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Expanding the spectrum of impulse control disorders in Parkinson's disease: the phenomenology of sweet craving

Brown, Caitlin Harrington
Boston University

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Boston University
EXPANDING THE SPECTRUM OF IMPULSE CONTROL DISORDERS IN PARKINSON’S DISEASE: THE PHENOMENOLOGY OF SWEET CRAVING

by

CAITLIN HARRINGTON BROWN

B.A., University of California, Los Angeles, 2007

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EXPANDING THE SPECTRUM OF IMPULSE CONTROL DISORDERS IN PARKINSON’S DISEASE: THE PHENOMENOLOGY OF SWEET CRAVING

CAITLIN HARRINGTON BROWN

Boston University School of Medicine, 2013

Major Professor: Vickery Trinkaus Randall, Ph.D; Professor of Biochemistry

ABSTRACT

Background: The recognized spectrum of impulse control disorders in Parkinson’s disease (PD) includes pathologic gambling, hypersexuality, compulsive buying, and binge eating, and is commonly related to exposure to dopamine agonist medications. Sweet craving in the general population is a phenomenon that is closely linked to several factors, including poor impulse control. Craving for sweets, though recognized to occur in PD, has not previously been studied.

Methods: First, patients with idiopathic PD and normal controls who reported craving sweets completed craving questionnaires (CQ), taste threshold testing, assessment of mood symptoms and olfactory testing. CQ scores were correlated with these results and other demographic information. A pathologic craving score was identified as the 75th percentile of the mean CQ score for all PD patients. Second, patients with PD and controls completed a series of questionnaires addressing the presence of a variety of
impulse control disorders and sweet craving to determine the prevalence of sweet craving in PD and disease and medication-related factors that are associated with each.

**Results:** Craving for sweets is present in about 5.5% of patients with idiopathic PD. Similar to the determinants of other ICDs, determinants of sweet craving include female gender \((p=0.0001)\), decreased olfactory function \((t\text{-test}: p=0.0001; \text{fisher’s exact method: comparing QSIT scores of 0 and 2 (p=0.0179), 0 and 3 (p=0.0182)})\), self-reported current or past history of depression \((p=0.048)\) and obsessive-compulsive traits \((p=0.044)\), higher Hoehn & Yahr staging \((p=0.0001; \text{fisher’s exact method: no significance})\), younger onset of disease \((p=0.015)\), and longer duration of disease \((p=0.003)\).

**Conclusions:** Craving for sweets in PD is similar in its phenomenology to other recognized ICDs in this population of patients. Though the potential implications of this behavior may be less hazardous than those of other pathologic behaviors, it broadens the spectrum of ICDs that should be recognized in PD and discussed with patients.
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ABBREVIATIONS

CB  Compulsive Behavior
COMT  Catechol-o-methyl transferase
CQ  Sweet Craving Questionnaire
DA  Dopamine Agonist
DA+  Taking dopamine agonist therapy
DA-  Not taking dopamine agonist therapy
DAWS  Dopamine Agonist Withdrawal Syndrome
DRT  Dopamine Replacement Therapy
FFQ  Food Frequency Questionnaire
H&Y  Hoehn & Yahr Staging of Parkinson’s disease
ICD  Impulse Control Disorder
ICD+  Has one or more impulse control disorders
ICD-  Does not have any impulse control disorders
L-Dopa  Levodopa
MAO-B  Monoamine Oxidase B
MRI  Magnetic Resonance Imaging
OCD  Obsessive-Compulsive Disorder
PD  Parkinson’s Disease
QUIP  Questionnaire for Impulsive Compulsive Disorders in Parkinson’s Disease

Q-SIT  Quick Smell Identification Test

SCL-90-R  Modified Symptom Checklist-90-R

SCS  Sexual Compulsivity Scale

SOGS  South Oaks Gambling Screen

UPDRS  Unified Parkinson’s Disease Rating Scale

YBOCS-SV  Yale-Brown Obsessive Compulsive Screen – Shopping Version

YBOCS-CUV  Yale-Brown Obsessive Compulsive Screen – Computer Use Version

YBOCS-BE  Yale-Brown Obsessive Compulsive Screen – Binge Eating
INTRODUCTION

Parkinson’s disease (PD) is a neurological disorder that is characterized by the slow degeneration of dopamine-producing nerve cells in the brain. Dopamine is a neurotransmitter that helps to control movement. As a result of its loss, patients suffer from motor disability including tremor, stiffness, slowness of movement and loss of balance (Davie, 2008). Although there is no cure for PD, different treatment options aim to alleviate some of the motor and non-motor symptoms. Dopaminergic therapies are most common, including levodopa and dopamine agonists (DAs). Levodopa, a form of dopamine, can be taken orally and crosses the blood-brain barrier where it is converted to dopamine and exerts central nervous system effects. DAs stimulate dopamine receptors, thereby mimicking the effects of levodopa. Side effects of DAs include hypotension, nausea, disorientation, aggravation of emotional states like anxiety, obsessionality-compulsivity and depression, hallucinations, dyskinesia and impulse control disorders (Perez-Lloret 2010).

Impulse control disorders (ICDs) in Parkinson’s disease (PD) are thought to occur in approximately 5.9 to 13.6% of patients and are closely linked to dopamine agonist exposure (Kenangil 2010, Weintraub 2010). Risk of ICDs in PD also vary according to age, gender, marital status, tobacco use, age at PD onset, and family history of gambling or alcoholism (Weintraub 2010, Voon 2007). Personal history of alcohol use, impulsive traits, and novelty seeking traits are also associated with greater risk of ICDs.
(Voon 2007). Recognized ICDs include pathologic gambling, compulsive buying, binge eating, hypersexuality and other behaviors, such as punding, hobbyism, and dopamine dysregulation syndrome (Weintraub 2010). The pathophysiology of ICDs in PD is likely related to dopamine receptor stimulation in the reward systems of the nucleus accumbens and dorsomedial frontal lobes (Okai 2011, Muresano 2012, Cardinal 2001).

ICDs can have a negative impact on a patient’s quality of life. Pathologic gambling and compulsive buying can have serious financial implications, whereas binge eating and hypersexuality can lead to major health risks. All of these conditions cause great personal stress on the patient and his or her family, and thus should be seriously considered, assessed and discussed throughout the course of treatment (Vilas 2012).

Specific Aims

Craving for sweets is a recognized but currently un-studied phenomenon in PD. The purpose of this study is to determine the prevalence and correlates of sweet craving and other impulse control disorders in Parkinson’s disease and to investigate whether sweet craving represents a form of ICD in PD. Our specific aims are to:

1. describe the phenomenology of sweet craving in PD,

2. study factors that might influence or correlate with sweet craving in PD and controls such as olfactory loss, taste perception, underlying affective disorder and various PD-related features (e.g., PD duration, PD severity, and PD medications),
3. determine the prevalence of sweet craving in a PD cohort, and
4. identify the correlates of sweet craving and other ICDs in the same population of patients

We hypothesize that sweet craving in PD represents a form of ICD. Shedding light on the phenomenon of sweet craving in PD will help practitioners recognize this occurrence, and counsel or manage patients accordingly.
BACKGROUND

PD and Treatment

Parkinson’s disease is a neurodegenerative disorder characterized by loss of the dopamine-producing neurons in the substantia nigra, leading to dopamine deficiency in the central nervous system. In a healthy patient, dopamine from the substantia nigra influences basal ganglia pathways to control complex movements. In a patient with Parkinson’s disease, the lack of dopamine signaling and other degenerative changes cause a variety of motor and non-motor symptoms to occur (Davie, 2008).

Motor deficits take the form of tremor, bradykinesia, rigidity of the neck and limbs, and postural instability. In addition, patients may display reduced arm swing on the affected side of their body, shuffling or freezing gait, micrographia, and loss of facial expressions. Non-motor symptoms of PD include low voice volumes, mood disorders (depression or anxiety), constipation, hallucinations, cognitive impairment, orthostatic hypotension, loss of sense of smell, pain, drooling and sleep disturbances (Davie, 2008).

While there is no cure for Parkinson’s disease, treatment options aim to alleviate the symptoms of PD. Because many of these symptoms are caused by a lack of dopamine, it is beneficial to treat patients with drugs that can replace the dopamine, block its degradation or stimulate dopamine receptors. Levodopa (L-dopa) is an oral medication that crosses the blood-brain barrier and is converted to dopamine. The medication can be administered in several formulations, and side effects include nausea,
low blood pressure, somnolence, and hallucinations. Long-term complications of L-dopa therapy include dyskinesias. Drugs that inhibit breakdown of dopamine can also enhance the effects of dopamine replacement therapy by allowing dopamine to be maintained in the brain for a longer period before degradation. Examples include monoamine oxidase (MAO) inhibitors and catechol-o-methyl transferase (COMT) inhibitors. By contrast, dopamine agonist (DA) drugs bind to dopamine receptors, mimicking the effects of dopamine. Ropinirole, pramipexole, rotigotine, and apomorphine are all examples of DAs. Side effects of DAs are low blood pressure, hallucinations, nausea, hypersomnolence and impulse control disorders (Davie, 2008).

Impulse Controls Disorders

Impulse control disorders (ICDs) are behavioral disorders in which one’s ability to resist temptation is limited, even if that temptation can lead to the harm of oneself or others (Vilas 2012). The spectrum of ICDs includes pathological gambling, binge eating, pyromania, compulsive shopping, kleptomania, intermittent explosive disorder, compulsive computer use, hypersexuality, and compulsive skin picking (Muresano 2012). Like substance abuse disorders, ICDs are thought to initially provide relief to a certain tension. However, over time, the behavior becomes habitual despite the fact that the patient stops feeling the same relief or pleasure from committing the act (Muresano 2012).
ICDs are thought to occur in Parkinson’s disease patients as a result of dopaminergic therapy. Out of the entire spectrum of ICDs, studies have identified compulsive gambling, compulsive shopping, hypersexuality, and binge eating in PD, along with disorders like hobbyism, punding and dopamine dysregulation syndrome (DDS) (Kim 2012, Leeman 2011, Weintraub 2010, Weintraub 2012). Understanding the presence of ICDs amongst Parkinson’s disease patients is important because ICDs can have serious financial, medical and psychological consequences for the patient. Unfortunately, the presence of ICDs is not always recognized or acknowledged by affected patients or family members. It has been speculated that this might be due to embarrassment, or perhaps because patients and their families do not identify that the behavior might be linked to their treatment for PD (Bastiaens 2013, Weintraub 2012). Early recognition of the development of an ICD in PD is important in order to prevent the behaviors from becoming habitual (Vilas 2012).

The estimated prevalence of ICDs amongst Parkinson’s disease patients ranges from 5.9% (Kenangil 2010) to 13.6% (Weintraub 2010), with one prospective study showing that 39.1% of PD patients developed an ICD over time (Bastiaens 2013). The largest and most cited study evaluating the prevalence of ICDs in PD is the DOMINION cross-sectional study (N=3090) from North America. This study reported an overall prevalence of 13.6%, with 3.9% of patients experiencing 2 or more ICDs. They found that 5% of patients experienced gambling, 3.5% experienced compulsive sexual behavior, 5.7% compulsive buying and 4.3% binge-eating disorder (Weintraub 2010). In order to
obtain this data, the DOMINION study designed an interview that used formal diagnostic criteria to diagnose these four types of ICDs. One major strength of this study was the strong effort taken to avoid selection bias. Every third patient with a diagnosis of idiopathic PD that fell into a specified age range and a defined pattern for treatment was interviewed. The interviewer had no previous knowledge as to whether a patient had a current ICD or not. This selection plan diminished the chances of a patient being selected for the study based on the investigator's knowledge of whether or not an ICD was present. A possible weakness of this study was that the interview was limited to only inquiring about gambling, hypersexuality, computer use and binge eating. As a result, the overall prevalence of ICDs in PD patients might be underestimated.

Kenangil et al (2010) examined 554 PD patients in a prospective study over a 3 year period at an outpatient clinic in Turkey. From this group, 33 patients were found to have ICDs (5.9%). 65 PD patients without ICDs were selected as controls and matched to the PD/ICD group by disease duration, gender and age and then these groups were compared over PD-related factors. There were no significant differences between these groups in severity of PD, L-dopa equivalent doses of DAs, or presence of L-dopa induced motor complications. 5.9% is a lower prevalence than what has been found in Western studies. A possible explanation for this is that there are no casinos in Turkey, which means that the incidence rate of compulsive gambling might be lower due to location. The study did not use a standardized screening questionnaire for ICDs, which also may have contributed to a lower prevalence.
In 2013, Bastiaens et al published a 4 year prospective study of ICDs in PD patients. They examined a cohort of outpatients with PD and no previous ICDs (N=164), 46 of whom were either given DA treatment for the first time or were continuing their DA treatment. 18 patients out of the 46 on DAs developed new-onset ICDs (39.1%). Diagnosis of an ICD was made by a physician after interviewing the patient and those that observe the patient’s behavior. A behavior was considered to be an ICD if it caused disruption to work or social interactions or if it had psychological penalties for the patient. The most common ICD was compulsive eating, affecting 16 out 18 patients. 6 out of 18 experienced hypersexuality, 5 subjects experienced compulsive shopping and 1 patient experienced compulsive gambling. Affected patients typically developed an ICD 3.0 to 114.0 months after they started taking a dopamine agonist. This study is significant in that it examined the prevalence of ICDs in PD in a prospective manner, with the majority of past studies being cross-sectional or respective by design. Another strength of the study is that the interview was not limited to certain ICDs – they inquired about all repetitive behaviors and asked follow-up questions to define the scope and pattern of such behavior. Limitations to the study were its relatively small sample size and the use of clinical diagnosis instead of the formal diagnostic criteria for ICD diagnosis, which may have resulted in an overestimation of the prevalence of ICDs (Bastiaens 2013).
Risk Factors for ICDs in PD

Studies have found that PD patients with ICDs are more likely to be unmarried (Leeman 2011, Weintraub 2010), have more formal education (Weintraub 2010) and have a past or current history of cigarette smoking and a personal or familial history of gambling (Bastiaens 2013, Weintraub 2010). They are likely to be younger (Kim 2012, Voon 2007 Weintraub 2010) with a younger onset and longer duration of PD (Kim 2012), which is possibly explained by the fact that younger patients are often first treated with DAs because of the risk of developing complications associated with levodopa treatment such as dyskinesia (Bastiaens 2013) and DA treatment, especially in high doses, has been suggested to increase the likelihood of ICD development (Rana 2013). In the DOMINION study, however, this “age effect” was tested and remained significant after controlling for DA exposure (Weintraub 2010). Possible implications for these findings are that younger patients are more physically fit and are culturally different than older patients, which can affect the type of compulsive behaviors that they adopt. For example, compulsive computer use might be a behavior that becomes more common in future generations. Compulsive gambling and hypersexuality have been associated with the male gender (Vilas 2012, Weintraub 2010), whereas compulsive buying and binge-eating have been associated with the female gender (Weintraub 2010). ICDs have also been associated with obsessionality-compulsivity, anxiety and depression (Voon and Stacy 2011, Leeman 2011).
**Dopamine Agonists and ICDs**

Based on current literature, the most consistent predictor for the development of ICDs in PD patients is treatment with DAs (Bastiaens 2013, Ondo 2008, Weintraub 2010). This linkage is consistent across the DA class, with similar frequencies of ICDs occurring with pramipexole and ropinirole treatment (Vilas 2012, Weintraub 2010). The DOMINON study found that the odds of having an individual ICD were 2 to 3.3 times higher in patients treated with DAs compared to patients not treated with DAs (Weintraub 2010). The study also found that L-dopa therapy is associated with an increased likelihood of ICDs independently of DA treatment, but that the odds of having an ICD were higher in patients treated with a DA without L-dopa treatment, than in patients treated only with L-dopa (OR, 2.60; 95% CI, 1.97-3.43; P<0.001) (Weintraub 2010). Patients who are taking a combined therapy of both DA and L-dopa were found to have increased odds of developing an ICD by close to 50% when compared with patients only on DA treatment (OR, 1.42; 95% CI, 1.02-1.98; P<0.001) (Weintraub 2010).

The conclusion that DA usage is the probable cause of a development of ICDs in PD patients is strengthened by the Weintraub study (2013) that compared de novo untreated PD patients with healthy controls to determine if PD itself somehow causes an increased risk for ICDs, instead of that risk coming from treatment only. The study recruited 168 untreated PD patients of recent diagnosis and 143 healthy controls. They looked for current ICDs and related behavioral symptoms based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s disease (QUIP) Short Form. This
study found no significant difference in prevalence of ICDs between untreated PD patients and healthy controls. The authors suggest instead that the greater incidence of ICDs amongst treated PD patients is likely caused by dopamine replacement or other therapies, in combination with risk factors like familial or personal history of ICDs and other demographic variables (Weintraub 2013). However, this study was cross-sectional in nature, and did not follow untreated PD patients over a length of time to determine if separate disease related factors could also contribute to the presence of ICDs.

There are multiple theories that attempt to explain why dopamine agonist treatment seems to be more highly associated with ICDs in PD than L-dopa treatment. One theory is referred to as the “overdosing” hypothesis. Degeneration of dopamine producing neurons in PD is thought to initially occur in the ventrolateral and caudal areas of the substantia nigra pars compacta, which limits dopamine projections to the dorsal striatum and causes impaired motoric behaviors (Leeman 2011). By contrast, the ventral striatum, which projects to the brain’s reward system, is unaffected in the beginning stages of PD (Voon and Hallet 2011, Leeman 2011). The overdosing theory hypothesizes that dopamine replacement therapy that is titrated to treat motor symptoms, and hence dorsal striatal deficits may cause an overdosing of the intact ventral striatal cognitive and limbic pathways. This results in increased stimulation to areas of the brain that have been associated with both behavioral addictions and substance abuse disorders (Voon and Hallet 2011).
In opposition to the overdosing hypothesis, which assumes that the ventral striatal pathways of the brain are intact in PD patients with ICDs, some studies have hypothesized that ICDs are a result of disruption or dysfunction of this area of the brain. In 2012, Bentivoglio et al published a study that compared 17 Parkinson’s disease patients with ICDs to 17 Parkinson’s disease patients without ICDs. They matched the patients according to disease duration, age, education, scores on UPDRS-part III and overall cognitive status, with the goal of discovering variables that might lead to the development of an impulse control disorder. The study could not find any significant differences between the two groups; however, they did notice trends of lower scores in the PD ICD group on tests that detected dysfunction of ventral fronto-striatal pathways by measuring inhibition of automatic responses. The study noted that this disruption might decrease a patient’s ability to resist the immediate reward, even if that means that they suffer a long term detriment (Bentivoglio 2012).

The increased frequency of ICDs with dopamine agonist treatment versus L-dopa treatment might be explained by examining dopamine-receptor binding preferences of each drug (Weintraub 2010). Second generation non-ergot dopamine agonists like pramipexole and ropinirole exhibit relative selectivity for D₃ receptors over D₂ and D₁ receptors (Levant 1999). D₃ receptors, which are abundant in the ventral striatum (Gurevich 1999), may mediate reward, while D₂ and D₁ receptors, which are abundant in the dorsal striatum (Gurevich 1999), may mediate movement. Therefore, drugs that preferentially act on D₃ receptors, like dopamine agonists, may lead to an
overstimulation of the ventral striatum. L-dopa, on the other hand, demonstrates relative selectivity for D₂ and D₁ receptors over D₃ (Gerlach 2003). The DOMINION study postulates that these binding preferences explain why DAs are more strongly associated with ICDs (Weintraub 2010).

**Craving for Sweets**

Craving for sweets is a phenomenon that occurs in the general population. People tend to have specific types of sweets that they crave over others – for example, hard candy, chocolate or sugary beverages. Past studies have found that in the general population, women tend to crave sweets over savory foods, whereas men tend to crave savory foods over sweets (Zellner 1999).

In the normal aging population, there is a decrease in the size of the olfactory bulb and other cellular structures related to smell perception whereas no diminution of taste receptor density is found (Kaneda 2000). In support of this, in 2010, Deeb et al found that olfactory deficits that occur in PD were not associated with taste deficits. It is well recognized that taste and smell senses are closely linked, and that most taste perceptions rely to some degree on olfactory sensations (Mojet 2005). It has been suggested that patients with PD have enhanced taste perception, perhaps to compensate for olfactory deficits (Sienkiewicz-Jarosz 2005). However, in opposition to this theory, Shah et al found significant taste impairment in PD patients when compared with healthy controls (Shah 2009). This finding was repeated in 2011 when Kashihara et al
found that both smell and taste impairment occur in a higher frequency in PD patients than in controls (p<0.0001 and p=0.0142). In the general population, females were more likely to experience carbohydrate cravings than men (Zellner 1999), and these sweet cravings were commonly associated with “negative” mood states like depression (Jeffery 2009). Past studies have reported the prevalence of depression in PD patients to be as great as 40% (Prado 2005). A report of 7 PD patients experiencing binge eating after beginning a dopamine agonist also described the presence of food and sweet cravings in 3 of the subjects, with subsequent resolution of symptoms after discontinuation of the offending agent (Nirenberg and Waters 2006). However, craving was not formally assessed.

Although craving for sweets in Parkinson’s disease patients is a relatively un-studied phenomenon in comparison to other compulsive behaviors, it has been acknowledged in previous literature. In 2009, Wolz et al mailed questionnaires to 498 PD patients and their healthy partners to determine if consumption of chocolate and other types of sweets was significantly higher in PD patients. 274 of the PD questionnaires and 234 of the control questionnaires were eligible for analysis. The study found that weekly chocolate consumption was significantly higher in PD patients when compared to healthy controls (p<0.0001). This association remained true despite possible confounding factors such as age and gender. Although weekly consumption of non-chocolate sweets was also higher in the PD group than in healthy controls, the study did not find significance in this disparity (p=0.45) (Wolz 2009). Limitations to the study were the use
of an at-home anonymous self-questionnaire, which removed the physician’s ability to analyze the validity of certain factors like depression and body weight, and the use of spouses as healthy controls, which is considered to be a weak comparison group for eating studies (Wolz 2009).

Based on our experience of PD patients reporting a new craving for sweets and on our review of the above data, we sought to explore the relatively un-reviewed relationship between sweet craving and PD. Our study aimed to identify the prevalence and correlates of sweet craving in PD in order to establish whether sweet cravings represent another form of ICD in PD.
METHODS

Our examination of sweet cravings in PD patients was completed in two parts, with the following objectives:

- **Part One**: To explore possible determinants of sweet craving in PD, including non-PD factors.

- **Part Two**: To examine the prevalence of sweet-craving in PD, PD-related factors that might have influenced the craving, and sweet craving in the broader context of ICDs.

**Part One**

Patients with probable idiopathic PD (Gelb 1999) seen at the Parkinson’s Disease Center and Movement Disorders Clinic (PDCMDC) of Baylor College of Medicine were asked to participate in a study aimed at identifying factors that might influence sweet craving in PD. Control subjects were comprised of unaffected spouses or caregivers of PD patients. Subjects were excluded from participation if they were unable or unwilling to complete all assessments by themselves or with the assistance of a caregiver or study coordinator. All subjects completed the following assessments:

1. **Quick Smell Identification Test (Q-SIT, Sensonics, Inc.)**: This is a short scratch-and-sniff test of three odors based on the University of Pennsylvania Smell Identification Test (Doty et al 1984).

2. **Taste threshold testing**: Various concentrations of solutions (Table 1) representing the four taste sensations [sweet (sucrose), salty (sodium chloride),
bitter (quinine hydrochloride), sour (citric acid)] and plain water were soaked onto circles of filter paper and dried. Subjects placed each filter disc (in a blinded fashion in a predetermined random order) on their tongue for at 5-10 seconds and were asked to identify the taste (Mueller et al, 2003). The taste threshold is identified as the lowest concentration at which the subject could correctly identify the flavor, with a lower threshold indicating more sensitive taste.


4. Sweet Food Frequency Questionnaire (FFQ): Modified from the Arizona FFQ (Martinez et al, 1999). Subjects quantified the average frequency of intake of sweet foods before and after development of PD symptoms.

5. Sweet Craving Questionnaire (CQ): Modified from the Alcohol Craving Questionnaire, Short Form, Revised (ACQ-SF-R) (Singleton et al, 2003). If subjects stated they craved sweets, they answered 12 questions about their craving based on the food item they reported wanting or eating the most. CQs were scored according to published guidelines for the ACQ (Singleton et al, 1994).

Those with a CQ score >75th percentile within their group (PD patients or controls) were considered “problem cravers”. Differences in continuous variables
between cravers and non-cravers were tested by the two-tailed Student’s t-test. For Q-SIT and Hoehn & Yahr scores, the specific scoring groups were compared using Fisher’s exact method and the mean scores were compared using a student’s t-test. Taste thresholds were also compared using Fisher’s exact method. In the patients identified as problem cravers, correlations between the CQ score and various factors were performed.

PD patients were compared with controls using the same methods. Levodopa equivalent doses were calculated based on Tomlinson 2010.

Part Two

We asked a second group of patients with probable PD (Gelb 1999) and controls (comprised of spouses of PD patients and non-PD patients seen in our clinic) to complete a series of self-rated questionnaires derived from the literature addressing various possible impulse control disorders:

1. South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987)
3. Yale-Brown Obsessive Compulsive Screen – Computer Use Version (YBOCS-CUV; modified from the YBOCS-SV)
5. Sexual Compulsivity Scale (SCS; Kalichman and Rompa, 2001)
We obtained the following data for each PD patient: age, duration of PD, current or past history of psychiatric problems, basic demographic information, PD medications, and UPDRS Part III. In control patients, we made note of their age, and current or past history of psychiatric problems. All subjects completed all questionnaires. In case of incomplete questionnaires, subjects were contacted to score the missing items.

Mean scores on the various questionnaires were compared between controls and PD patients, controls and PD patients taking dopamine agonists and controls and PD patients not taking dopamine agonists, using two-tailed z-hypothesis testing. Scores on each scale were correlated with various factors by calculating Pearson’s correlation coefficients. PD patients with a compulsive behavior (ICD and/or sweet craving) were compared over various factors with PD patients without any ICDs or cravings.
RESULTS

Part One

62 PD patients and 23 control subjects were enrolled in the first part of the study seeking to identify the determinants of craving in PD (Table 2). PD patients had significantly worse olfactory function (t-test: p=0.0001, Fisher’s exact method comparing scores of 0 and 3: p=0.019, scores of 0 and 2: p=0.088) and scored significantly higher on mood scales (anxiety, p=0.028; OCD, p=0.048). PD patients were more likely to be male (p=0.0001).

In this part of the study, subjects only completed the CQ if they stated that they craved sweets. 33 PD subjects (53%) identified themselves as cravers, with a mean CQ of 4.51 (SD 1.3). Of these, 22 PD subjects (67%) indicated they experienced craving before being diagnosed with PD. 9 control subjects (39%) identified themselves as cravers, with a mean CQ of 3.92 (SD 1.3). The 75th percentile of CQ scores amongst PD cravers was 5.5, with 9 PD subjects (15%) scoring at or higher than this (mean CQ 6.06, SD 0.4). These subjects were designated “problem cravers”. By contrast, only 1 control craver (4%) scored above this range (CQ = 6.5). CQ scores were predominantly driven by strong responses to questions pertaining to expectancy (urges and desires to eat the craved sweet food in anticipation of the positive benefits of doing so) and purposefulness (urges and desires coupled with intent and planning to eat the craved sweet food).
Table 3 compares PD subjects with problem craving (PD cravers) \( (n=9) \) with PD subjects who were “non-cravers” \( (n=53) \) and control subjects. When compared with PD non-cravers using t-tests for continuous variables and fisher’s exact method for categorical variables, PD cravers were more likely to be female \( (p=0.0001) \), have a higher H&Y stage \( (t\text{-test: } p=0.0001, \text{fisher’s exact method: insignificant differences between scoring groups}) \), have a longer duration of disease \( (p=0.009) \), a lower Q-SIT score \( (t\text{-test: } p=0.0001; \text{fisher’s exact method: insignificant differences between scoring groups}) \) and higher SCI-90-R depression score \( (p=0.048) \). There were no significant differences in age, smoker status, UPDRS Part 3 score, levodopa equivalent doses, or anxiety and obsessive-compulsive SCL-90-R scores. PD subjects with problem craving did report a higher food frequency for sweet foods than non-cravers and control subjects, though it was only significant when compared with control FFQ scores \( (p=0.02) \).

When comparing PD cravers with control subjects, PD cravers also scored significantly lower on Q-SIT \( (t\text{-test: } p=0.001; \text{fisher’s exact method comparing scores of 0 and 2 } (p=0.0179); 0 \text{ and 3 } (p=0.0182)) \) and had higher scores on depressive and obsessive-compulsive subscales \( (p=0.013 \text{ and } p=0.013) \). There was no difference between PD cravers and controls in terms of age, gender, smoker status or anxiety.

When analyzing a patient’s ability to taste sweet, salty, bitter or sour, thresholds were extrapolated to a 4-point scale \( (1= \text{taste threshold at the lowest concentration and 4 = unable to identify taste, Figure 1}) \). There was no association found between taste thresholds and Parkinson’s disease (comparing PD patients and controls), or between
taste thresholds and craving in Parkinson’s disease (comparing PD cravers and PD non-cravers) for any of the four taste types fisher’s exact method. Additionally, there was no correlation between CQ scores in PD patients with problem craving and taste threshold for any of the four taste types (data not shown).

Amongst PD patients stating they craved sweets (n=33), 12 (36%) stated the craving was for chocolate foods, 7 stated that they craved cookies (21%), and 6 craved ice cream (18%). Pastries, sweet beverages, fruits, and candies were each craved by 2 PD subjects (6% each). CQs assessed according to type of sweet food craved did not demonstrate any apparent pattern, though cravings for chocolate, ice cream, and sweet beverages were the strongest cravings.

**Part Two**

To assess the prevalence of sweet craving in PD and the relationship of PD-related factors and other ICDs, 128 PD patients and 69 control subjects completed questionnaires as previously described. The average age of PD subjects was 63.8 years, and the average age of controls was 59.8 years (p=0.008). Average age at PD onset was 56 years (± 10.5), and average duration of PD at time of participation was 8 years (± 4.9). Mean UPDRS part III score assessed while on medications was 20.2 (± 11.4, n=94) and mean levodopa equivalent dose was 798.80 (± 491.3 mg). 80 subjects (63%) were taking a dopamine agonist at the time of participation.
We found the prevalence of sweet craving to occur in 5.5% of our sample of patients with PD and in 4.3% of controls (non-significant, p=0.36). Table 4 shows the prevalence of ICDs in our cohort of PD patients and controls; except for differences in compulsive gambling (p=0.048), there was no significance differences in the prevalence of ICDs between PD patients and controls.

Figure 2 shows the mean scores on the various questionnaires according to disease state and exposure to dopamine agonist medications. PD patients scored significantly higher than controls on SOGS (p=0.0006), and trended towards significance with higher scores on the CQ (p=0.064). When separating the PD group into those taking dopamine agonists (PD+DA) and those not taking a dopamine agonist (PD-DA), the PD+DA group scored significantly higher on SOGS (p=0.024), YBOCS-CUV (p=0.046), and CQ (p=0.046) than controls. The PD-DA group’s scores were not significantly different from controls on any of the questionnaires (Table 5).

Factors that positively correlated with scores on the CQ (Pearson’s correlation coefficient, r) included duration of PD (p=0.003), levodopa equivalents (p=0.009), history of OCD (p=0.044), and history of depression (p=0.049), while age at onset of PD negatively correlated with CQ scores (p=0.015) (Table 6). History of anxiety had a trend of significance in its positive correlation with CQ (p=0.086). The correlates of scores on the CQ and other ICD scales are shown in Table 6. Age at onset, duration of PD and history of OCD were the most common correlates.
The proportions of subjects with at least one compulsive behavior (CB) or craving were compared using the z-test for two proportions. 10.1% of controls (n=7) were found to have a CB or craving. When compared to the 12.5% (n=16) of all PD patients with a CB using a 1-tail confidence level of 95%, the difference was not significant (p=0.31). 13.8% (n=11) of PD patients taking a dopamine agonist were found to have a CB or craving, also non-significant when compared to controls (p=0.25). Only 10.4% (n=5) of PD patients not taking a dopamine agonist were found to have a CB. When compared to the proportion in controls using a 2-tailed z-test, differences were once again not significant (p=0.96). 6 PD patients and one control subject had more than one CB. As a group, PD patients with CBs (including craving for sweets) had a longer duration of PD (p=0.031) and younger age at onset (p=0.012), and scored significantly higher on all scales than PD patients without CBs (Table 7).

Taken together, levodopa equivalent doses and dopamine agonist equivalent doses were not significantly different in PD patients with a CB or craving compared to those without (Table 8). Of the 16 PD patients with an impulse control disorder or craving, seven subjects (1 in monotherapy) were taking pramipexole, three subjects (none in monotherapy) were taking ropinirole, 1 subject was taking pergolide (not in monotherapy), and two subjects were taking levodopa in monotherapy. The mean dopamine agonist equivalent doses in those with a CB or craving separated by type of dopamine agonist were also no different. The odds ratio for the presence of any
compulsive behavior or craving was 1.07 for pramipexole, 1.06 for ropinirole, and 0.31 for levodopa.
<table>
<thead>
<tr>
<th></th>
<th>Sweet</th>
<th>10%</th>
<th>25%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Salty</td>
<td>1.25%</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Sour</td>
<td>0.25%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Bitter</td>
<td>0.025%</td>
<td>0.1%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of PD and control subjects participating in a pilot study of sweet craving

<table>
<thead>
<tr>
<th></th>
<th>PD patients (N = 62)</th>
<th>Controls (N = 23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>64.4 years (±10.7)</td>
<td>64.4 years (±10.3)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>35M (56%)</td>
<td>7M (30%)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Mean PD Duration (± SD)</strong></td>
<td>7.1 years (±4.9)</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td><strong>Mean UPDRS – Pt. 3 (± SD)</strong> (N = 50)</td>
<td>26.7 (±12.2)</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td><strong>Mean Hoehn &amp; Yahr (± SD)</strong> (N = 50)</td>
<td>1.9 (±0.6)</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td><strong>Mean FFQ (± SD)</strong></td>
<td>14.8 (±9.0)</td>
<td>13 (±6.2)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Mean CQ (± SD)</strong></td>
<td>4.51 (±1.32) (N=33)</td>
<td>3.92 (±1.30) (N=9)</td>
<td>0.24</td>
</tr>
<tr>
<td>*<em>Mean Q-SIT (± SD)</em></td>
<td>1.27 (±0.9)</td>
<td>2.17 (±0.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Mean Depression subscale of SCL-90-R (± SD)</strong></td>
<td>1.0 (±0.85)</td>
<td>0.70 (±0.58)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Mean Anxiety subscale of SCL-90-R (± SD)</strong></td>
<td>0.9 (±0.77)</td>
<td>0.50 (±0.61)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Mean OCD subscale of SCL-90-R (± SD)</strong></td>
<td>1.2 (±0.85)</td>
<td>0.80 (±0.72)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*Using fisher’s exact method, there was a significant association between PD and lower Q-SIT scores when comparing Q-SIT scores of 0 (no correct answers) and 3 (all correct answers) (p=0.019) in PD patients and controls.
Table 3. Characteristics of PD patients with problem sweet craving (CQ>5.5) in a pilot study

<table>
<thead>
<tr>
<th></th>
<th>PD cravers (N=9)</th>
<th>PD non-cravers (N=53)</th>
<th>P value</th>
<th>Controls (N=23)</th>
<th>P value (vs. PD cravers)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs (SD)</strong></td>
<td>66.3 (±11.4)</td>
<td>64.0 (±10.7)</td>
<td>0.56</td>
<td>64.4 (±10.3)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3M (33%)</td>
<td>32M (60%)</td>
<td>0.0001</td>
<td></td>
<td>7M (30%)</td>
<td>0.524</td>
</tr>
<tr>
<td><strong>Current/Past Smoker</strong></td>
<td>4 Yes (44%)</td>
<td>21 Yes (40%)</td>
<td>0.41</td>
<td>10 Yes (43%)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>UPDRS-3 (SD)</strong></td>
<td>31.6 (±11.5)</td>
<td>25.9 (±12.3)</td>
<td>0.26</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td>N=7</td>
<td>N=43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>H&amp;Y</em> (SD)</em>*</td>
<td>2.10 (±0.38)</td>
<td>1.9 (±0.61)</td>
<td>0.0001</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td>N=7</td>
<td>N=43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PD duration (SD)</strong></td>
<td>10.9 (±5.90)</td>
<td>6.42 (±4.4)</td>
<td>0.009</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td><strong>Levodopa equivalents, mg (SD)</strong></td>
<td>382 (±242)</td>
<td>483 (±458)</td>
<td>0.52</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td><strong>FFQ (SD)</strong></td>
<td>19.3 (±7.7)</td>
<td>14.1 (±9.1)</td>
<td>0.11</td>
<td>13.0 (±6.2)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Q-SIT</strong> (SD)**</td>
<td>1.0 (±1.1)</td>
<td>1.32 (±0.89)</td>
<td>0.0001</td>
<td>2.17 (±0.72)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>SCL-90-R Anxiety (SD)</strong></td>
<td>1.10 (±1.10)</td>
<td>0.80 (±0.71)</td>
<td>0.29</td>
<td>0.50 (±0.61)</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>SCL-90-R Depression (SD)</strong></td>
<td>1.50 (±1.15)</td>
<td>0.90 (±0.76)</td>
<td>0.048</td>
<td>0.70 (±0.58)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>SCL-90-R OCD (SD)</strong></td>
<td>1.6 (±0.88)</td>
<td>1.10 (±0.83)</td>
<td>0.103</td>
<td>0.80 (±0.72)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*Using fisher’s exact method, no association was found between craving and H&Y scoring.

**Using fisher’s exact method, there was a significant association between craving in PD and lower Q-SIT scores when comparing Q-SIT scores of 0 and 2 (p=0.0179) and 0 and 3 (p=0.0182) between PD cravers and controls. There was no significant association between craving and Q-SIT scores when comparing scores for PD cravers and PD non-cravers.
<table>
<thead>
<tr>
<th></th>
<th>PD patients (N=128)</th>
<th>Controls (N=69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambling</td>
<td>3.9% (N=5)</td>
<td>0</td>
<td>0.048</td>
</tr>
<tr>
<td>Shopping</td>
<td>1.6% (N=2)</td>
<td>0</td>
<td>0.148</td>
</tr>
<tr>
<td>Computer use</td>
<td>1.6% (N=2)</td>
<td>1.4% (N=1)</td>
<td>0.475</td>
</tr>
<tr>
<td>Binge eating</td>
<td>3.1% (N=4)</td>
<td>2.9% (N=2)</td>
<td>0.465</td>
</tr>
<tr>
<td>Sexuality</td>
<td>6.3% (N=8)</td>
<td>4.3% (N=3)</td>
<td>0.290</td>
</tr>
<tr>
<td>Sweet craving</td>
<td>5.5% (N=7)</td>
<td>4.3% (N=3)</td>
<td>0.366</td>
</tr>
</tbody>
</table>
Table 5. Mean Scores on Various Questionnaires:
Control vs PD, Control vs PD: DA+, Control vs PD: DA-

<table>
<thead>
<tr>
<th></th>
<th>Control N=69</th>
<th>PD All N=128</th>
<th>p-value</th>
<th>PD: DA+ N=80</th>
<th>P-value</th>
<th>PD: DA- N=48</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOGS (SD)</td>
<td>0.13(0.48)</td>
<td>0.61(1.87)</td>
<td>0.0006</td>
<td>0.65(1.99)</td>
<td>0.024</td>
<td>0.54(1.68)</td>
<td>0.100</td>
</tr>
<tr>
<td>YBOCS-SV (SD)</td>
<td>1.46(2.69)</td>
<td>1.88(3.59)</td>
<td>0.35</td>
<td>2.03(3.72)</td>
<td>0.28</td>
<td>1.65(3.39)</td>
<td>0.75</td>
</tr>
<tr>
<td>YBOCS-CUV (SD)</td>
<td>2.46(3.81)</td>
<td>3.45(4.87)</td>
<td>0.12</td>
<td>3.95(5.26)</td>
<td>0.046</td>
<td>2.63(4.06)</td>
<td>0.82</td>
</tr>
<tr>
<td>YBOCS-BE (SD)</td>
<td>2.06(4.62)</td>
<td>2.10(4.54)</td>
<td>0.95</td>
<td>2.16(4.91)</td>
<td>0.90</td>
<td>2.00(3.88)</td>
<td>0.94</td>
</tr>
<tr>
<td>SCS (SD)</td>
<td>1.13(0.43)</td>
<td>1.16(0.40)</td>
<td>0.63</td>
<td>1.17(0.35)</td>
<td>0.54</td>
<td>1.15(0.47)</td>
<td>0.81</td>
</tr>
<tr>
<td>CQ (SD)</td>
<td>3.07(1.26)</td>
<td>3.42(1.28)</td>
<td>0.064</td>
<td>3.49(1.31)</td>
<td>0.046</td>
<td>3.32(1.22)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Table 6: Factors influencing scores on CB questionnaires in 128 PD patients  
(Pearson’s correlation coefficient, r)

<table>
<thead>
<tr>
<th></th>
<th>SOGS</th>
<th>YBOCS-SV</th>
<th>YBOCS-CUV</th>
<th>YBOCS-BE</th>
<th>SCS</th>
<th>CQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0770</td>
<td>-0.0705</td>
<td>-0.1565</td>
<td>-0.1562</td>
<td>-0.0818</td>
<td>-0.1014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>-0.0131</td>
<td>-0.0845</td>
<td>0.0517</td>
<td>0.1172</td>
<td>0.2884</td>
<td>-0.0516</td>
</tr>
<tr>
<td>Duration PD</td>
<td>0.0757</td>
<td>0.2152</td>
<td>0.1363</td>
<td>0.0836</td>
<td>0.3282</td>
<td>0.2615</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of PD</td>
<td>-0.1002</td>
<td>-0.1601</td>
<td>-0.2019</td>
<td>-0.1824</td>
<td>-0.2308</td>
<td>-0.2155</td>
</tr>
<tr>
<td>History of depression</td>
<td>0.0748</td>
<td>0.0597</td>
<td>-0.0339</td>
<td>0.1203</td>
<td>-0.1689</td>
<td>0.1745</td>
</tr>
<tr>
<td>History of anxiety</td>
<td>0.2128</td>
<td>0.1917</td>
<td>0.0005</td>
<td>0.1530</td>
<td>-0.0304</td>
<td>0.1525</td>
</tr>
<tr>
<td>History of OCD</td>
<td>0.2475</td>
<td>0.2146</td>
<td>0.1118</td>
<td>0.1528</td>
<td>0.2106</td>
<td>0.1786</td>
</tr>
<tr>
<td>Levodopa equiv. (mg)</td>
<td>0.0082</td>
<td>0.2034</td>
<td>0.1579</td>
<td>0.1046</td>
<td>0.0847</td>
<td>0.2300</td>
</tr>
<tr>
<td>UPDRS motor (n=94)</td>
<td>-0.0329</td>
<td>-0.0549</td>
<td>-0.2651</td>
<td>0.0580</td>
<td>-0.0890</td>
<td>0.0884</td>
</tr>
<tr>
<td></td>
<td>At least 1 CB (n=16)</td>
<td>No CB (n=112)</td>
<td>p value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD duration (yrs)</td>
<td>10.1 (5.82)</td>
<td>7.29 (4.68)</td>
<td>0.031</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS score (n=94)</td>
<td>18.22 (14.9)</td>
<td>20.41 (11.0)</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td>(n=85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60.2 (9)</td>
<td>64.3 (9.5)</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset PD</td>
<td>50.1 (9.0)</td>
<td>57.1 (10.4)</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa equiv. (mg)</td>
<td>955.5 (618.4)</td>
<td>779.5 (481.1)</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOGS</td>
<td>2.88 (4.24)</td>
<td>0.29 (0.86)</td>
<td>0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS-SV</td>
<td>5.31 (6.73)</td>
<td>1.39 (2.58)</td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS-CUV</td>
<td>8.63 (7.37)</td>
<td>2.71 (3.92)</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCS</td>
<td>1.83 (0.81)</td>
<td>1.07 (0.14)</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS-BE</td>
<td>7.19 (7.83)</td>
<td>1.40 (3.32)</td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CQ</td>
<td>4.89 (1.51)</td>
<td>3.22 (1.1)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 8. Levodopa equivalent doses of PD patients with and without ICD

<table>
<thead>
<tr>
<th></th>
<th>With ICD n=16</th>
<th>No ICD n=112</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total levodopa equivalent dosage</td>
<td>955.5±618.4</td>
<td>779.1±481.1</td>
<td>0.19</td>
</tr>
<tr>
<td>DA equivalent dosage</td>
<td>281.9±266.1</td>
<td>190.3±210.1</td>
<td>0.12</td>
</tr>
</tbody>
</table>
There was no association found between taste thresholds and Parkinson’s disease (comparing PD patients and controls), or between taste thresholds and craving in Parkinson’s disease (comparing PD cravers and PD non-cravers) for any of the four taste types using Fisher’s exact method.
Figure 2: Mean Questionnaire Scores for Controls, PD Patients, PD Patients on DAs, PD Patients not on DAs
DISCUSSION

This study was developed after the observation that several patients reported a craving for sweets after diagnosis and treatment of PD. Several lines of evidence suggest that this is a true phenomenon rather than being an epiphenomenon of aging or similar to trends in the general population. Levine et al (2003) studied alcohol-preferring rats and found that they consume more of a sucrose solution than non-alcohol preferring rats. This is supported by studies demonstrating that increased sucrose/saccharin consumption in rats also leads to greater self-administration of drugs of abuse, including morphine, cocaine, and amphetamine (DeSousa 2000, Gosnell 1995, Levine 2003) but when a glucose or saccharin solution is made available, self-administration of cocaine is reduced (Carroll 1989, Levine 2003). Others have found that ingestion of sucrose increased dopamine release in the nucleus accumbens, mostly in rats classified as high-sugar feeders (Hajnal 2001, Sills 1998) and administration of dopamine antagonists caused a reduction in the intake of sucrose solutions (Hsiao 1995, Weatherford 1990). Past studies have noted that the sweet taste of candies, chocolates and other cravable sweets is an indicator to our brain that the food has a high calorie per unit weight ratio (Green 2012) and these highly caloric foods tend to activate reward pathways in the brain (Fortuna 2010). Together, these studies suggest that there is a relationship between the intake of sweet substances and drugs of abuse, as well as dopamine mediated reward systems.
In a study of food craving in a general population sample, the target for craving was chocolate in 49% of subjects compared to baked goods in 11%, “something sweet” in 16%, and savory foods in 12% (Bruinsma and Taren, 1999). Wolz et al (2009) have since reported that chocolate consumption, though not sweet consumption in general, was significantly higher in a group of 274 PD patients compared to 234 household controls. The authors also found that PD patients were more likely to be older, male, and have depression.

In a functional MRI study of subjects reporting chocolate craving, Rolls and McCabe (2007) found activation of the mid and medial parts of the orbitofrontal cortex and ventral striatum, with a varied time response depending on whether a visual or actual taste stimulus was provided. Interestingly, similar areas of the brain are activated in PD patients suffering from pathologic gambling (Frosini 2010). This connection can be seen again in the effects of opioid receptor antagonists, like nalmefene and naltrexone, which bind to opioid receptors and block the body from responding to opiates and endorphins. This can have many effects, one of which is dampening the reported pleasantness of palatable foods (including sweets) in normal subjects (Kelley 2002, Yeomans and Wright 1991), and alleviating pathologic gambling in both non-PD subjects (Grant et al, 2006) and PD patients (Bosco 2012). Bosco et al found that treatment with naltrexone resulted in remission of pathological gambling in 3 PD patients when discontinuation of DAs and treatment with serotonin reuptake inhibitors did not improve the ICD. Together these studies support the notion that sweet cravings
in PD have a neuro-biologic basis, may share common pathophysiologic underpinnings with other disorders of impulse control, and may be related to dopamine-mediated reward systems.

In Part One of our study, we found that PD patients felt more anxious and reported more OCD symptoms than controls. They were also more likely to be male and have greater olfactory deficit. These findings are consistent with known population characteristics of PD. By contrast, we found that PD cravers, when compared with PD non-cravers, were more likely to be female, have more severe H&Y staging and have a longer disease duration (Table 3). PD cravers had significantly greater olfactory dysfunction and were more depressed than PD non-cravers, indicating that severity of olfactory loss and depressive symptoms amongst all PD patients are relevant to the presence of sweet craving. Levodopa equivalents were not different between PD cravers and PD non-cravers. In summary, we found that the determinants of craving in Parkinson’s disease are female gender, longer disease duration and greater PD severity, more advanced olfactory dysfunction and greater symptoms of depression. Thus, there were no relevant non-disease related factors that were associated with sweet craving, e.g., smoking, nasal surgery, taste perception, etc. This suggests that craving sweets in PD is intrinsic to the disease process and not simply related to general population trends.

The objects of sweet cravings in our cohort of patients were chocolate, cookies, ice cream, pastries, candies, fruits and sweet beverages. These foods are also the focus of
sweet craving in the general population, which tells us that the object of craving doesn’t necessarily change in PD.

In Part 2 of this study, scores on CQ, regardless of if a patient reported cravings or not, significantly correlated with duration of PD (positive), age at onset of PD (negative), history of OCD (positive), history of depression (positive) and total levodopa equivalents (positive), with trends to significance for correlation with history of anxiety (positive) (Table 6). Age at onset of PD was not examined in Part 1, but was assessed in Part 2 as a known factor associated with development of ICDs, and was found to significantly and negatively correlate with scores on CQ, similar to other CBs. When analyzed according to DA exposure, CQ scores were highest amongst PD patients exposed to a DA, followed by those unexposed to a DA, and finally control subjects (Table 5). As a group, PD patients scored significantly higher on the SOGS than controls. Similarly to craving sweets, this was determined mostly by dopamine agonist exposure, as the relationship was not significant in DA unexposed patients. These findings support our original conclusions from Part 1 that craving for sweets is a disease-related phenomenon and additionally, is possibly related to medications used to treat PD.

Furthering this notion is the positive correlation between total levodopa equivalents, which included calculations of dopamine agonist equivalent doses, and CQ scores (Table 6). This correlation can be attributed to the probable combination of both levodopa and dopamine agonists in a significant proportion of these patients. Indeed, the DOMINION study found that a combination of both therapies could increase the
likelihood of ICD development by nearly 50%. The DOMINION study also linked both DA and L-dopa treatments independently of one another to an increased likelihood of ICDs, but found that the DA association to ICDs was higher than the L-dopa association. Interestingly, the only other ICD that held a significant correlation with levodopa equivalent dosing in our cohort of PD patients was compulsive shopping. The reasons for this selectivity are unclear, but may pertain to sample size.

PD patients with at least one ICD (including craving for sweets) also had younger age at PD onset and longer PD duration (Table 7). We saw this relationship in part 1 of the study, and it also seems to be a consistent finding across ICD studies in PD (Kim 2012, Voon 2007, Leeman 2011). A possible explanation for this phenomenon may be that physicians often treat younger patients with DAs first and often at higher dosing to avoid and/or delay the motor complications of L-dopa treatment (Bastiaens 2013, Rana 2013).

Patients with ICDs were taking more PD medications including DAs, but this was not statistically significant, possibly due to sample size. The risk of developing an ICD on dopamine agonists was higher than with levodopa, as found in the DOMINON study. There was no difference in risk of ICD development between pramipexole and ropinirole, confirming it is a drug class effect, and excluding the possibility that the nature of the drug exposure determines the presence of an ICD.

In general, PD patients with at least one ICD including craving (regardless of type) scored significantly higher on all ICD scales (including craving). This suggests that
general trends to greater compulsivity exist amongst PD patients diagnosed with an ICD, but the reasons for manifestation as one CB over another are not clear. It also suggests that if one ICD is present, patients should be screened for and counseled about the presence of others, including craving for sweets.

Our correlation analysis (Table 6) across CBs demonstrated that factors that influence how PD patients answer questions about sweet craving are the same as factors that would influence how they answer questions about other compulsive behaviors, indicating that craving for sweets has the same demographic and disease-related determinants as other ICDs. Specifically, the phenomenon of craving for sweets in PD should be considered in the same category as other disorders of impulse control, and has features of a compulsive behavior.

In summary, this report finds that craving for sweets is a disease-related phenomenon in PD. It is most likely to occur in patients who are female with younger age of onset, longer duration of disease, a history of depression and/or OCD, and a higher Hoehn & Yahr staging. It may take the form of craving for chocolate, cookies, ice cream, candies or sweet beverages. DA exposure appears to play a significant role, and other disorders of impulse may also be present in individuals who crave sweets. As a phenomenon, sweet craving closely resembles ICDs in PD based on our findings. Notably, in the largest cross-sectional study conducted to date (Weintraub 2010), all factors for sweet craving in the present study are also reported as relevant factors for other ICDs.
We therefore suggest that the spectrum of ICDs in PD be expanded to include craving for sweets. Patients should be counseled about the spectrum of ICDs upon diagnosis and then continuously assessed for any developments throughout the course of PD therapy. Clinicians should evaluate their patient for any risk factors that have been associated with ICDs in PD and discuss these factors and different treatment options with their patient (Leeman 2011). This initial analysis may serve as a way of preventing the development of an ICD in an at-risk individual (Leeman 2011), or even minimizing the consequences of sub-threshold symptoms if already present. This first step is important because once an ICD has developed, it can be difficult to manage (Vilas 2012). The most effective treatment is to decrease or discontinue DA therapy (Bastiaens 2013, Leeman 2011, Nirenberg and Waters 2006). Nirenberg and Waters (2006) reported that in addition to other ICDs, craving for sweets improved after DA reduction. Some patients, however, may not tolerate this process due to development of dopamine agonist withdrawal syndrome, which may include panic attacks, anxiety, orthostatic hypotension, diaphoresis, fatigue, dysphoria, pain, and drug cravings (Bastiaens 2013, Vilas 2012). While DA dose reduction is certainly a reasonable strategy to consider if problematic sweet cravings occur, prospective studies are needed to verify the emergence of craving for sweets after PD diagnosis, relationship to PD treatment, and response to interventions.

Our study is limited by a number of weaknesses. One major weakness is the small sample size in Part 1. With only nine problem cravers with Parkinson’s disease in
the first part of our study, we were forced to use the less accurate t-test to analyze our continuous data, which meant that even when our p-values showed significance, they were less impactful than a z-test. When using fisher’s exact method for H&Y and QSIT scores, these low numbers also made it more difficult to find significance between groups. Our cut-off of the 75th percentile on the CQ in patients who self-identified as cravers may have artificially elevated the threshold for diagnosis of sweet craving, and we therefore may have under-reported the true prevalence of craving for sweets in PD in the 2nd part of the study. Indeed, 53% of patients in part 1 identified themselves as cravers, although a smaller percentage were designated “problem cravers”. This holds true of established ICDs as well, in which “sub-threshold” abnormal behaviors may exist but do not meet criteria for an ICD diagnosis. Our subjective clinical experience suggests that more than 5.5% of the PD population experiences craving for sweets, and it may in fact be more common than other ICDs. Similarly, the reported prevalence rates of various ICDs in our study (Table 4) differ from those in the published literature. The lack of standardized and comprehensive neuropsychological measures and the reliance on historical and self-reported symptomatology (rather than concurrently measured neuropsychiatric symptoms), likely account for a major proportion of this discrepancy. At the time this study was implemented, the self-administered Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP) (Weintraub 2009) had not been validated. Finally, we have drawn inferences regarding the biologic underpinnings of craving for sweets in PD from several lines of evidence in the basic
and clinical scientific literature, but did not measure these directly in our patients (e.g.,
functional MRI, measurement of how highly caloric foods activate reward pathways in
the brain, etc).

For the most part, however, our data was distributed with similar standard
deviations, allowing us to assume equal variances, which lent to more accurate results.
Furthermore, in the second part of our study, we had use of larger sample sizes,
allowing us to use z-tests in many cases. Another major strength in our study is that it
offers information on a subject that has been, for the most part, ignored in the previous
literature but may have relevance to our understanding of PD and disorders of impulse
control. Several significant associations were found, and are replicated in the context of
other known ICDs within our own study. Our findings regarding sweet cravings in the
PD population should be reproduced in a larger study.

The overlying goal of this study was to not only establish sweet craving as a
compulsive behavior in PD, but also to expand our knowledge on impulse controls
disorders in general. By increasing our awareness of this complication and by reaching a
greater understanding of what variables make impulse control disorders more likely to
develop, we can improve the quality of care that clinicians can provide for their patients.
REFERENCES


VITA

CAITLIN HARRINGTON BROWN
Born 1985
5423 Creekbend Dr • Houston, TX 77096
PHONE: (C) 832-421-6441
E-MAIL: C.HARRINGTONBROWN@GMAIL.COM

EDUCATION

Masters of Arts in Medical Sciences, Expected May 2013
Boston University School of Medicine, Boston, MA
First year Grade Point Average: 3.84

Bachelor of Arts in Political Science, December 2007
University of California, Los Angeles; Los Angeles, CA
Global Major Grade Point Average: 3.58 Overall Grade Point Average: 3.224

PUBLICATIONS / PRESENTATIONS / RESEARCH EXPERIENCE

Clinical Research in Neurology
Parkinson’s Disease Center and Movement Disorders Clinic
Baylor College of Medicine, Houston, TX


Biotechnology Student Intern
Applied Biosystems, Foster City, CA

• Student Intern responsible for conducting directed research using DNA sequencers such as ABI’s 3100; computer data entry of research findings
CLINICAL EXPERIENCE / PHYSICIAN SHADOWING

Neurology Research / Clinic Coordinator
July 2010 – June 2011
Parkinson’s Disease Center and Movement Disorders Clinic
Baylor College of Medicine, Houston, TX
- Assisted with patient care in the clinic by rooming patients, taking their vitals, reviewing current medications/allergies, and providing prescription/refill assistance; attended weekly video rounds to discuss challenging patient cases with faculty

Surgical Shadowing Rotation
July 2006 – August 2006
University of Glasgow Medical School, Glasgow, Scotland, UK
- I sought out and was admitted to a surgical placement designed for medical residents at Glasgow University.
- During my placement, I shadowed surgeons on surgical rounds and during breast cancer clinics, I scrubbed in to observe surgeons closely in the OR (GI Cancer, Breast Cancer) and I sat in on multiple disciplinary presentations of patients cases by surgeons, oncologists, and radiologists with the purpose of determining cancer treatment.

Surgical Shadowing
December 2005
Dr. Nicola Butler-Mooyoung, Chicago, IL
- Shadowed in surgery and on rounds

Surgical Shadowing
August 2002
Dr. Hamid Motamed, South San Francisco, CA
- Shadowed in surgery and on rounds

NON-MEDICAL WORK EXPERIENCE

Precalculus/Prealgebra Teacher
October 2012 – Current
St. Thomas Episcopal School, Houston, TX

Public Relations Intern
October 2008 – March 2010
Elmore Public Relations, Houston, TX

International Arbitration Project Assistant
January 2008 – January 2010
ConocoPhillips Company (Contractor through Providus), Houston, TX

HONORS AND ACTIVITIES
- 2009 NYC Marathon Finisher, November, New York, New York
- 2009 Half Marathon Finisher, April, Dallas, TX
• Prince Charles Pipe Band Member of 10 Years, San Francisco, CA, 1995-2005
• 2000 World Pipe Band Champion, Grade 2 with PCPB, Glasgow, Scotland
• 1999 Silver Award (Leadership), Diamond Crest Girl Scout Awards

VOLUNTEER WORK

Math and Science Tutoring  
**January 2013- current**
- Volunteer tutoring outside of classroom hours to help with math and science topics for other classes and the SAT.

March to Malawi, Boston, MA  
**March, 2012 - current**
- Part of a group of 40 individuals from around the world that is collectively walking 8,474 miles (the distance from the UK to Malawi) to raise money for RippleAfrica, a nonprofit organization that supports healthcare, education and environmental efforts in Malawi, Africa.
- Projects include running and/or assisting eight nursery schools, five primary schools, a secondary school and a secondary school bursary scheme, a community library, two community health clinics, a disabilities and rehabilitation project, tree-planting and fruit tree projects, fuel-efficient cookstoves, forest conservation, and more.

MAMS Program Advocate, Boston, MA  
**January, 2012 - current**
- Advocating on behalf of the Medical Sciences program at Boston University Medical School by contacting accepted students to offer advice, answer questions about the program, etc.

Pink Ribbons Project, Houston, TX  
**2009 – 2010 (inconsistently)**
- Served on the marketing/communications committee of this Arts-based Breast Cancer Awareness organization.
- Served to increase exposure of the organization and their work to help reach out to more cancer survivors and patients to provide support and resources.

81 Miles for a Cure, Various Locations  
**October 2008 – December 2009**
- Designed fundraising plan to run 81 competitive miles by the end of 2009 to raise money for Parkinson’s disease research through the Michael J. Fox Foundation’s grassroots organization “Team Fox.”
- Major races included the New York City 2009 Marathon, the Dallas Texas Half Marathon in April, 2009
- Minor races – 5K, 10K, and 5 Miles races across Texas in 2008 and 2009.
- Amount that was raised: $6,049. Fundraising Goal: $5,000.