity. A recent meta-analysis of 28 randomized clinical trials has found that combining obesity pharmacotherapy with lifestyle modifications produced additional weight loss relative to diet/exercise modifications alone (Khera et al., 2016). The weight loss outcome ranged from 3 kg for Orlistat (Ballinger & Peikin, 2002) and Lorcaserin® (Fidler et al., 2011; Smith et al., 2010) to 6 kg for Liraglutide® (Pi-Sunyer et al., 2015; Wadden et al., 2013) and Contrave® (Apovian et al., 2013; F. L. Greenway et al., 2010; Wadden et al., 2011) after 1 year of intervention. Nevertheless, the discontinuation rate due to side effects was between ~ 57% for Loracesrin® to ~70% for Liraglutide® and Contrave® (Khera et al., 2016). Such a high attrition rate is limiting the appeal of long-term use of anti-obesity drugs (Yanovski & Yanovski, 2014).

The anti-obesity medications target various pathways to suppress appetite and reduce food intake, thus producing weight loss. Nevertheless, despite the growing body of evidence that indicates the importance of reward-induced feeding in obesity development and weight regain,

changes in the behavioural aspects of feeding are not reported in anti-obesity drug trials. Of particular relevance to this topic is Contrave®, which is a Naltrexone/ Bupropion combination therapy. Naltrexone in Contrave® is a μ-opioid antagonist, and it is known to selectively reduce the consumption of highly palatable food in individuals with obesity (Billes, Sinnayah, & Cowley, 2014; Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1995; Yeomans & Gray, 1996, 1997). Thus, Contrave® might produce at least part of its appetite-suppressing effects by targeting the food reward circuitry. However, large-scale clinical trials did not report the long-term effects of Contrave® on food reward and food palatability (Apovian et al., 2013; F. L. Greenway et al., 2010; Wadden et al., 2011). Reporting drug-induced changes in feeding behaviour aspects, like food palatability and motivation to eat, might help to broaden the uses of anti-obesity drugs instead of only reporting their weight loss outcome. Thus, testing the effects of MPH on non-homeostatic contributors to appetite and feeding behaviour like olfaction and food palatability, in individuals with obesity would help to identify its potential effects on energy intake and body weight in individuals with obesity.

2.5 Summary

The failure of traditional dietary interventions to curb the increasing rates of obesity, together with the recent designation of obesity as a disease by leading health organizations necessitate the development of complementary or alternative treatment options. Obesity pharmacotherapy is proposed as an effective strategy to combat obesity, and the discoveries in the field of feeding control have provided new targets for pharmaceutical management of obesity. There is growing evidence of the contribution of non-homeostatic factors to appetite, energy intake, and weight gain. Research has shown that increased food palatability and changes in oro-sensory cues like

olfactory performance correlate with increased food intake and possibly weight gain. Dopamine plays a vital role in modulating various contributors to food reward, like food palatability and olfaction, which might stimulate appetite and increase energy intake. The reduced dopaminergic tone in the brain is thought to cause overconsumption of palatable food to correct the blunted brain dopamine activity, leading to obesity development.

Additionally, the intake of DAT inhibitors like MPH was shown to suppress appetite and to decrease food intake in healthy individuals. However, no studies have explored the impact of MPH on non-homeostatic contributors to appetite like food palatability and olfaction. Moreover, to use MPH as a part of comprehensive obesity treatment, its impact on appetite, palatability, and olfaction, along with its energy intake and weight-reducing changes need to be investigated for a longer time. This study investigated the effects of a two-month administration of MPH on i) olfaction, appetite variables, and food palatability in individuals living with obesity, ii) energy intake and weight loss, and iii) the correlation between changes in olfaction function and changes in appetite.

3 Study Objectives and Hypotheses

3.1 Study Objectives

In this research, the participants were prescribed short-acting MPH for two months in a randomized, double-blind placebo-controlled two-arm parallel-group design. The study included individuals with obesity aged 16-40 years old. The primary objectives were to determine whether the intake of (0.5 mg/kg body weight) MPH for two months would produce favourable changes in appetite sensations, odour threshold, and food palatability, in individuals with obesity compared to their counterparts in a placebo-controlled group. The secondary objectives were to investigate whether free-living energy intake and body weight differed between the MPH and placebo group. Thirdly, we explored the relationship between changes in the olfactory threshold scores and changes in appetite sensations and palatability in each group.

3.2 Study Hypotheses:

I. Appetite sensations, odour threshold, and food palatability were predicted to show more decreases in the MPH group after the intervention compared to the placebo group.

II. The MPH group was expected to have lower body weight and free-living energy intake at two months, whereas we expected no change in the body weight and energy intake for the placebo group.

III. Change in the odour threshold were expected to be positively correlated with changes in appetite variables in MPH group.

4 Methods

4.1 Study Population

Twelve participants (6 males; 6 females) aged 28.9±6.9 years were included in the final study after initially screening 19 participants, and randomizing in 14 participants. The 14 participants were randomized into 7 participants in either MPH or placebo group. The final study sample contained 12 participants in placebo (n= 7; 4 males, 3 females) and MPH group (n=5; 2 males, 3 females). The study recruitment and conduct were per the CONSORT guidelines and are illustrated in **Figure 3**. The participants completed the study in the Behavioural and Metabolic Research Unit (BMRU) at the University of Ottawa, Lees campus.

Participants were recruited through:

- Posting flyers at community centres, local universities, and buses.
- Social media (Facebook)
- Kijiji ads
- Referrals from participants

The following were the inclusion and exclusion criteria

4.1.1 Inclusion Criteria:

- Males and females 16 to 40 years old.
- BMI in the obese category (> 29.9 kg/m^2).
- Willing to comply with procedures, and sign an informed consent form.
- Able to swallow the study pill.

4.1.2 Exclusion Criteria

- Smoker (smoking is known to affect appetite).

- Known serious food allergies, including lactose.
- History of previous MPH use or allergy to MPH.
- History of ADHD or current diagnosis of an axis one psychiatric disorder (for example, depression, panic disorder, schizophrenia) as measured by self-reports, the Wender-Utah rating scale, and the Beck depression inventory (McCann et al., 2000).
- Current use of antidepressants, thyroid medication, or any medication that could affect appetite.
- Pre-existing cardiovascular disorders, including uncontrolled hypertension, heart failure, and myocardial infarction.
- Diabetes.
- Excessive use of alcohol or alcoholism, or current addictions to opiates, cocaine or stimulants as measured by the drug abuse screening test.
- Attempts to lose weight within the last six months.
- A restrained eater based on cut-score (11 or higher) on the Three-Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985).
- Personal or family history of seizure disorders, motor tics, or Tourette syndrome.
- Pregnancy as determined by a commercially available pregnancy test taken by female participants before the test dose of MPH.
- Abnormal reaction to MPH test dose, including:
    - Systolic blood pressure exceeding baseline reading by 20 mmHg, diastolic blood pressure exceeding the baseline reading by 10 mmHg, blood pressure > 160/100, or resting pulse increased by 20 beats/minute from the baseline.

- Severe side effects like severe headache, nervousness, and insomnia. (see **Appendix A**).

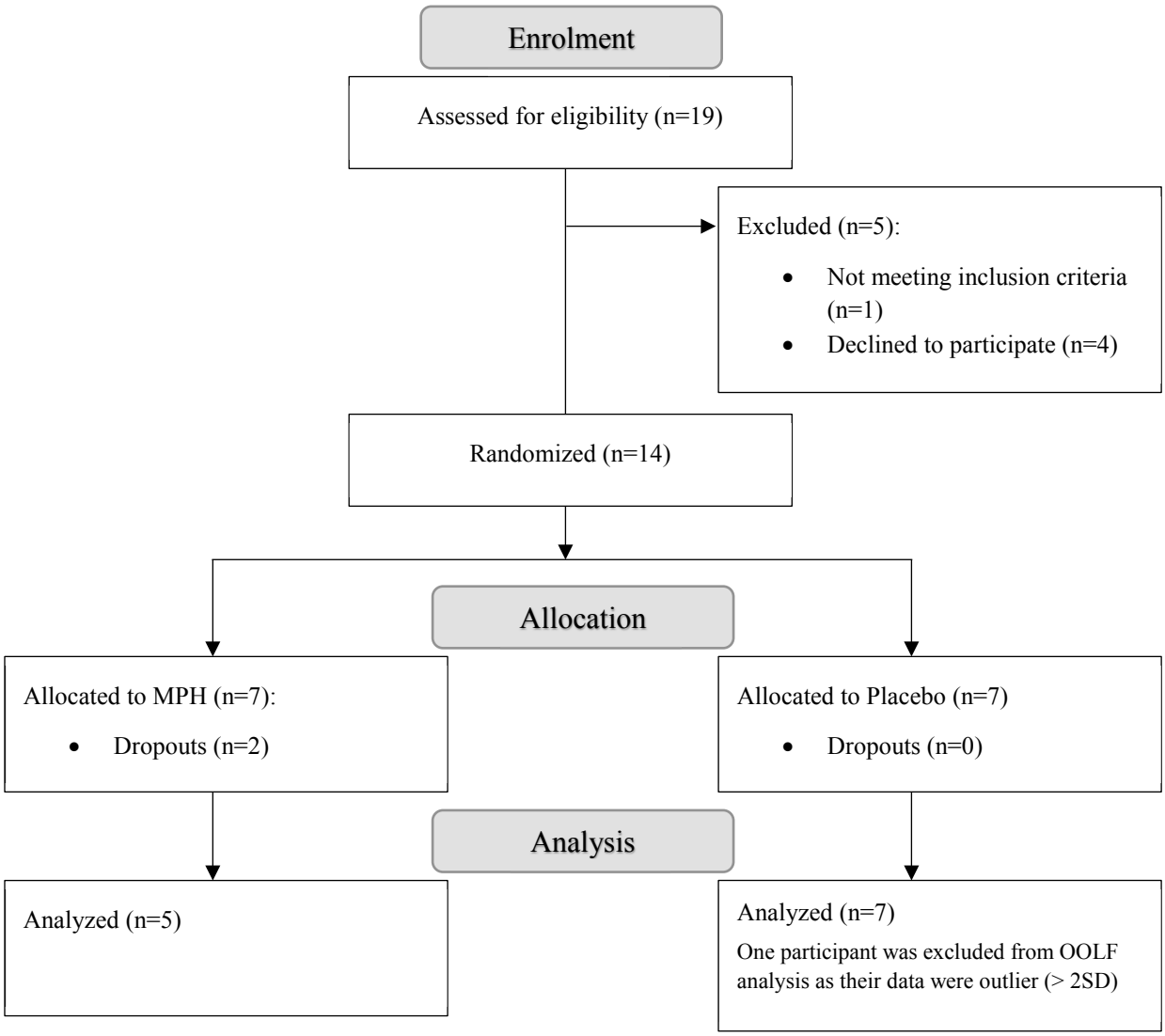

Figure 3: Consort flow chart of study population from enrollment to data analysis

4.2 Study Design

The study was a randomized, double-blind, placebo-controlled, two-arm, parallel clinical trial. 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 to the Placebo group or MPH group. The participants were prescribed either a placebo or short-acting MPH twice daily 1 hour after having lunch and dinner for two consecutive months. Children's Hospital of Eastern Ontario (CHEO) pharmacy led the randomization process, but it was blinded to the researchers and the participants. The randomization process was computerized using a 1:1 ratio in blocks of 2, stratified by sex.

4.3 Study Procedure

The study outlined in **Figure 4** consisted of five visits to the laboratory for a total of 18 hours, as follows: the initial screening visit (4 hrs), two repeated measures test days (6hrs each; Baseline Visit (Day 1) and Final Visit (Day 60), a mid-point visit (to get the drug pills refill), and a Food box visit (to get food boxes).

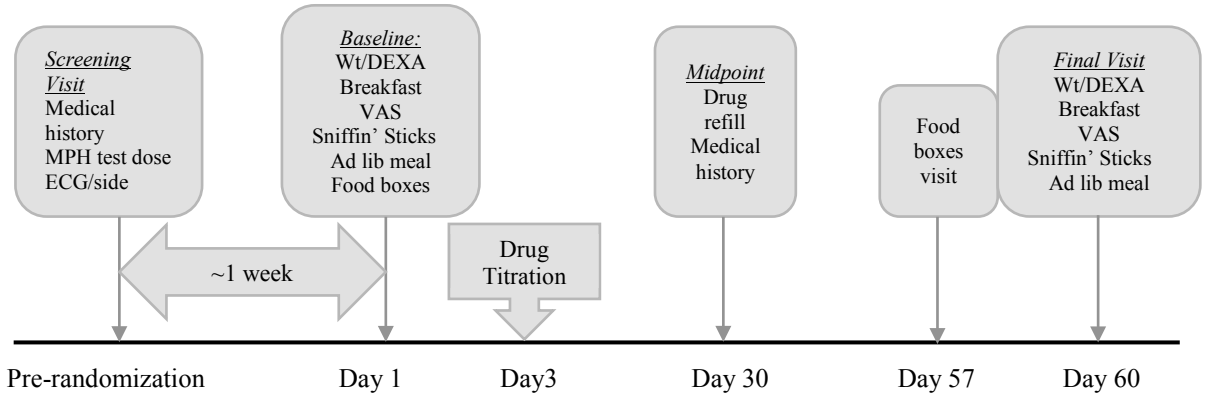

Figure 4: Diagram of Study outline

After the initial laboratory visit and informed consent (*i.e.,* clinical screening visit), participants were randomized before the baseline visit to either receive placebo or MPH two times daily for two consecutive months. Upon leaving the baseline test day, participants received a 3-day supply of food (Food Boxes), and they were instructed to eat exclusively from this food supply. The participants selected food items for their 3-day Food Boxes from a validated food menu (McNeil et al., 2012). These items were placed into coolers for them to take home, in a manner that resembled grocery shopping. More food than needed was provided for a measurement of 3 days of feeding starting once they departed the first day of the experiment (baseline visit) and ending three days after. Similarly, participants ate exclusively from the Food Boxes for the three days leading into the final visit. Participants returned to the laboratory to complete the study at the final visit repeated measures test day.

For the mid-point visit (day 30), participants were weighed and reported any perceived side effects from the MPH or placebo. At this mid-point visit, participants brought in their pill containers to verify compliance and to receive a final 30-day supply of drug or placebo. At this time, participants were asked if they had begun any new medication or had started any over-the-counter medication as part of the study's safety monitoring protocol. Data collection was done between October 2017 and August 2018.

4.4 Initial Clinical Screening Visit

After phone screening, participants were asked to come to an initial screening visit to be assessed medically, psychologically, and nutritionally to check if they meet the inclusion criteria (see **Appendix B**). As soon as they arrived, potential participants were introduced to the study goals and procedures and were asked to sign an informed consent form. Then, weight and height were

measured to ensure that their BMI was > 29.9 kg/m^2. The participant completed a number of questionnaires and was clinically examined by the research doctor Dr. Philippe Robaey. Female participants were asked to take a pregnancy test to confirm that they were not pregnant at the time of the experiment **(Appendix B)**.

After clearance from the doctor, the participant was given a test dose of MPH (0.5 mg/ kg BW) under the supervision of a research nurse who assessed their side effects and vital signs every hour for three hours following the ingestion of the test dose **(Appendix B)**. Electrocardiogram readings were also collected for three hours and were monitored by a research cardiologist. Any participant who exhibited one or more characteristics of the exclusion criteria mentioned above was excluded from the study.

4.5 Dose Rationale

Since there are no data on the effective doses of MPH in healthy individuals, we decided to use the same dose that was found effective in Leddy *et al.* study (2004). This study used the same design and participant inclusion criteria as our study. They tested two doses of MPH (0.5 mg/kg body weight and 1 mg/kg body weight) and assessed its effects on energy intake and hunger for one meal one hour after exposure to MPH. The results confirmed that the moderate dose of MPH reduced the energy intake of most of their participants (7 out of 9) by 23% and this percentage did not change much when the higher dose of MPH was prescribed (Leddy et al., 2004). Thus, we proposed to use the same dose of 0.5 mg MPH/kg body weight. As per the National Institute of Health and Clinical Excellence (NICE), the maximum allowed dose for treating patients with ADHD is 100 mg/day. Consequently, we set the maximum dose at 100 mg /day and the limit for the subject's weight inclusion criteria at 200 kg.

In this experiment, the drug was titrated gradually from day 3 until reaching the optimal dose (0.5 mg MPH/ kg body weight) on the 10th day of the experiment. The dose titration began at 0.25 mg/kg and increased by 15% daily increments for seven days. Participants were asked to rate their side effects online (see **Appendix A**) for the first 14 days of drug intake and were to contact the study coordinator (Dr. Jameason Cameron) promptly if they experienced any side effects as moderate; however, no such incident occurred.

The pills were given to the participants by the study coordinator twice during the study at day 1 and day 30 in a calendar-style blister-card dispensary system to monitor compliance and ensure that pills were taken as prescribed.

4.6 Sample Size

There were no intervention studies looking at the effect of MPH on energy intake. To estimate effect sizes, we extrapolated from the previous two pilot studies that explored MPH effect on energy intake. In the first laboratory study, Leddy *et al.* (2004) had an effect size of 0.93 in 9 adult males living with obesity for the primary outcome of food intake with mean energy intake for MPH (0.5 mg/kg) and placebo of 843.5 $\pm$ 393.4 kcal and 1095.9 $\pm$ 271.1 kcal, respectively. In the second study, Goldfield *et al.* (2007) obtained an effect size of 0.69 in MPH (0.5 mg/kg) session for food intake in an open buffet lunch with mean difference of -133 kcal and a standard deviation of 192 kcal. We chose the more conservative effect size of 0.69, and determined that we need 18-20 participants per group to detect a significant difference ($p < 0.05$; power = 80%) in kcals consumed over a 60-day period between MPH and placebo.

4.7 Repeated Measures Days (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 (~7:30 am) after a 12-hour overnight fast and after having refrained from any vigorous physical activities for at least 48 hours. See **Figure 5**.

7:30 Arrive at the laboratory after an overnight fast. Participants were asked questions about their level of physical activity during the last three days to ensure that they did not perform strenuous exercise in the past 48 hours.

7:40 An assessment of the body composition was done (weight, fat mass, fat-free mass, and percent body fat). Participants were asked to rate their appetite on a 150mm visual analog scale (VAS) with the assistance of our research staff. They continued to rate their appetite sensations throughout the morning at 60-minute intervals (from 8 am until study completion).

9:05 to 9:20 A standardized breakfast was served (white bread, butter, strawberry jam, cheddar cheese, and orange juice).

10:00 to 10:30 The participant completed a 15-minute smell test.

12:30 to 13:00 The participant was provided with an *ad libitum* buffet, after which appetite and palatability were assessed with VAS.

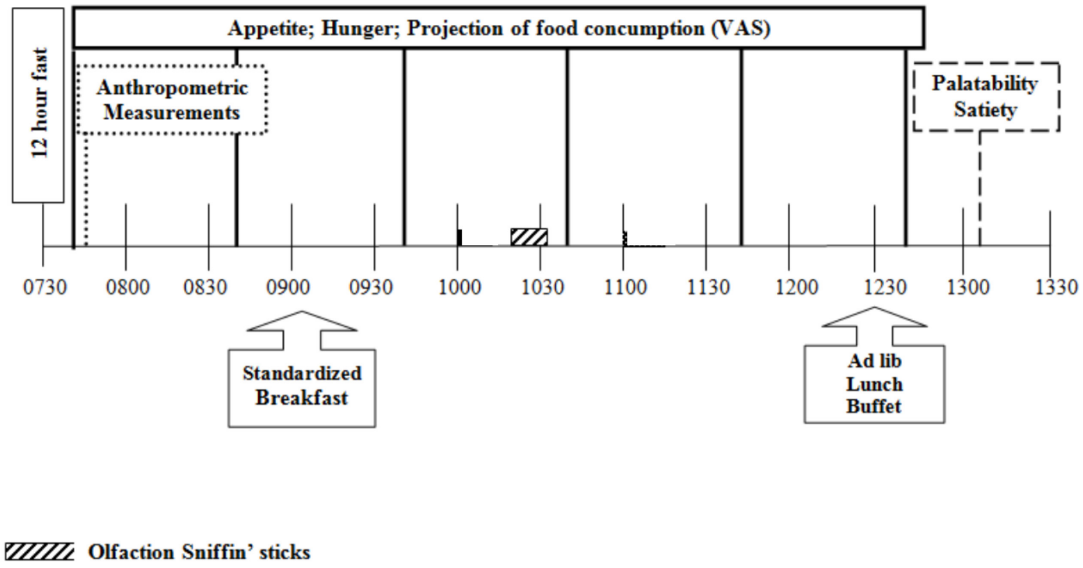

Figure 5: Procedure of Repeated Measures Days

4.7.1 End of the experimental session

These same procedures were repeated for the three experimental sessions, with the following exceptions. For the baseline visit repeated measures session, the participants did not have any placebo or MPH before eating the standardized breakfast nor the *ad libitum* buffet, whereas, for the final visit, the participants ingested either placebo or MPH one hour before each of the meals.

4.8 Measurements:

4.8.1 Measures of appetite variables and palatability

Food palatability and different sensations of appetite that are related to food wanting and motivation to eat (desire to eat and prospective food consumption) along with sensations related to hunger and fullness were measured. The measurements were done using a 150-mm visual analog scale (VAS) in one-hour intervals during the participant presence in the experimental sessions, as explained above. The use of VAS to assess these variables was previously validated

in single meal studies (Flint, Raben, Blundell, & Astrup, 2000); see **Appendix C** for VAS form. We assessed appetite sensations globally by calculating the area under the curve (AUC) of appetite ratings over three hours using the trapezoid method (Drapeau et al., 2007). AUC values have better reproducibility than single time point values (Kirkmeyer & Mattes, 2000; Raben, Tagliabue, & Astrup, 1995) and are better predictors of energy intake (Drapeau et al., 2005).

4.8.2 Olfaction (smell function)

Sniffin' sticks® (Burghart Instruments, Wedel, Germany) 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 gum for ~ one hour before the test. The olfactory threshold test consisted of a set of 3 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 concertation 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). Since 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 to 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-second 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 (**See Appendix D**).

4.8.3 Body weight, height and body composition

Body weight 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 (percentage of body fat, fat mass, fat-free mass) was measured using the "dual-energy X-ray absorptiometry (DEXA method). This assessment was performed while the participant wore a hospital gown on an examination table while an x-ray of low intensity scans the participant's body. The total duration of this test is 10 minutes.

4.8.4 The measures of energy intake

Food intake was measured in two ways. First, in lab feeding (ILF) was assessed by employing our previously validated lunch buffet (McNeil, Riou, Razmjou, Cadieux, & Doucet, 2012) in order to objectively measure *ad libitum* feeding *inside* of the laboratory during baseline and final repeated measures visits. Food was offered in large amounts, and the participants were instructed that they had 30 minutes to eat until satiation was achieved. All food was weighed to the nearest 0.1 g before and after ingestion. For the analysis of free-living food intake (out of lab feeding (OOLF)), 3-day food boxes were provided at the beginning and the end of the study as previously explained. All items and packages were weighed to the nearest 0.1 g before and after to determine the amounts consumed during the two 3-day periods.

4.9 Data analysis

Baseline characteristics for age, body weight, and fat mass 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 2 (MPH versus placebo) x 2 (baseline (day 1), final visit (day 60) Analysis of Variance (ANOVA) was performed to test the effect of MPH on changes in odour threshold, AUC of appetite variables and food palatability as well as body weight, ILF and OOLF. Statistical significance of results was set as $p < 0.05$, and effect sizes were reported as partial η^2 to assess the magnitude of observed effects (partial eta squared, η^2). 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).

Person's correlations were performed to test the relationship between (pre-post) changes in odour threshold and (pre-post) changes in appetite variables and food palatability in MPH and placebo groups. Significant correlations were reported when $p < 0.05$.

4.10 Safety Protocol

There were several measures to ensure the safety of the participants in the study. During the initial screening visit, vital signs (blood pressure and pulse) and effects/symptoms were monitored every hour for three hours. Any participant who reported or showed heightened blood pressure or heart rate side effects from the test dose of MPH would have been excluded from the study; however, no such incident was reported.

Upon finishing the baseline visit, each participant was supplied with a "study enrolment card" that entailed the study title, along with the emergency contact information for the CHEO pharmacy technician (in control of study blinding) and for the Qualified Investigator (Principal

Investigator). Participants were also followed up for the first two weeks after initiating the study as they were asked to report any side effects/adverse events using CHEO's REDCAP web-based system. If any participant had rated symptoms higher than moderate severity, then a multi-phase screening and safety protocol would have been implemented. This protocol included contacting the participant who reported the severe side effect by the research coordinator, Dr. Jameason Cameron. Dr. Cameron would page the on-call licensed psychiatrist, Dr. Philippe Robaey. Dr. Robaey would have contacted the participant by phone and asked the participant to come to CHEO for further examination and evaluation if required. Nevertheless, this procedure was not needed for any of the participants.

4.11 Data Safety and Monitoring Board

The Data and Safety Monitoring Board (DSMB) was an independent group of experts who functioned independently and at arm's length from the Study Investigators and the Steering Committee of the Study. Their responsibilities included to review data regarding participants safety, the blinding process and the progress of the study. Terminating the study was done following meeting with the DSMB members as per protocol.

5 Results

5.1 Participants Characteristics

Table 1 presents the baseline characteristics of participants in the placebo versus the MPH group. There were no statistically significant differences between the groups for age, height, baseline body weight, fat mass, and body mass index (BMI). None of the participants were adolescents.

Table 1: Baseline characteristics of Placebo and MPH groups

Variable	Placebo Group	MPH Group	*p*-value
Age (yrs)	29.14 (7.19)	28.60 (6.66)	0.867
Height (cm)	168.79 (9.38)	168.70 (11.64)	0.989
Body weight (kg)	104.89 (21.84)	102.36 (25.55	0.857
Fat mass (kg)	46.61 (13.30)	45.49 (10.17)	0.877
BMI (kg/m^2)	36.44 (3.82)	35.62 (5.75)	0.771

Data presented as mean (SD); Placebo (n=7, 4M, 3F), MPH (n=5, 2M, 3F)

5.2 Effects of MPH on Appetite Variables

The AUC scores for all appetite sensations were statistically different between MPH and placebo groups overtime with large effect sizes ($F(1, 10) = 27.164$, $p < 0.001$, partial $\eta^2 = 0.731$; $F(1, 10) = 19.977$, $p = 0.001$, partial $\eta^2 = 0.666$; $F(1, 10) = 11.014$, $p = 0.008$, partial $\eta^2 = 0.524$; $F(1, 10) = 15.300$, $p = 0.003$, partial $\eta^2 = 0.605$). As illustrated in **Figure 6**, the MPH group exhibited reductions in desire to eat (M = 13650.00, SE = 2772.12, p= 0.008), hunger (M= 13650, SE = 4382.89, p= 0.017) and PFC (M=12804.000, SE = 3810.902, p = 0.028) over time compared to increases in placebo group (M= -362.14, SE = 1166.18, p = 0.767; M= -615, SE = 1138.98, p = 0.609; M= 222.857, SE = 518.081, p = 0.682, respectively). On the other hand, the fullness AUC scores increased overtime in MPH group (M= -10621.2 SE = 3155.16, p= 0.028) compared to a decrease in the placebo group (M= 2354.57, SE = 2423.91, p = 0.369).

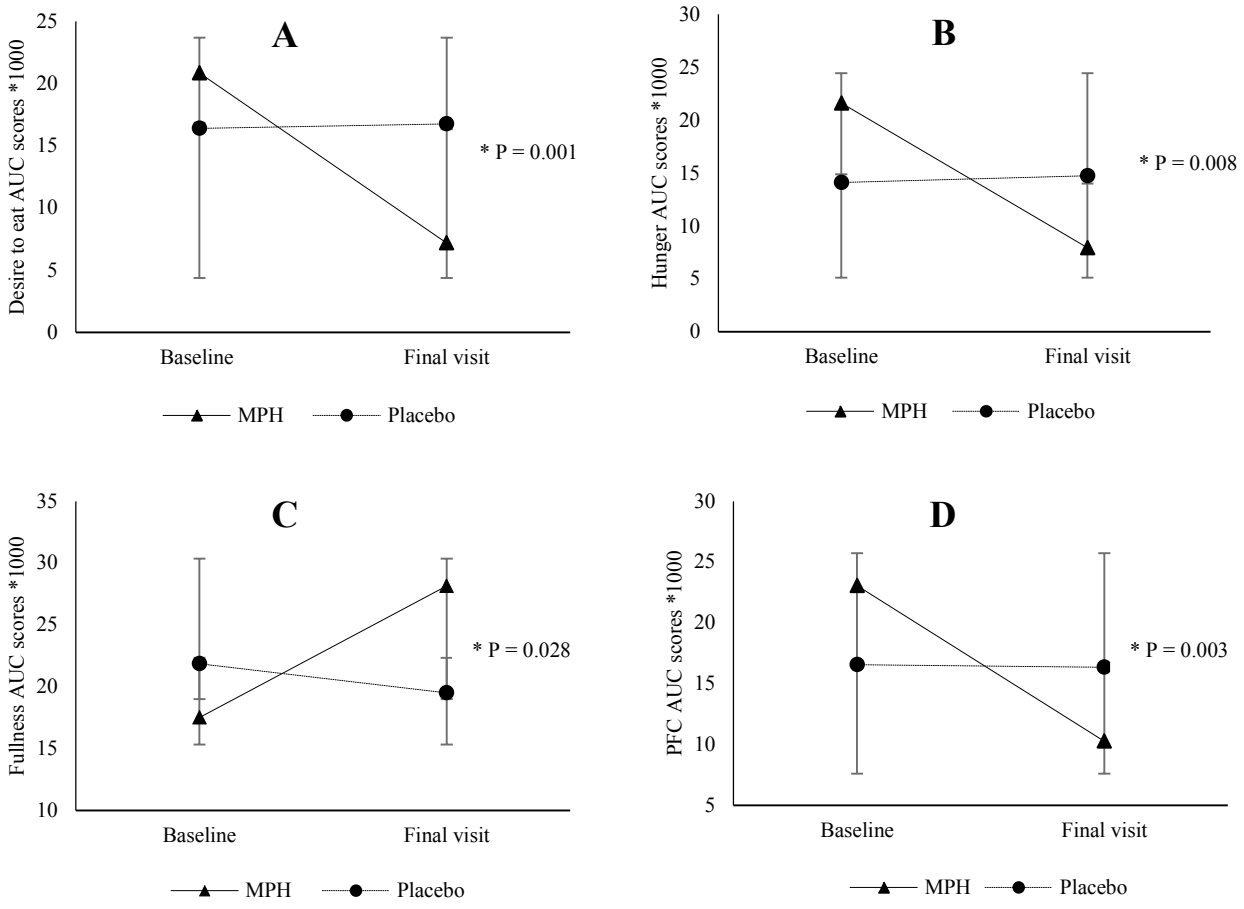

Figure 6: Appetite AUC scores for Desire to eat (A), Hunger (B), Fullness (C) and Prospective Food Consumption-PFC (C) in MPH versus placebo groups, *represents a significant group*time interaction

5.3 Effects of MPH on Odour Threshold

As shown in **Figure 7**, there was a statistically significant interaction between the intervention (MPH vs. Placebo) and time for odour threshold, ($F(1, 10) = 6.536$, $p = 0.029$, partial $\eta^2 = 0.395$), whereby MPH produced significant increases in odour threshold scores over time ($M = -3.080$, $SE = 0.786$, $p = 0.017$) as compared to no change in the placebo group ($M = 0.029$, $SE = 0.856$, $p = 0.974$).

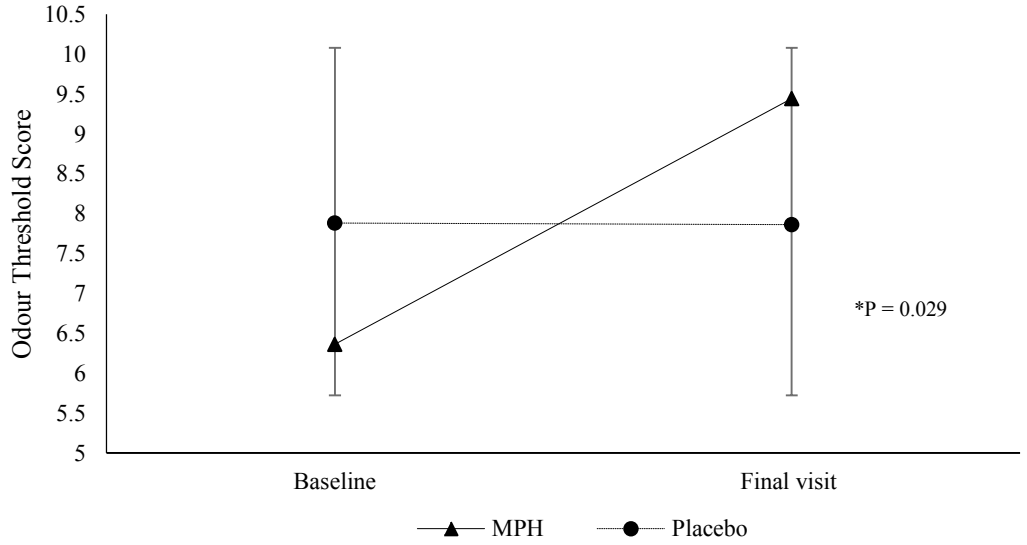

Figure 7: Effect of MPH on odour threshold scores in placebo vs MPH group from baseline to final visit, *represents a significant group*time interaction

5.4 Effects of MPH on food palatability

As shown in **Table 2**, there was no significant group*time interaction on post breakfast, post lunch or AUC scores of food palatability (F(1, 10) = 1.441, p = 0.258, partial η^2= 0.126; F(1,10) = 0.873, p = 0.372, partial η^2= 0.080; F(1, 10) = 2.595, p = 0.138, partial η^2= 0.206 respectively). No group differences were noted, and the change over time was not significant, and.

Table 2: Changes in food palatability scores in MPH versus placebo groups

Variables	Baseline 1		Final Visit		P-value (time)	P-value (group*time)
	Placebo	MPH	Placebo	MPH		
Post B food palatability	81.00 (34.77)	84.40 (31.53)	83.85 (30.67)	59.20 (52.57)	0.362	0.258
Post L food palatability	110.71 (45.12)	121.20 (35.20)	125.00 (16.39)	110.80 (27.45)	0.886	0.372
AUC Palatability	23005.71 (3344.04)	24672.00 (6177.14)	25062.85 (5415.27)	20400.00 (7061.16)	0.585	0.138

Data presented as mean (SD); Placebo (n=7, 4M, 3F), MPH (n=5, 2M, 3F).

5.5 Effects of MPH on body weight and energy intake

Body weight, ILF and OOLF energy intake decreases were significant over time (P = 0.005; p=0.021 and p = 0.01, respectively) with large effect sizes favouring greater reduction in the MPH group (η^2 = 0.559; η^2 = 0.429; η^2= 0.540, respectively) (**Table 3**). No group*time interaction was noted for any of the variables. Changes in fat mass were not significant for any of the groups.

Table 3: Changes in Body weight and ILF in MPH versus Placebo group

Variables	Baseline 1		Final Visit		P-value (time)	P-value (group*time)
	Placebo	MPH	Placebo	MPH		
BW (Kg)	104.89 (21.84)	102.36 (25.55)	103.64 (25.55)	99.70 (26.86)	0.005*	0.225
Fat mass (Kg)	46.62 (13.30)	45.48 (10.18)	46.15 (11.60)	43.25 (11.02)	0.116	0.177
ILF (Kcal)	1559.93 (512.87)	1587.88 (546.31)	1402.15 (369.67)	1347.38 (455.75)	0.021*	0.582
OOLF+	8513.18 (2680.20)	9702.66 (3514.80)	5765.40 (702.61)	8025.18 (4502.45)	0.010*	0.452

Placebo (n=7, 4M, 3F), MPH (n=5, 2M, 3F). Mean (±SD). *p<0.05, **p<0.005.
+Placebo (n=6, 3M, 3F), MPH (n=5, 2M, 3F)

5.6 Correlation between changes in olfaction threshold scores and changes in appetite variables AUC scores in MPH versus Placebo groups

As seen in **Table 4**, there were no statistically significant correlations between changes in olfactory threshold scores and changes in appetite sensations AUC scores in MPH or placebo groups.

Table 4: Correlation between changes in olfaction threshold scores and changes in appetite variables AUC scores

Variables		Odour threshold	
		placebo	MPH
AUC desire to eat	*r* value	0.027	-0.518
	p value	0.955	0.371
AUC hunger	*r* value	0.272	-0.569
	p value	0.555	0.417
AUC fullness	*r* value	0.591	0.755
	p value	0.162	0.140
AUC PFC	*r* value	0.132	-0.531
	p value	0.777	0.357
AUC palatability	*r* value	-0.721	-0.708
	p value	0.068	0.181

($p < 0.05$)

6 Discussion

The objective of this study was to examine the effects of MPH intake on appetite variables, olfaction, food palatability and energy intake in individuals with obesity to evaluate, in a preliminary manner, the potential benefits of MPH as a weight loss medication. The findings partially support our hypothesis that MPH administration for two months would result in significant reductions over time in appetite, and palatability compared to placebo. Our results showed that, overtime, the MPH group exhibited greater reductions in the desire to eat, hunger, and PFC ratings, along with significantly greater increases in fullness scores compared to placebo. However, our data did not support the hypothesis that food palatability would be more reduced in the MPH group than in the placebo group. Contrary to our hypothesis, we found that participants in MPH group exhibited significant increase in odour threshold compared to placebo. As for our second aim, we observed that body weight and energy intake significantly decreased over time, but we found no evidence to support that decreases in body weight and energy intake were higher in the MPH group. Finally, we found no significant correlations between delta scores for odour threshold and appetite variables or food palatability.

6.1 Appetite Suppression

Our study showed that MPH intake for two months resulted in significant reductions of appetite sensations, as well as a significant increase in fullness, which provides evidence to the appetite suppressing effect of MPH. The anorexic effects of MPH are well documented in populations with ADHD. A meta-analysis of 62 clinical trials noted that MPH intake resulted in decreased appetite in 30% of children and adolescents with ADHD (Schachter et al., 2001). Similarly, a systematic review of 26 placebo-controlled trials reported that reduced appetite was observed in

37% of adults with ADHD who were treated with MPH (Godfrey J., 2009). The results of our study are also consistent with the reported acute effects of a single dose of MPH on appetite sensations in healthy individuals without ADHD. Goldfield *et al*., (2007) showed that, following the administration of a single dose of 0.5 mg/kg MPH, the increase in pre-meal hunger scores were smaller with MPH than with placebo in healthy normal-weight individuals (Goldfield et al., 2007). Also, Davis *et al.,* (2012) found that women, but not men, 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 the impact of a two-month administration of MPH on appetite sensations in individuals with obesity and who do not have ADHD.

Clinically meaningful changes in appetite sensations should reflect alterations in appetite and energy intake, which is not clearly identified in the literature. It was proposed that at least a 10% change in appetite sensations is required to be clinically significant (Blundell et al., 2010), and a recent analysis of 23 randomized controlled trials have noted that 15-25% change in VAS measurements of appetite sensations was the minimum required change to trigger alterations in subsequent energy intake (Sadoul, Schuring, Mela, & Peters, 2014). Our data demonstrated that the % change differences in appetite sensations between baseline and final visit in the MPH group were between 55-65% lower than the baseline appetite scores; thus, the observed changes in appetite sensations in our MPH group was clinically relevant and might lead to a subsequent appetite and energy intake suppression. Our findings showed that MPH-induced appetite suppression persisted for two months despite weight loss. In a weight loss state, appetite sensations related to desire to eat, hunger and prospective food consumption are stimulated, whereas satiety (fullness) is inhibited (Doucet et al., 2000, 2003; Drapeau et al., 2007; P. S. MacLean, Bergouignan, Cornier, & Jackman, 2011). It is suggested that baseline appetite

sensations might predict final weight loss (Drapeau et al., 2007; Gilbert, Drapeau, Astrup, & Tremblay, 2009) and weight regain (McGuire et al., 1999; Pasman et al., 1999), as well, changes in appetite variables tended to persist for more than one year after initial weight loss (Sumithran et al., 2011). In an attempt to quantify the changes in appetite sensations relative to weight loss, Gilbert *et al.* (2009) reported that for each 1 kg of fat loss, there is a delta increase in fasting desire to eat of 5.8mm and a 3.6mm decrease in fasting fullness in their rating on 150mm VAS (Gilbert et al., 2009). Though not statistically significant, our placebo group demonstrated heightened appetite sensations and depressed fullness scores following a modest weight loss; however, MPH administration seemed to curb the weight loss-induced appetite stimulation.

Our study presents some evidence of the mechanisms of MPH-mediated appetite suppression. For one, MPH intake suppressed appetite by reducing food wanting as could be expected from the decrease in the desire to eat and PFC scores in our MPH sample. Since food wanting is associated with reduced dopamine activity and greater energy intake (Epstein, Leddy, Temple, & Faith, 2007), it is tempting to speculate that MPH-amplification of dopamine signalling at least partly modulated appetite suppression. Additionally, MPH intake caused a significantly greater reduction in hunger sensations and an increase in fullness rating contrary to the placebo group. The reduction in hunger rating indicates that MPH might affect the homeostatic control of appetite. Indeed, MPH is a known sympathomimetic drug, a known class of appetite suppressant drugs that modulate appetite by stimulating the sympathetic nervous system and activating anorexigenic pathways in the hypothalamus (Heisler et al., 2006; Kintscher, 2012; Marston, Garfield, & Heisler, 2011). Besides its sympathomimetic effects, MPH intake might have decreased plasma ghrelin levels and increased plasma leptin levels, as it has in children and adolescents with ADHD (Gurbuz et al., 2016), although these peptides were not measured in the

current study. Ghrelin is a hunger signal, while leptin is known for its hunger suppressing effects. Other studies have also shown that MPH intake for a long duration correlates with changes in plasma ghrelin and leptin levels (Iseri, Kilic, Senol, & Karabacak, 2007; Sahin et al., 2014; Yalcin, Iseri, Bukan, & Ercin, 2014). Hence, though speculative, the noted reduction in hunger rating might be at least partly caused by a reduction in peripheral hunger signals or an increase in satiety signals or both. The effects of MPH on peripheral energy signals need further investigation, in studies of MPH effects on appetite and energy intake.

6.2 Olfactory Performance

Our study is the first to indicate that a two-month intake of MPH is associated with a higher mean olfactory threshold score in individuals with obesity compared to placebo. A high olfactory threshold score corresponds to a lower odourant concentration to detect the presence of the odour, which reflects higher odour sensitivity, as opposed to a low threshold score. Therefore, the observed increase in the olfaction threshold in our MPH group suggests that they had improved olfactory sensitivity. The sum of odour threshold (T) along with odour discrimination (D) and identification (I) in a composite TDI score is usually used to assess the olfactory function globally (Kobal et al., 2000). TDI scores, as well as the scores for the separate subtests, are used to clinically assess the olfactory performance in patients and monitor their progress. For clinical assessment purposes, normative TDI scores are set at 30.75 or higher, and normative odour threshold score is set at 5.75 or higher (Oleszkiewicz, Schriever, Croy, Hähner, & Hummel, 2019). A study by Gudziol *et al.* (2006) showed that patients reported an improvement in olfactory sensitivity when their TDI scores increased by ~5.5 points, and their odour threshold scores increased by ~1.3 points (Gudziol, Lötsch, Hähner, Zahnert, & Hummel, 2006). At

baseline, our participants in both placebo and MPH group were in the normative odour threshold range (7.88 ± 2.29 *vs.* 6.36 ± 1.43, respectively). MPH intake increased odour threshold at the final visit (9.44 ± 2.14) suggesting an improvement in olfactory sensitivity. Our results are inconsistent with the results of other studies that have examined the effects of MPH intake on the olfactory function in patients with ADHD. Romanos *et al.,* (2008) found that non-medicated children with ADHD have heightened odour sensitivity (assessed by high odour threshold scores) compared to healthy controls, while children on chronic MPH treatment (MPH intake > 2 months) had lower odour threshold scores that are comparable to healthy controls. Another study has shown that acute cessation of MPH treatment for two 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 might explain the contradictory results between our study and studies that examined the effect of MPH on olfactory function in patients with ADHD. For one, we only reported changes in odour threshold scores, while a global assessment of olfactory function based on TDI scores might help to understand the overall changes in olfactory function better. Also, the type of odourant used in the sniffin' sticks® test might affect the results of the test (Croy et al., 2009; Zernecke et al., 2010). While we used butanol as the test odourant, the other studies (Romanos et al., 2008; Schecklmann et al., 2011) have used phenylethanol. Butanol is a mixed odour, which means that it activates both the olfactory pathway, through the olfactory bulb, and the trigeminal nerve (cranial nerve V) to perceive the smell. While, phenylethanol, is a pure olfactory stimulus that is only detected through the olfactory pathway (Doty et al., 1978; Frasnelli, Hummel, Berg, Huang, & Doty, 2011). Changes in dopamine activity are known to affect the olfactory pathway (Huisman et al., 2004), but its effects on the trigeminal nerve are unclear. So, it would be more reasonable to use

a pure odour, like phenylethanol, as the test odourant to examine the dopaminergic-mediated changes in olfaction. Nevertheless, the test-retest reliability of butanol has been well established (Albrecht et al., 2008; Hummel, Kobal, Gudziol, & Mackay-Sim, 2007; Kobal et al., 2000; Pössel, Freiherr, & Horstmann, 2019) whereas that of phenylethanol is not formally validated (Zernecke et al., 2010). Moreover, pure olfactory stimuli are rarely encountered in daily life so it might be clinically irrelevant to assess olfactory function using pure odourants, especially given that the sniffin' sticks® test results of butanol and phenyelthanol are poorly correlated (Zernecke et al., 2010).

Besides differences in methodology, it is worth noting that the studies mentioned above (Romanos et al., 2008; Schecklmann et al., 2011) recruited children with ADHD who had heightened olfactory function. In contrast, our sample of adults with obesity exhibited normative olfactory sensitivity, which improved with MPH intake. This discrepancy might attest to the complex role of dopamine in modulating olfaction and suggest that enhancing brain dopamine levels could play a role in optimizing olfactory function regardless of baseline olfactory performance.

As proposed by the Reward Deficiency Syndrome (RDS) model of feeding behaviour, individuals with obesity may have low brain dopaminergic tone (Blum et al., 1996). Reduction in brain dopamine levels is accompanied by an increase in inhibitory dopaminergic neurons in the olfactory bulb in Parkinson's disease patients (Berendse et al., 2001; Huisman et al., 2004). 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. However, it is yet to be elucidated whether MPH acts directly on the dopaminergic neurons in the olfactory bulb or whether they exert their effects indirectly through the brain dopaminergic

pathways. Interestingly, our findings pointed out the effectiveness of MPH in optimizing olfactory function without enhancing appetite, despite weight loss. Diet-induced weight loss is linked with heightened smell function and an increase in appetite (Aimé et al., 2007; Pager et al., 1972), an effect that could be mediated by increased hunger signalling and reduced leptin levels following weight loss (Palouzier-Paulignan et al., 2012; Trellakis et al., 2011). Odour sensitivity is closely related to changes in ghrelin and leptin levels (Han et al., 2018; Morrison, 2009; Tong et al., 2011; Uygun et al., 2017). Though MPH intake was associated with reduced ghrelin signalling (Gurbuz et al., 2016), it is not clear whether changes in peripheral energy signals mediate the MPH effects on improving olfactory function.

Collectively, our study showed for the first time that MPH intake resulted in improved olfactory sensitivity in healthy individuals with obesity. The olfactory function contributes to the sensory stimulation of food and modulates satiety (R. D. Mattes, 1997). Though some studies have shown transient heightened olfactory sensitivity in acute hunger conditions (Albrecht et al., 2009; Cameron et al., 2012; Stafford & Welbeck, 2011; Trellakis et al., 2011), other findings indicated that eliminating oro-sensory stimulation of food by gastric feeding resulted in increased hunger and decreased fullness ratings compared to oral feeding (French & Cecil, 2001; Wijlens et al., 2012). Also, several studies have shown that inhalation of pleasant odours before food intake suppresses appetite and might contribute to long-term weight loss (Hirsch & Gomez, 1995; Mayer, Davidson, & Hensley, 1999; Sørensen, Møller, Flint, Martens, & Raben, 2003; Warwick, Hall, Pappas, & Schiffman, 1993). It could be possible that improving basic olfactory acuity in individuals with obesity will potentially increase the intensity of perceived flavours of the sweet and fatty food making them less pleasant (Miras & Le Roux, 2010). Those speculated changes in olfactory sensitivity might eventually lead to changes in food choices and food

consumption. So, improved smell function might be implicated in feeding control by regulating satiety. Further investigations on the plausible central and peripheral mechanisms that mediate the MPH effects on improving smell function are needed to understand its role in food intake and obesity management better.

6.3 Food palatability

Our study tested, for the first time, the effects of MPH administration on food palatability scores in individuals living with obesity. Although the changes in food palatability were not statistically significant, post breakfast food palatability showed a decrease in the MPH group between baseline and final visit with large effect size while a slight increase in food palatability scores was noted in the placebo group. The increase in food palatability accompanied a decrease in body weight in the placebo group, which is expected after weight loss. Research has shown that food palatability increases after weight loss and is thought to be one of the reasons behind increased energy intake, and weight regain (Cameron et al., 2008; Esses & Herman, 1984; Frankham et al., 2005; Nisbett et al., 1973). The changes in food palatability as a result of changes in energy stores was coined "*alliesthesia"* by Cabanac *et al.* (1971), and researchers have concluded that *alliesthesia* indicates that changes in energy stores might adjust appetite through particular modulators. It is now known that leptin plays a central role in signalling energy stores to the brain and in modulating appetite (Klok, Jakobsdottir, & Drent, 2007). In addition, leptin repletion following weight loss blunts increases in neural activity of brain areas that are associated with the hedonic control of energy intake (Rosenbaum et al., 2008). Interestingly, research has shown that MPH intake is associated with increased plasma leptin levels (Gurbuz et al., 2016), and our participants in the MPH group displayed a reduction in food

palatability despite losing more body weight compared to the placebo group. Altogether, these findings, along with our results, suggest that the administration of MPH might curb *alliesthesia* after weight loss, possibly by regulating leptin levels. In sum, though the MPH-mediated reduction of food palatability failed to reach statistical significance, MPH appears to hold potential to influence food palatability. Future studies need to further explore the MPH effects on food palatability along with whether it is associated with a reduction of intake of highly palatable food and weight loss.

6.4 Changes in Body Weight and Energy Intake

Our results showed that the change in body weight 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), which is in line with our hypothesis. Unintentional weight loss as a side effect of MPH treatment was reported in patients with ADHD (J. A. Mattes & Gittelman, 1983; Poulton et al., 2012; Schertz, Adesman, Alfieri, & Bienkowski, 1996). Furthermore, Levy *et al.* (2009) noted that adults with ADHD and refractory obesity lost 18 kg in ~ 16 months when they were treated with MPH compared to the untreated group. Thus, our findings along with the previously documented impact of MPH on weight loss warrant further investigation in future studies with larger sample size.

The observed percentage of weight loss in the MPH group is less than the minimum clinically important difference of 5-10% to reduce obesity-related risk factors (Lipid Research Clinics Program, 1984), as well, it is not comparable to the weight loss outcome of other approved anti-obesity medications (Khera et al., 2016). It is worth noting that our study did not include a

weight loss program and was only 8 weeks compared to trials of other anti-obesity drug medications, which typically approximate 1-year in duration. So, it is recommended to run an MPH clinical trial in adjunct to weight loss regime.

Contrary to the hypothesis, there was no significant group*time interaction on either ILF or OOLF. Our data showed that energy intake decreased significantly overtime in both MPH and placebo groups. In addition, the reported change in OOLF did not reflect the observed changes in body weight in either the MPH or placebo groups. When calculating the expected weight loss in two months based on our reported OOLF changes, and the fact that each 1 kg of body fat requires a deficit of 7,000 calories, the expected weight loss would be ~ 5 kg and 8 kg for the MPH and placebo groups, respectively. However, these numbers are far superior to our measured weight loss outcome (2.66 kg; 1.2 kg in the MPH and placebo groups, respectively) which implicate that the changes in OOLF were likely overreported in a manner similar to food questionnaires or food diaries (Bedard, Shatenstein, & Nadon, 2004; Fricker, Baelde, Igoin-Apfelbaum, Huet, & Apfelbaum, 1992; Horner et al., 2002; Voss, Kroke, Klipstein-Grobusch, & Boeing, 1997). A possible explanation is that participants failed to return all the food leftovers especially in Baseline visit, which led to a higher-than-expected change in energy intake in both placebo and MPH groups. Such discrepancy indicates the challenges of accurately measuring energy intake (Schoeller et al., 2013) and justifies the need for further investigations into the potential effects of MPH on energy intake.

6.5 Limitations, Strengths, and Recommendations

The most important limitation of this study was the small sample size, n=12, which limits the statistical power of the study. As well, the participants were all healthy individuals with

moderate obesity (BMI < 40 kg/m^2), hence, limiting the generalizability of the results to this specific population. It is possible that with larger sample sizes, the observed patterns in weight loss, energy intake, and food palatability with large effect sizes (as inferred by partial η^2 values), would have approached statistical significance. Our *a priori* aim was to recruit 18-20 participants, including adolescents, in each group to reach a statistical power of 0.8 and we have run the experiment for 11 months. However, we struggled with recruiting the required number of participants (3-4 persons/month) for reasons that include the rigorous exclusion criteria, the reluctance of potential participants, especially adolescents, to join a drug-based trial, and the low monetary compensation given the amount of time that people needed to dedicate for the study.

Another limitation of the current study is the relatively short duration of the experiment, which is substantially less than the standard 52-56 weeks of intervention for most anti-obesity drug clinical trials. Furthermore, not including a diet or exercise component in this pilot trial limited the clinical meaningfulness of the results in the context of the standard drug plus dietary or behavioural interventions for obesity treatment. Therefore, it is recommended for future research to test the effects of MPH as an adjunct to dietary or behavioural weight loss plans for an extended period. Also, we monitored compliance with drug administration by asking participants to return their pill containers to the lab on day 30 and at the final visit. Though this method might not be 100% reliable, measuring biomarkers of drug metabolism in blood or urine might be expensive and not feasible, as well it might add another barrier to recruitment in future studies.

As for the methods of testing dependent variables, we used olfactory threshold sniffin' sticks® test as a proxy for olfactory function, however, measuring TDI scores are more common to clinically assess changes in olfactory function (Hummel et al., 2007; Oleszkiewicz et al., 2019). Also, adding a self-reported questionnaire so participants can evaluate their smell function

subjectively is important to have more insight into how subjective perception of smell is linked to its objective assessment and the feeding behaviour.

We employed methods for measuring energy intake directly inside the lab and outside the lab. Direct methods of assessing energy intake are commonly used in the literature, and they have good reliability and validity compared to the self-reporting of food intake (Goris, Westerterp-Plantenga, & Westerterp, 2000; Tanofsky-Kraff, Haynos, Kotler, Yanovski, & Yanovski, 2007). Nevertheless, laboratory assessed energy intake paradigms are inherently limited by factors like desirability, which means that participants reduce their intake to be viewed favourably by researchers (Horner et al., 2002). For example, our participants in the placebo group have shown either comparable energy intake reduction as in the ILF (the difference was only 5% between MPH and placebo groups in final visit) or even greater energy intake reduction (as in the OOLF measurements in final visit). The reduction in energy intake in the placebo group means that we need to interpret the effects of MPH on energy intake with caution since a good portion of the reduced intake in the MPH group might, as well, be explained by the desirability effects. Moreover, failure to return some of the leftovers to the lab could compromise the results of OOLF and might suggest that this method is no better than self-reporting. Another variation of this method would be to use the recently introduced and validated Remote Food Photography Method (RFMP), which allows participants to take pictures of their food intake at their homes and analyzes the estimated energy intake using a computer application (Martin et al., 2014). It is also worth noting that though the appetite-suppressing effects of MPH were significant in our sample, the changes in appetite did not correlate with similar changes in measured energy intake. A recent systematic review of 462 studies has found that appetite ratings failed to correspond with changes in energy intake in 52% of the reviewed studies and only 6% of all the evaluated

studies shown a direct statistical correlation between appetite ratings and energy intake (Holt et al., 2017). Together, these findings indicate the importance of developing new models to either predict or measure energy intake directly.

Though not explored in this study, there is marked inter-individual differences in MPH metabolism (Faraone, 2018; Lyauk et al., 2016) and the lowest effective dose might differ among individuals (Leddy et al., 2004). Causes of the inter-subject variability in MPH clinical response are not well understood, yet, research has shown that specific genotypes (Lyauk et al., 2016); gender (Davis et al., 2012; Goldfield et al., 2011); and personal trait differences (Davis, Levitan, Kaplan, Kennedy, & Carter, 2014) might affect the individuals' response to MPH. So ideally, future studies need to investigate the various determinants of MPH effectiveness for better dose prescription.

Despite the presence of some limitations, this study presents several methodological strengths. Firstly, the study design as a double-blind placebo-controlled randomized clinical trial is a gold standard in clinical testing (Hariton & Locascio, 2018). Randomized clinical trials provide high-quality evidence with regards to the effectiveness of the intervention, and our pilot trial demonstrated that the two-month MPH administration was effective in suppressing appetite and in improving olfactory sensitivity in individuals with obesity with potential to induce greater weight loss compared to placebo. Since 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. In fact, most anti-obesity drugs clinical trials focus on weight loss outcome with little emphasis on the possible mechanisms of

action. Hence, a strength in our study is that it explored potential changes in various aspects of feeding, including appetite, olfaction, food palatability, food reward, and energy intake.

In conclusion, we have demonstrated for the first time that MPH intake for two months improved olfactory sensitivity, suppressed appetite and increased fullness in individuals with obesity. We found no evidence to support that the decreases in weight and energy intake were statistically significantly different between the MPH and placebo group. Further investigations are required to test the possible homeostatic and hedonic mechanisms by which MPH modulates olfactory function, appetite and body weight.

7 General Discussion and Future Perspective

Extensive research over the past few decades has shed light on the pathways that are involved in feeding control and obesity development (Berthoud, 2006; Cameron & Doucet, 2007). While lifestyle modifications are the cornerstone of obesity management, they often lead to counter-regulatory changes in appetite and feeding behaviour that eventually blunt the weight loss outcome (F. Greenway, 2015). Obesity pharmacotherapy holds promise to enhance the effectiveness of traditional obesity management methods, possibly by curbing the weight loss-induced changes in appetite and feeding behaviour (Halford et al., 2010). However, the discontinuation rate of anti-obesity medications is high due to unpleasant side effects or other reasons like the high cost of the drug or its route of administration (Khera et al., 2016).

Since obesity is a multifactorial disease with complex pathogenesis that involves a number of genetic, physiological, and behavioural factors, its treatment should also be a combination therapy that targets different pathways. Additionally, the pathogenetic factors involved in obesity might affect individuals with obesity to various degrees (Paul S MacLean et al., 2006), so, the treatment plans of obesity need to be individualized accordingly. For example, individuals with a heightened response to food reward might benefit from treatments that would target food reward compared to individuals with normal response to food reward.

Feeding behaviour is affected by the interaction between the internal physiological needs of the individual and the rewarding properties of food. In other words, food intake is not only regulated by homeostatic signals, such as leptin and ghrelin, but is also influenced by the hedonic properties of food which are mainly modulated by dopamine signaling and the oro-sensory properties of food (Cameron et al., 2017). Understanding the contribution of food reward and oro-sensory stimuli, like the smell and palatability of food, to feeding behaviour is central to

understanding appetite regulation and its changes in individuals with obesity. Indeed, in order to tailor individualized treatment plans, more data regarding the changes in oro-sensory stimuli, food reward and appetite need to be collected in studies of obesity and weight loss. The inclusion of tests for different aspects of eating behaviour, such as food reward, liking, appetite, and olfaction as a standard procedure in weight loss trials might help to understand the behavioural differences among the individuals with obesity. Since feeding behaviour is not only affected by hedonic variables, exploring the changes in homeostatic factors like leptin and ghrelin and how they affect weight loss outcome is also warranted. For example, changes in leptin and ghrelin during weight loss mirror changes in appetite and food reward, as well, they might be implicated in oro-sensory food cues.

Another area that needs close attention is the challenges that are associated with maintaining weight loss. In oftentimes lifestyle modifications are rendered ineffective due to weight relapse despite initial weight loss. Diet-induced weight loss is usually associated with an increased drive to eat, heightened food reward, and changes in peripheral energy signals (Doucet, 2018) that can persist for a year after initial weight loss (Sumithran & Proietto, 2013). These changes will progressively sabotage the individual's efforts to maintain weight loss resulting in weight relapse (Doucet, 2018). With the advent of obesity medicine, standardized tests of appetite and aspects feeding behaviour that are easy to use in clinical setting need to be developed. The development of these tests entails that clinically meaningful criteria of normal scores are well established. Also, clinicians need to be trained to collect, interpret, and continuously monitor data regarding the pattern of appetite and feeding behaviour of their patients with obesity. Knowledge of the behavioural changes associated with weight loss would allow the clinician to set realistic and individualized weight loss goals with their patients that can be maintained for a long duration

without inducing weight relapse. If these measures were not sufficient to enhance and maintain weight loss outcome, then anti-obesity drugs can be used adjunctly to control specific weight loss-induced changes in feeding behaviour. Indeed, this ambitious scheme demands performing trials that explore the potential homeostatic and non-homeostatic targets of the drugs, and their relation to its weight loss outcome. Providing data regarding the mechanisms of action of the drugs will help to broaden the concept of drug efficacy and allow the clinicians to make informed decisions on which drugs are better to use in a case by case scenario.

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9 Appendices

Appendix A— Side Effects Checklist:

Side Effect	None	Mild	Moderate	Severe
1) Insomnia/Disordered Sleeping				
2) Nausea				
3) Headache				
4) Anxiety				
5) Palpitations				
6) Drowsiness/Sedation				
7) Abnominal Pain/ Cramps				
8) Irritability				
9) Confusion/Disorientation				
10) Sweating				
11) Flushing				
12) Dryness of Mouth				
13) Blurred Vision				
14) Motor Tics				
15) Nervousness				
16) Restlessness				
17) Skin Rash				
18) Excessive Sweating				
19) Depression/Moodiness				
20) Sore Throat/Runny Nose				
21) Other				

Additional Comments:

Appendix B: Case Report Form—Initial Screening Visit

Case Report Form (CRF)
SCREENING VISIT

CONSENT INFORMATION

Date Consent Signed _ _ / _ _ _ / _ _
DD / MMM / YY

Demographic information

Date of Visit: _ _ /_ _ _ /_ _
DD / MMM / YY

Date of Birth: _ _ /_ _ _ /_ _
DD / MMM /YY

Inclusion and Exclusion Criteria:
BMI≥30

Weight:_ _ _ . _ **Pounds** ☐ **Kilograms** ☐

Height: _ _ _ **cm** ☐ **Inches** ☐

Waist Circumference: _ _ _ **cm** ☐ **Inches** ☐

BMI: _ _ _ **Is BMI ≥30.0? Yes** ☐ **No** ☐

If no, participant is excluded.

Concomitant Medications

Is patient presently on any medication? No ☐ **Yes** ☐ **If yes please add to Concomitant Med page** _____

Inclusion and Exclusion Criteria
Summary Checklist

Inclusion Criteria: All must be checked "YES" for the patient to be eligible

Yes	No		
☐	☐	1	**Written informed Consent or Assent**
☐	☐	2	**Between the age of 16 and40 (must be ≥16 or ≤40 when starting trial)**
☐	☐	3	**BMI>29.9 (class I obesity or greater)**

Exclusion Criteria: All must be checked "NO" for the patient to be eligible

Yes	No		
☐	☐	1	**Is a current smoker**
☐	☐	2	**Known food allergies (e.g. lactose, gluten, etc.)**
☐	☐	3	**History of Methylphenidate use or known allergy to Methylphenidate**
☐	☐	4	**History of ADHD or current diagnosis of an axis 1 psychiatric disorder (e.g., depression, panic disorder, schizophrenia) as measured by clinical interview and self-report, the Wender-Utah Rating Scale and the Beck Depression Inventory**
☐	☐	5	**Current use of antidepressants, thyroid medication, or any medication that could affect appetite**
☐	☐	6	**Pre-existing cardiovascular disorders including uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomyopathies, myocardial infarction, and cardiac arrhythmia**
☐	☐	7	**Diabetic**
☐	☐	8	**Excessive use of alcohol or alcoholism, or current addictions to opiates, cocaine or stimulants as measured by the Drug Abuse Screening Test**
☐	☐	9	**Restrained Eater (score of ≥11 from Three Factor Eating Questionnaire**
☐	☐	10	**Glaucoma**
☐	☐	11	**High Blood Pressure**
☐	☐	12	**Personal or family history of seizure disorders**
☐	☐	13	**Currently taking MAO inhibitors, pressor agents, coumarin, anticonvulsants, phenylbutazone, or tricyclic antidepressants**
☐	☐	14	**History of thyroid disease**
☐	☐	15	**Personal or family history of motor tics or Tourettes's Syndrome**
☐	☐	16	**After test dose of MPH, systolic blood pressure exceeding baseline reading by 20mmHg**
☐	☐	17	**After test dose of MPH diastolic blood pressure exceeding the baseline reading by 10mmHg**
☐	☐	18	**After test dose of MPH heart rate exceeds 20 beats per minute above baseline**
☐	☐	19	**Pregnant or breastfeeding**

Inclusion and Exclusion Criteria:
Psychological Self-Report

1) ***Depression:*** **Has the participant been diagnosed or is the participant currently diagnosed as having clinical depression?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____

2) ***Schizophrenia:*** **Has the participant been diagnosed or is the participant currently diagnosed as having schizophrenia?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____

3) ***Panic Disorder:*** **Has the participant been diagnosed or is the participant currently diagnosed as having panic disorder?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____

4) ***Restrained Eating:*** **Did the participant score 11 or higher on the restraint subscale of the Three Factor Eating Questionnaire?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments: _____

Inclusion and Exclusion Criteria:
Alcohol Use—AUDIT-C Questionnaire

1. **How often do you have a drink containing alcohol?**

   ☐ **a. Never**
   ☐ **b. Monthly or less**
   ☐ **c. 2-4 times a month**
   ☐ **d. 2-3 times a week**
   ☐ **e. 4 or more times a week**

2. **How many standard drinks containing alcohol do you have on a typical day? A standard drink is defined as a 12oz beer or cooler (~5% alcohol), 8-9oz malt liquor (~7% alcohol), 5oz table wine (~12%), or 1.5oz spirits (~80% alcohol).**

   ☐ **a. 1 or 2**
   ☐ **b. 3 or 4**
   ☐ **c. 5 or 6**
   ☐ **d. 7 to 9**
   ☐ **e. 10 or more**

3. **How often do you have six or more drinks on one occasion?**

   ☐ **a. Never**
   ☐ **b. Less than monthly**
   ☐ **c. Monthly**
   ☐ **d. Weekly**
   ☐ **e. Daily or almost daily**

Scoring: Each question has 5 answer choices and points allotted are: a=0 points, b=1 point, c=2 points, d=3 points, e=4 points.

Did the participant score 8 or higher on the AUDIT-C questionnaire? Yes ☐ No ☐

****If yes was answered above the participant is excluded**

Comments:

_____

_____

Inclusion and Exclusion Criteria:
Clinical Assessment Questionnaires

Beck Depression Inventory: **Was the participant's score on the Beck Depression Inventory 17 or greater?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____
_____
_____

Wender-Utah Rating Scale (ADHD screening): **Was the participant's score on the Wender-Utah Rating scale 46 or greater?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____
_____
_____

Drug Abuse Screening Test: **Was the participant's score on the Drug Abuse Screening Test 11 or higher?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____
_____
_____

Note: **If the participant is excluded due to a clinically relevant diagnostic score for any of the 3 above Axis 1 Disorder Tests they will be advised to follow-up with their family doctor and if they do not have a family doctor they will be encouraged to visit a walk-in clinic to follow up.**

Inclusion and Exclusion Criteria:
LAB TESTS

Date of Urine for Pregnancy _ _ / _ _ _ / _ _ Neg ☐ Pos ☐ if positive, exclude
DD / MMM / YY

Date EKG Performed _ _ / _ _ _ / _ _ Abnormalities Yes ☐ No ☐
If Yes Specify:_____

_____

_____

_____
____

NOTE *:* QTc > 440 msec or arrhythmia other than sinus bradycardia; conduction abnormalities, Prolonged QTc or other, exclude **

BASELINE VITAL SIGNS

Temperature: _ _ . _ °C oral ☐ tympanic ☐

Heart Rate: Lying _ _ _ Blood Pressure: Lying _ _ _ / _ _ _

Heart Rate : Standing _ _ _ Blood Pressure: Standing _ _ _ / _ _ _

Comments:
_____
_____
_____

Inclusion and Exclusion Criteria:
VITAL SIGNS AT 30min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____
_____
_____

VITAL SIGNS AT 60min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____
_____

VITAL SIGNS AT 90min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____
_____
_____

VITAL SIGNS AT 120min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____
_____

THE EFFECT OF TWO-MONTH ADMINISTRATION OF METHYLPHENIDATE ON APPETITE, OLFACTION AND ENERGY INTAKE IN INDIVIDUALS WITH OBESITY

MEDICAL HISTORY

None □

Body System	Past	Current	Condition	Treatment Yes/No	Code Data Use
Nervous					
Cardiovascular: uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomypathies, myocardial infarction, and cardiac arrhythmia					
Respiratory					
Endocrine: Thyroid, Diabetes					
Skin					
Digestive					
Musculoskeletal: Seizure Disorders					
Blood					
Urinary					
Female Reproductive					
Mental Health: axis 1 psychiatric disorder (e.g., depression, panic disorder, schizophrenia) as measured by self-report, the Wender-Utah Rating Scale and the Beck Depression					

Inventory					
Other					

Signature (Qualified Investigator):_____ **Date** _____

PHYSICAL EXAM

SYSTEM	NORMAL	ABNORMAL	Specify Abnormalities	Code Data Use
General Appearance				
Lymph Nodes				
Musculoskeletal/Extremities				
Cardiovascular				
Lungs				
Abdomen				
Eyes/Ears/Nose/Throat				
Other				

Final Eligibility

Patient meets all eligibility criteria? No ☐ Yes ☐

Signature (Cardiologist):_____ **Date** _____

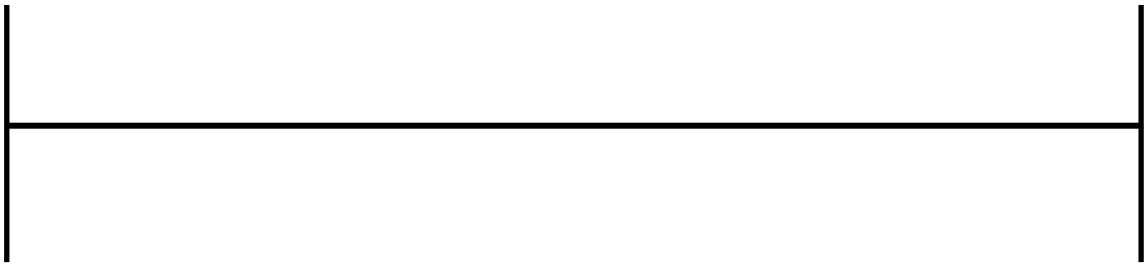
Signature (Qualified Investigator):_____ **Date** _____

Appendix C - Visual Analogue Scales

Visual Analog Scale (150 mm)

Directive	Please quantify your sensation for the following aspect. Consider this line like extreme values of your sensation. Draw a vertical line to represent your sensation at this precise moment.

1. To what extent do you feel like eating?



Very low desire — Very strong desire

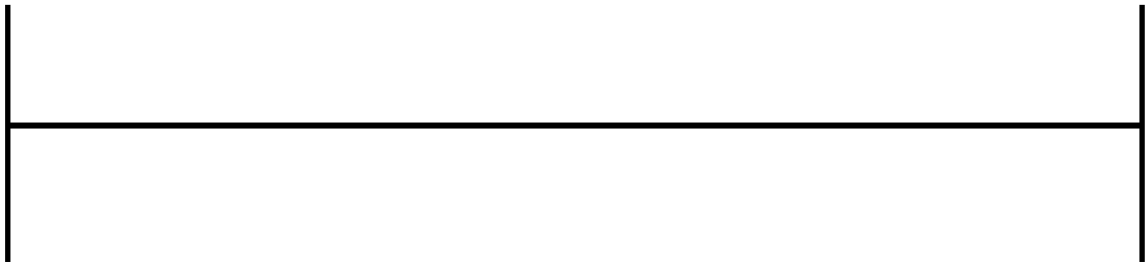
Mesure #1 : _____ Initiales : _____

Mesure #2 : _____ Initiales : _____

Visual Analog Scale (150 mm)

Directive	Please quantify your sensation for the following aspect. Consider this line like extreme values of your sensation. Draw a vertical line to represent your sensation at this precise moment.

2. To what extent do you feel hungry?



Very low desire Very high desire

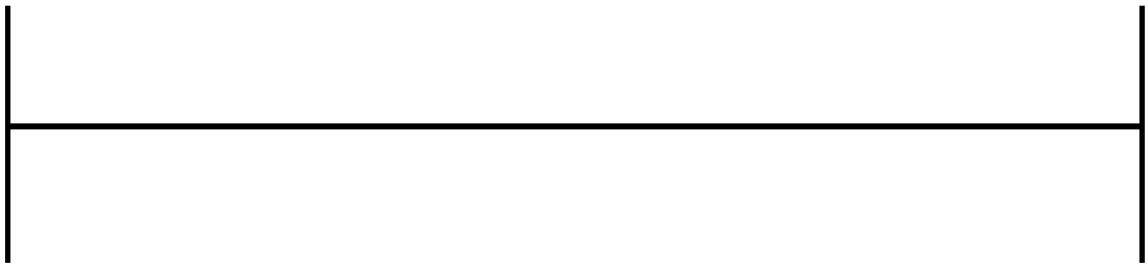
Mesure #1 : _____ Initiales : _____

Mesure #2 : _____ Initiales : _____

Visual Analog Scale(150 mm)

Directive	Please quantify your sensation for the following aspect. Consider this line like extreme values of your sensation. Draw a vertical line to represent your sensation at this precise moment.

3. How do you feel fulfilled?



Not fulfilled at all Very fulfilled

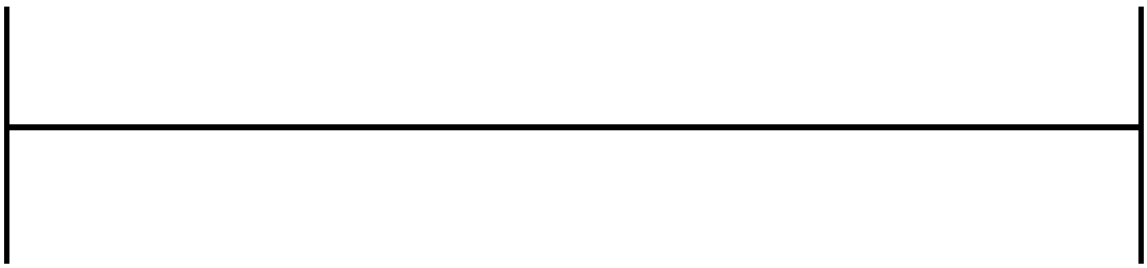
Mesure #1 : _____ Initiales : _____

Mesure #2 : _____ Initiales : _____

Visual analog Scale (150 mm)

Directive	Please quantify your sensation for the following aspect. Consider this line like extreme values of your sensation. Draw a vertical line to represent your sensation at this precise moment.

4. How much food could you eat immediately?



Nothing **A large quantity**

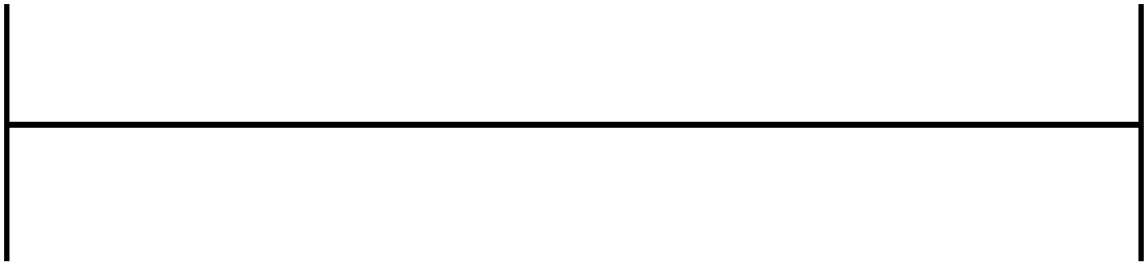
Mesure #1 : _____ Initiales : _____

Mesure #2 : _____ Initiales : _____

Visual Analog Scale (150 mm)

Directive	Please quantify your sensation for the following aspect. Consider this line like extreme values of your sensation. Draw a vertical line to represent your sensation at this precise moment.

5. To what extent did you enjoyed the meal?

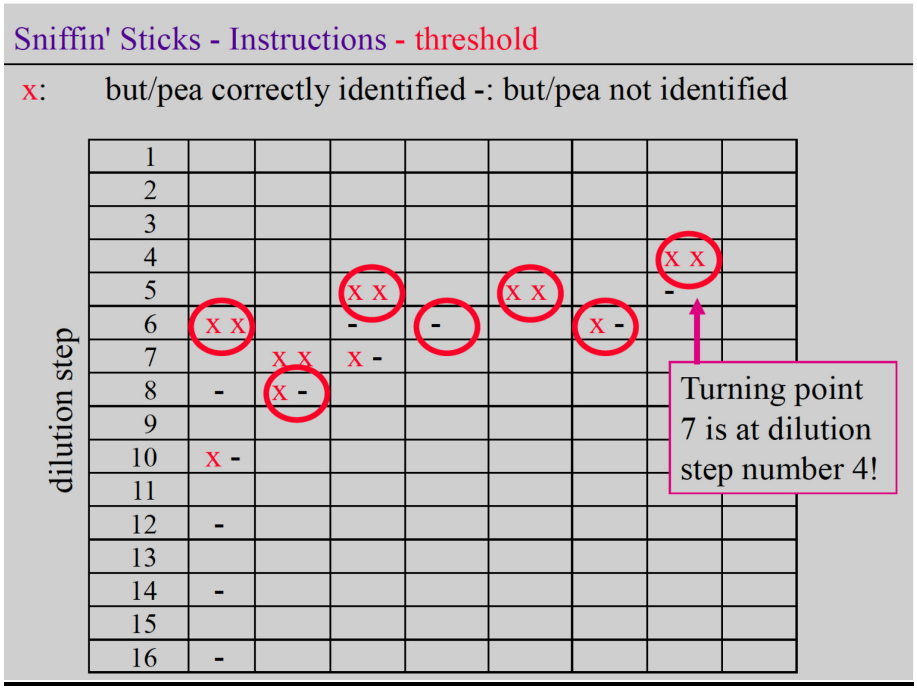


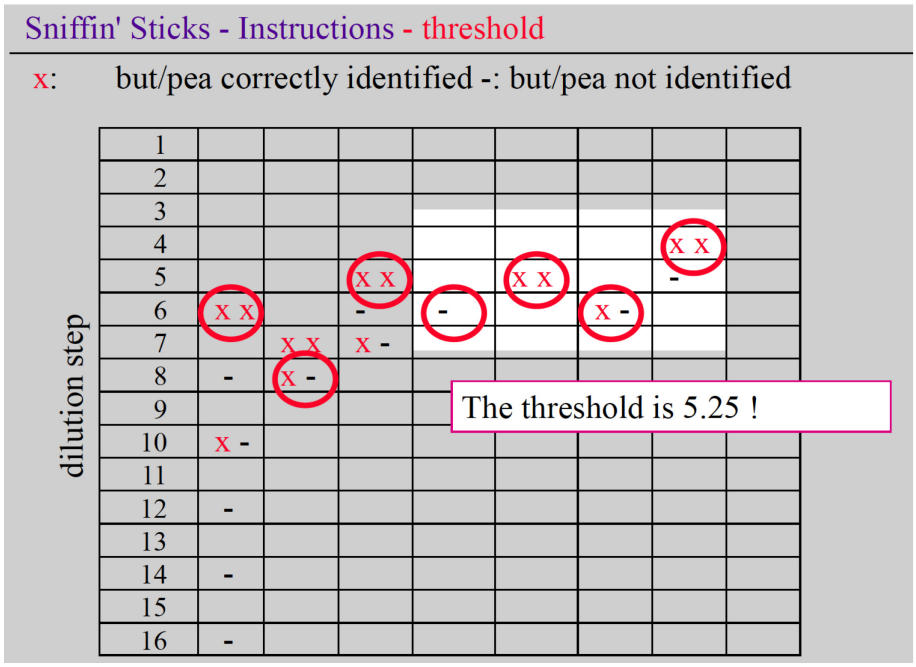
Not appreciated at all **Much appreciated**

Mesure #1 : _____ Initiales : _____

Mesure #2 : _____ Initiales : _____

Appendix D: Odour threshold mean calculation





Adapted from "Sniffin' Stick Instructions Manual; Hummel Mar 13". https://www.uniklinikum-dresden.de/de/das-klinikum/kliniken-polikliniken-institute