Title: BRAIN STIMULATION METHOD FOR WEIGHT CONTROL

Abstract: Disclosed are methods for achieving weight loss or gain in a subject using deep brain stimulation (DBS). In one aspect the invention provides a method for achieving weight loss using deep brain stimulation, comprising positioning an electrical lead in the brain of a subject, in a target region of the brain associated with appetite or eating. Electrical stimulation is applied to the lead under conditions suitable to cause weight loss in the subject. The invention further provides methods of treatment for a wide variety of weight disorders, including conditions involving excess weight, e.g., obesity, and insufficient weight, such as eating disorders, e.g., anorexia nervosa, bulimia nervosa and binge-eating disorder.
For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.
BRAEV STIMULATION METHOD FOR WEIGHT CONTROL

CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

The invention relates generally to methods for achieving desired weight loss or weight gain by a subject, and to treatment methods for eating disorders leading to abnormal weight gain or loss, in particular health-threatening conditions that are unresponsive to conventional forms of treatment such as modification of diet and exercise. More specifically, the invention relates to the use of electrical stimulation of areas of the brain associated with appetite and eating, to achieve weight loss or gain.

BACKGROUND

Eating is controlled by many factors, including appetite, food availability, family, peer, and cultural practices, genetic makeup, and attempts at voluntary control. Disorders affecting the body weight of individuals are numerous and varied, and include conditions involving a state of overweight (e.g., obesity) or underweight (generally referred to as "eating disorders").

Body mass index (BMI) closely correlates with body fat and can help predict the development of health problems related to excess or inadequate body weight. BMI is calculated by dividing weight in kilograms by height in meters squared (or weight in pounds by height in inches squared and multiplied by 703). The U.S. National Institutes of Health identifies obesity as a BMI of 30 kg/m² or greater. Obesity is further broken down into Class I (BMI of 30-34.9 kg/m²); Class II (BMI of 35-39.9 kg/m²); and Class III (BMI of 40 kg/m² or greater), the latter also called extreme obesity.

Obesity is a significant risk factor for many serious conditions, including type 2 diabetes, dyslipidemia, hypertension, sleep apnea, ischemic heart disease, and nonalcoholic steatohepatitis, lower extremity edema, thromboembolic disease, respiratory insufficiency (Pickwickian syndrome), skin...
compression (ulcers), and fungal infections.

Approximately 30 percent of adults in the United States are obese, up from 15 percent two decades ago. As the prevalence rates continue to rise, most health care providers can expect to encounter obese patients and their associated medical problems in their practices.

Several forms of refractory obesity have been described. Some of these conditions have been linked to particular genetic loci. The most common form of obesity due to genetic causes is Prader-Willi syndrome (PWS), which is associated with absence of expression of the paternally active genes in the PWS-associated region on human chromosome 15q11-ql3. This syndrome is characterized by extreme overeating (hyperphagia), progressive obesity, as well as mental retardation, short stature, and hypogonadism.

On the other end of the scale are weight disorders involving states of extreme underweight, popularly termed "eating disorders." Dieting to a body weight leaner than needed for health is highly promoted by current fashion trends, sales campaigns for special foods, and in some activities and professions. Eating disorders involve serious disturbances in eating behavior, such as severe overeating with subsequent purgative activity or extreme and unhealthy reduction of food intake, as well as feelings of distress or extreme concern about body shape or weight. Researchers are investigating how and why initially voluntary behaviors, such as eating larger or smaller amounts of food than usual, at some point move beyond control in some people and develop into an eating disorder.

The main types of eating disorders are anorexia nervosa and bulimia nervosa. A third type, binge-eating disorder, has been suggested but has not yet been approved as a formal psychiatric diagnosis. Eating disorders frequently develop during adolescence or early adulthood, but some reports indicate then-onset can occur during childhood or later in adulthood. Females are much more likely than males to develop an eating disorder. Only an estimated 5 to 15 percent of people with anorexia or bulimia and an estimated 35 percent of those with binge-eating disorder are male.

There is recognition that many weight disorders are medical illnesses in which maladaptive
patterns of eating have a physiological basis, often with a psychological component. Eating disorders frequently co-occur with other psychiatric disorders such as depression, substance abuse, and anxiety disorders. People who suffer from eating disorders can experience a wide range of physical health complications, including serious heart conditions and kidney failure, which may lead to death.

Studies on the basic biology of appetite control and its alteration by prolonged overeating or starvation have uncovered great complexity. Results of some laboratory studies over the years, mainly in rodents and lower mammals, have led to the recognition that certain areas of the brain, in particular the hypothalamus, comprise collections of cell bodies (nuclei) involved in regulating sensations associated with hunger and thirst. In one of the earliest reports, it was demonstrated that lesions in the hypothalamus could induce abnormally increased appetite for food (hyperphagia) and obesity in rats (Hetherington and Ranson, 1942). Using the rat model, it was later shown that these animals became obese after hypothalamic lesions, despite limited availability of food, leading to the conclusion that a metabolic effect was involved (Cox and Powely, 1981).

In similar lesion studies using higher mammals, it was demonstrated that monkeys with lesions in the ventromedial nucleus of the hypothalamus exhibited hyperphagia and increased feeding-efficiency ratios, leading to obesity (Hamilton et al., Am. J. Physiology, Vol. 230 No. 3, March 1976).

Based in part on these studies, one form of therapy currently available to treat PWS and other forms of retractive obesity is surgical intervention in the brain, to lesion areas of the hypothalamus (Quaade, F. Lancet 1:267, 1974). Unfortunately, this approach is not always successful, carries significant risks, and is irreversible once the lesion has been made.

Several investigators have used deep brain stimulation (DBS) techniques at the experimental level to study the effects on eating behaviors and weight gain in several animal species (Brown et al., J. Neurosurg Vol. 60, June, 1984; Chabardes S., DEA, 1999; Takaki et al., American Physiol, 1992).

To avoid or reduce the complications of lesioning therapy for treatment of weight disorders in
human subjects, a reversible form of lesioning or brain stimulation effective for treating these conditions would be highly desirable.

SUMMARY OF THE INVENTION

The invention relates generally to methods for delivering deep brain stimulation (DBS) to target areas of the brain associated with eating and appetite control. The DBS weight control methods and treatments are reversible, and safer than lesion therapy.

In one aspect, the invention provides a method for achieving weight loss using deep brain stimulation (DBS). The method includes positioning an electrical lead in the brain of a subject, wherein the lead is positioned within a target region of the brain associated with appetite or eating. Weight loss is accomplished by applying electrical stimulation to the electrical lead under conditions suitable to cause loss of weight in the subject.

Some variations of the DBS method for weight loss utilize more than one lead. In some embodiments, two electrical leads are positioned bilaterally in anatomically or physiologically comparable anatomical target regions situated on the left and right sides of the brain. In other embodiments, electrical leads are positioned within two or more anatomically or physiologically distinct target regions of the brain.

In some embodiments of the method, the target region of the brain is the hypothalamus. An electrical lead can be positioned within a ventromedial hypothalamic nucleus of the brain of the subject. An electrical lead may also be positioned within a dorsomedial hypothalamic nucleus. In another embodiment, a lead is positioned at the border of a ventromedial and a dorsomedial hypothalamic nucleus of the brain.

In other embodiments, an electrode is positioned proximate to a hypothalamic nucleus. The electrode can be positioned in a lateral ventricle proximate to said nucleus.

The angle of the electrical lead with respect to the midline of the subject can vary in different embodiments of the method. In one preferred variation, the electrical lead is positioned at an angle of about 45° to the midline of the brain.

The method is practiced by applying electrical stimulation to the target region of the brain of the
subject. In variations of the method, electrical current is applied intermittently or continuously to at least one of the electrical leads.

In some embodiments utilizing more than one lead, the electrical current is applied alternatively to two electrical leads in target regions of the subject's brain.

In some embodiments of the method wherein the leads are in the hypothalamus, the frequency of the electrical current is low. In some embodiments, the frequency of the electrical current is between about 1.0 and 5.0 mA.

In another aspect, the invention provides a method of treatment for a weight disorder. The method includes positioning an electrical lead in the brain of a subject having a weight disorder, wherein the lead is positioned in a target region of the subject's brain associated with appetite or eating. Electrical stimulation is applied to the electrical lead under conditions suitable to cause a desired change of weight in the subject.

The method of treatment for weight disorders encompasses many variations appropriate to a wide variety of conditions in which the desired change is either a loss of weight or a gain of weight in the subject.

Some embodiments of the method are suitable for promoting weight loss in a variety of conditions.

These methods are expected to be particularly beneficial for treatment of severe obesity, and in particular forms of obesity that are refractory to conventional medical treatment, such as genetic forms of obesity, exemplified by Prader-Willi syndrome.

Other embodiments of the method are expected to be suitable for promoting weight gain in conditions such as anorexia nervosa, bulimia nervosa and binge-eating disorder.

Other aspects and advantages of the invention are discussed below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic diagram showing mapping of recognized areas of the brain of a primate.

Figure 2 is a photograph showing placement of two deep brain stimulation (DBS) electrodes in the brain of a monkey to induce weight loss, according to an embodiment of the invention.

Figures 3A and 3B are two photographs showing placement of a single electrode in the brain of a
monkey, according to an embodiment of the invention.

Figure 4 is a photograph and a superimposed drawing showing placement of an electrode in the brain of a monkey, according to an embodiment of the invention.

Figure 5 is a schematic diagram as in FIG. 1, showing the placement of an electrode at an angle to the midline, with its tip at the border of the ventromedial and dorsomedial hypothalamic nuclei, according to an embodiment of the invention.

Figures 6A and 6B are two photographs showing bilateral placement of two electrodes implanted at an angle of about 45 degrees to the midline in the brain of a monkey, according to an embodiment of the invention.

Figure 7 is a photograph as shown in FIG. 6B, with a superimposed drawing showing the placement of an electrode, according to an embodiment of the invention.

Figure 8 is a graph showing the reduction in weight over time of a monkey subject implanted with two DBS electrodes, according to an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods for using deep brain stimulation (DBS) techniques to stimulate selected groups of cells associated with weight control in the brains of subjects, and thereby achieve desired changes in weight in the subjects.

Unless otherwise defined, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Method for Weight Loss Using Deep Brain Stimulation

In one aspect, the invention provides a method for weight loss using deep brain stimulation. The method includes positioning an electrical lead in the brain of a subject, within a target region of the brain associated with appetite or eating. Upon placement of the electrode, electrical stimulation is applied to the electrical lead under conditions suitable to cause weight loss in the subject.
As used herein, the terms "deep brain stimulation" and "DBS" refer to a medical procedure in which an electrode is implanted in the brain of a subject such as a human patient. An electrical current is applied to the electrode, creating conditions that promote a desired physiological response or clinical outcome in the subject.

DBS involving human subjects is typically performed by a clinical team that includes neurologists, neurosurgeons, neurophysiologists and other specialists trained in the assessment, treatment and care of conditions having a basis in the brain or central nervous system. DBS is believed to have potential application in the treatment of a wide range of conditions, and presently has been shown to be effective in controlling symptoms of certain movement disorders, such as some types of Parkinson's disease, essential tremor, and dystonia, and has been approved by the FDA for treatment of these conditions.

Following selection of an appropriate subject and determination of the brain region to be targeted, precise placement of an electrode or lead in the subject's brain is carried out in an operating room setting, typically utilizing advanced brain imaging technology and stereotactic targeting. After administration of local anesthesia, the subject undergoing electrode implantation experiences little discomfort and, if the subject is a human, may be kept awake during the implantation procedure to allow communication with the surgical team.

Methods according to the invention can utilize any electrode or electrical lead suitable for DBS. The terms "electrode," "lead," or "electrical lead" are used interchangeably herein in their broadest sense, and include a stimulation lead, a sensing lead, a combination thereof, or any other elongated member such as a catheter, which may be usefully passed to a target in the brain.

Generally, stimulation of a target region in a subject's brain involves contacting the region with an electrode capable of delivering an electrical signal to the region. A variety of electrodes can be employed for delivering the stimulation. For example, suitable electrodes include the deep brain stimulation electrodes used in Katayama, "Characterization and Modification of Brain Activity with Deep Brain Stimulation in Patients in a Persistent Vegetative State: Pain-Related Late Positive Component of Cerebral
Evoked Potential,” Pace, 14:16-121 (1991), and the Medtronic™ DBS 3280 (Medtronic, Minneapolis, MN), which has flexible TEFLOM-SILASTIC™ coated, platinum iridium electrodes with 4 contacts, 4 mm tips, 2 mm mean tip separation, and an impedance of 5-7 kΩ within the brain, as described, for example, in Velasco et al., Electroencephalography and Clinical Neurophysiology 102:461-471 (1997).

Preferably the electrode is an implantable multipolar electrode designed for use with an implantable pulse generator that can be a radiofrequency controlled device operated by an external transmitter. The multipolar electrode contacts can allow for adjustment of frequency (or “rate”), amplitude, and pulse width within at least the following respective ranges: about 2-200 Hz, about 0.1-10 Volts, and about 50-500 microseconds. Preferably, the multipolar electrode contacts allow for adjustment in a broader range than those recited above, particularly toward higher intensities. Such preferred electrodes include a Medtronic™ 3387 electrode (Medtronic, Minneapolis, MN) and are described, for example, in Benabid et al., J. Neurosurgery, 84:203-214 (1996). Another suitable lead is a deep brain stimulation electrode combined with a microelectrode recording probe, for example as described in U.S. Patent No. 6,301,492 to Zonenshayn (2001) and in U. S. Patent No. 6,343,226 to Sunde et al. (2002).

At least one electrode of the subject invention is positioned within a target region of the subject's brain associated with appetite or eating (discussed infra). Electrodes used in accordance with the invention can be positioned in the brain by methods conventionally used. As is known in the art, the particular procedures used by teams of specialists skilled in DBS neurosurgery will vary according to the available equipment, training of the personnel and the circumstances of each case. Details of the surgical procedures employed by several groups are described, for example, in Benabid et al., Movement Disorders 17 (Suppl. 3): S123-129 (2002); and in Schrader et al., Movement Disorders 17 (Suppl. 3): S167-174 (2002).

Generally, the procedures for placement and testing of the single electrodes are divided into several steps including: mounting of a stereotactic ring (also known as a CRW head ring) on the patient's skull under general anesthesia; and imaging by high resolution stereotactic commuted tomographic (CT)
scanning of the head. The stereotactic CT scan is preferably preceded by high resolution, volumetric, three
telsa magnetic resonance imaging (MRI) in advance of placement of the stereotactic head ring.

Planning of the surgical target sites within the brain and trajectories for approach to the selected
targets is achieved using high quality MR images and computer software designed for stereotactic targeting
such as Stereoplan Plus 2.3 (Stryker-Leibinger, Friedburg, Germany); SNS 3.14 (Surgical Navigation
Specialists, Mississauga, Canada); or software which facilitates navigation in "atlas space" using a
three-dimensional orthogonal Cartesian coordinate system centered on the patient's mid-commissural point,
which is readily defined by identifying the anterior and posterior commissures (AC, PC, respectively) and a
non-collinear midpoint line in the patient's brain. Using these points as references, the target and trajectory
are selected in 'atlas space' and the corresponding coordinates on the stereotactic CRW head ring are
automatically generated and used to set the CRW ring.

Following selection of the target region and computer-assisted planning of the surgical approach as
described, the electrode is positioned in the brain of the subject through a burrhole that is made at a suitable
location in the subject's skull. The placement of the electrode within a millimeter or less of the optimal
target is generally required to improve symptoms and to avoid side effects. To improve accuracy of the
final electrode placement, placement of the electrode is preferably tested during the implantation procedure,
for example by microelectrode recording to measure characteristic electrical patterns produced by cells in
the target region. Methods for microelectrode recording for DBS electrode placement are described, for
example, in Schrader et al, supra.

The effectiveness of the electrode placement can be assessed intraoperatively by applying current
to the electrode (macrostimulation). With the patient awake and locally anesthetized, stimulation is
performed to define the borders of the target structures and to evaluate effects and side effects. The
microelectrode placement that shows the best results is used to determine the position of the permanent
electrode, which is positioned under fluoroscopic X-ray control. The electrode is fixed at the rim of the
burrhole, for example with a titanium miniplate. External macrostimulation with a screening device such as
a Model 3625 (Medtronic, Minneapolis, MN) is preferably performed immediately after fixation of the electrode, to reproduce the stimulation effects observed intraoperatively with the microelectrode, and to rule out unwanted side effects. Correct positioning of the electrode is subsequently documented by skull X-ray.

After placement, the electrode remains implanted and in a subsequent operation the patient under general anesthesia is subcutaneously implanted with a stimulator unit, such as an Intrell™ II (Medtronic, Minneapolis, MN), which is connected to the electrode to permit application of electrical current to the electrode.

At least one electrode of the subject invention is positioned within a target region of the subject's brain associated with appetite or eating. As used herein, the phrase "region of the brain associated with appetite or eating" is intended to broadly encompass any region of a subject's brain that is involved in control of the eating behavior of the subject. As discussed, some regions of the brain have been discovered to be associated with control of sensations of hunger and satiety, although it is likely that others, for example target sites in the thalamus, have yet to be elucidated.

In some embodiments of the method, more than one electrical lead is implanted in the subject's brain. In variations of the multiple lead embodiments, an electrical lead is positioned in two anatomically or physiologically comparable target regions situated, for example, bilaterally (on the left and right sides of the brain). In other embodiments, two or more electrodes are positioned remote to one another within the same target region. As used herein, the two or more leads can be "remote from one another" if the electrical stimulation from the two or more electrodes affects two or more anatomically or physiologically distinct regions of the brain, or if the fields of electrical stimulation generated by two leads within a particular target region of the brain do not overlap.

As used herein with respect to identifiable regions of the brain, the term "anatomically or physiologically distinct" refers to target regions of the brain that may be distinguished and localized to specific positions in 3-dimensional space by suitable techniques well known to those of skill in the art.
Typically such regions are comprised of cells or fibers with recognizable functional or physiological activity which may be detected, for example, by microelectrode recording. The anatomical distribution, spatial mapping coordinates within the skull, and functional significance of distinct groups of human and animal brain cells have been extensively studied and are the subject of numerous medical treatises in the field of functional neuroanatomy and neurosurgery. See, for example, well known stereotaxic atlases such as Schalebrandt and Baily, and Schalebrandt and Wharren and Buren et al., Variations and Connections of the Human Thalamus, Springer-Verlag, New York (1972).

In some preferred embodiments of the method, a target region of the brain is the hypothalamus. From studies of brain damage such as lesions affecting particular neuroanatomical pathways, there is recognition that a region of the brain associated with appetite or eating includes areas within the hypothalamus or proximate to the hypothalamus.

In some embodiments of the method, a target region for positioning an electrical lead is within the hypothalamus. The target region can be in a nucleus of the hypothalamus, such as a ventromedial nucleus or a dorsomedial nucleus, or in some embodiments the target region is at the border between these nuclei.

In yet other embodiments of the method, the electrode is positioned proximate to the hypothalamic nuclei, but at some distance from them. For example, the lead can be placed in a ventricle adjacent to the hypothalamic nuclei, such that its field of stimulation extends to these regions.

The angle of approach used in positioning the electrode in the brain can be any angle that avoids vulnerable sites along the trajectory to the target region. In one embodiment of the method, the lead is positioned at an angle of about 45° with respect to the midline of the brain. Specific embodiments are described and illustrated, for instance, in Example 3, and FIG. 5.

In the method of weight loss, electrical stimulation is applied to the electrical lead under conditions suitable for causing weight loss in the subject. As is routine in the practice of DBS methods, initiation and optimization of the electrical stimulation therapy is achieved in a series of DBS programming sessions with a health care specialist, during which adjustments are made to DBS settings (such as pulse width, frequency,
and amplitude) according to the individual patient's condition and needs, the site of electrode placement within the brain, and the patient's weight loss response upon testing.

As discussed, DBS therapy is reversible and advantageously can be tested and tailored to the subject's responses. To achieve the best outcome, many variations of the methods of applying the electrical stimulation are possible. For subjects implanted with a single electrode, electrical current can be applied intermittently, or continuously. In subjects having two leads, current can be applied alternatively to the two leads, or to both leads concurrently.

The frequency of the current may be an especially important factor to vary. Some studies suggest that low frequency stimulation may be preferable for weight loss.

For some embodiments of the method in which an electrode is implanted in the hypothalamus, preferably the voltage of the electrical current is between about 1.0 and 5.0 mA.

**Method of Treatment for Weight Disorders**

In another aspect, the invention provides a method of treatment for a weight disorder. The method comprises positioning one or more electrical leads in the brain of a subject having a weight disorder, wherein the leads are positioned within a target region of the brain associated with appetite or eating. Appropriate electrical stimulation is applied to the electrical leads under conditions suitable to cause a desired change in the weight of the subject.

The method is believed to be particularly appropriate for treatment of weight disorders that are refractory to conventional therapy to promote the desired weight change.

The method can be applied to conditions in which the desired change is a loss of weight in the subject, or a gain of weight in the subject.

One embodiment of the method is directed to treatment of weight disorders involving obesity. Subjects suitable for treatment by the method include, but are not limited to, those having genetic forms of obesity, for example Prader-Willi syndrome.

Other embodiments of the invention encompass treatments for conditions involving undesired
weight loss, for example anorexia nervosa, bulimia nervosa, binge-eating disorder, and the like.

Suitable electrode placement target sites and conditions of stimulation will vary with the individual subject's anatomy and the medical condition to be treated, and can be determined and appropriately adjusted by varying the duration, frequency, current, and location of the electrical stimulation and monitoring weight gain or loss, and other indicators of health.

The invention is further illustrated by reference to the following non-limiting examples.

EXAMPLES

The following Materials and Methods are generally useful in testing and carrying out the methods of the invention.

1. Baseline Measurements.

Several baseline measurements can be used to assess the efficacy of the inventive procedures in an animal subject, before and following placement of electrodes in the brain.

Weight and Feeding Behaviors:

Typically, four preoperative weight measurements can be made to establish the baseline weight of a subject. Assessment of baseline consumption is performed, for example, by observing during two daily *ad libidum* meal sessions and determining caloric intake.

Laboratory Measurements:

Hormonal Levels:

Effects of DBS on hormone levels can be determined by measuring hormone levels, typically in a blood sample of the subject. Suitable hormones for monitoring include Cortisol, ACTH, aldosterone, TSH/T4, LH, FSH, prolactin, GH, glucagons, LPL, FFA, leptin, and catecholamines. Hormone levels can be measured by suitable techniques, well known in the art.

Electrolyte Levels:

Suitable electrolytes to be monitored can include: \( \text{Na}^+ \), \( \text{K}^+ \), \( \text{Cl}^- \), BUN, Cr, glucose, \( \text{Ca}^{2+} \), \( \text{Mg}^{2+} \), \( \text{PO}_4 \), and serum osmolality.
Vital Signs:

Suitable vital signs to be monitored include: heart rate, blood pressure, respiratory rate and temperature.

Qualitative Behavior:

A useful record for animal behavior can be obtained by videotaping. Assessment of feeding and non-feeding behavior can be assessed by standard methods, for example using the Koegler scale.

Example 1- Bilateral Stimulation of Ventromedial and Dorsomedial Hypothalamic Nuclei in a Subject by Deep Brain Stimulation (DBS).

This example describes DBS stimulation of hypothalamic nuclei in a subject using bilateral electrodes positioned proximate to these nuclei in the third ventricle.

Materials and Methods:

In a study to assess efficacy and safety of the DBS procedure, one macaque (subject H-O; #N238) received two implants in the third ventricle via a lateral ventricular puncture. Passage of monopolar electrodes (Itrel I) was made through the foramen of Monroe using standard stereotactic procedures.

The purpose of this study was to stimulate bilateral ventromedial (VMH) and dorsomedial (DMN) hypothalamic nuclei at both high and low frequencies, to determine if this treatment can modify feeding behavior/metabolism, resulting in a stable change in global body weight. Under these conditions, stimulation at high frequency would be predicted to result in inhibition of the VMH/DMN, with resultant global increase in body weight. By contrast, low frequency stimulation would be expected to result in a global decrease in body weight.

Results:

Monkey H-O (# N238), a male, was initially implanted on August 24, 2002. A schematic diagram showing mapping of brain regions is shown in FIG. 1. In the diagram, the position of the hypothalamic nuclei is indicated by VMHVL. The positions of the two implanted electrodes in subject H-O are shown in FIG. 2.
To determine the effect of DBS, subject H-O was stimulated at both high and low frequencies at varying voltages. No appreciable effects on his global body weight or hormonal profiles were obtained one week after each change. Although X-ray evaluation had revealed no gross changes in electrode position relative to the time of original surgery, this could not be definitively ruled out without repeating the electrode imaging procedure (ventriculography).

Monkey H-O was returned to the operating room for a second procedure. The electrode tip was found to be slightly posterior to the intended target and the animal was re-implanted in the third ventricle using the identical technique, approached from the contralateral side.

Following the second implantation procedure, high frequency stimulation was performed systematically over a period of months using several varying parameters. No effect was observed on either global body weight or laboratory profiles. On June 16, 2003, subject H-O was changed to low frequency stimulation at 4.0 V. The animal exhibited no change in body weight or lab profile during the period of study.

On July 15, 2003, monkey H-O externalized the electrode, damaging the wiring. This event necessitated complete removal of the hardware, ending the study of this subject. Nevertheless, the pilot study demonstrated the safety of the procedure, as evidenced by the continuous good health of the implanted monkey during and after the study.

Example 2- Unilateral DBS Stimulation of Ventromedial and Dorsomedial Hypothalamic Nuclei in a Subject.

This example describes unilateral DBS stimulation of hypothalamic nuclei at high and low frequencies.

The purpose of this Example was to determine if stimulating the unilateral ventromedial (VMH) and dorsomedial (DMN) hypothalamic nuclei at high and low frequencies could modify feeding behavior/metabolism and result in a stable change in global body weight. As in the previous example, high frequency stimulation is expected to result in inhibition of the VMH/DMN, resulting in a global increase in
body weight, and low frequency stimulation is predicted to result in a global decrease in body weight.

Monkey subject H-I (#51264) was implanted unilaterally, directly in the VMHZDMN hypothalamic nucleus. Positioning of the electrode was intraparenchymal, on the right side, and was performed using methods generally as described above. More specifically, the electrode was placed at the following coordinates- X: 1.3 mm lateral from midline third ventricle; Y: 1.3 mm posterior to the anterior commissure (AC); Z: inferior border of contact 0-1 mm above the floor of the third ventricle. Images of the implanted electrode in the brain of monkey H-I are shown in FIGS. 3A, 3B, and 4.

DBS stimulation was commenced approximately two months following surgery. Various parameters were tested, including both high frequency stimulation (HFS) and low frequency stimulation (LFS). No significant weight changes were produced in this subject by the end of the test period.

Example 3- Bilateral Stimulation of Ventromedial and Dorsomedial Hypothalamic Nuclei by Electrodes Implanted at an Angle to the Midline.

This example describes bilateral DBS stimulation of hypothalamic nuclei in a subject using electrodes positioned at a 45° angle to the midline.

Li this surgical approach, monkey subject H-3 underwent bilateral intraparenchymal VMH/DMN implantations at 45 degrees off the midline. Figure 5 is a schematic diagram showing the angle of approach of electrodes in relation to the mapped areas of the brain. The tip of the electrode is positioned at the border of the VMH-DMN. The positioning of the electrodes in the brain of subject H-3 is shown by ventriculography in FIGS. 6A, 6B and 7.

This subject was used to test whether weight loss could be achieved using low frequency stimulation (LFS) of the VMH/DMN. Unilateral stimulation on the left side was started using the following settings: contact 0; Voltage (V) =1.25 mA; Frequency (F) =25 Hz; PW=60.

After one week of stimulation using these settings, no changes were seen in food intake or weight. The voltage was then increased to 3.0 mA. Stimulation on the right side, or bilateral stimulation, is also possible using this bilateral approach. Changes in weight loss over time in subject H-3 are shown in Fig. 8.
Example 4 - Comparative Regimens for Testing Efficacy of DBS Treatments.

The following Example provides two paradigms for a study design using experimental animals (in this case 5 monkeys, A, B, C, D, and E). The paradigms are useful to compare several variations of DBS procedures, to determine which provides the most efficient weight loss. Those of skill in the art will recognize that many other variations are possible.

In Paradigm 1, monkeys A-D undergo bilateral VMH/DMH implantation as described in Examples above. Monkey E, a control, undergoes bilateral implantation of electrodes in a subcortical, nonhypothalamic site such as the subthalamic nucleus (STN). Following bilateral implantation of the electrodes and a stabilization period, monkeys A and B undergo continuous bilateral VMH/DMH low frequency stimulation (LFS) that is titrated to maintain a target weight 20% below the baseline weight for a period of 8 weeks. Concurrently, monkeys C and D undergo continuous bilateral VMH/DMH high frequency stimulation (HFS) that continues for the duration of the LFS of Monkeys A and B. Monkey E undergoes continuous bilateral STN LFS that also continues for the duration of stimulation of monkeys A-D.

In Paradigm 2, involving monkeys designated A-E as described above, monkeys A and B are treated as described in Paradigm 1. Monkey C receives bilateral VMH/DMH LFS that is titrated to a target weight 20% below the baseline weight for a period of 8 weeks. Monkey A receives bilateral VMH/DMH HFS that continues for the duration of the LFS of monkey C. Monkey E receives bilateral STN HFS that also continues for the duration of monkey C's LFS. Monkeys B and D receive no additional stimulation during this phase of the experiment.

In both paradigms, the animals are weighed daily and hormonal/electrolyte levels are periodically monitored, for example weekly. The exact quantity of food consumed (chow, fruit, liquid diet, etc.) is recorded immediately following each of the twice-daily meal sessions. Water consumption (mL) is recorded once daily.
REFERENCES

It is believed that a review of the following references will increase appreciation of the present invention.


Chabardes, Stephan, 1999, DEA.


Hamilton et al., Am. J. Physiology, 1976, Vol. 230 No. 3 March


The disclosures of all references cited herein are incorporated herein by reference in their entireties. The invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements within the spirit and scope of the invention.
What is claimed is:

1. A method for achieving weight loss using deep brain stimulation, comprising:
   (a) positioning an electrical lead in the brain of a subject, wherein said lead is positioned within a target region of the brain associated with appetite or eating; and
   (b) applying electrical stimulation to said electrical lead under conditions suitable to cause weight loss in the subject.

2. The method according to claim 1, wherein an electrical lead is positioned in two anatomically or physiologically comparable target regions situated on the left and right sides of the brain.

3. The method according to claim 1, wherein an electrical lead is positioned within two or more anatomically or physiologically distinct target regions of said brain.

4. The method according to any of claims 1-3, wherein the target region of the brain is the hypothalamus.

5. The method according to claim 4, wherein the target region is a ventromedial nucleus of the hypothalamus.

6. The method according to claim 4, wherein the target region is a dorsomedial nucleus of the hypothalamus.

7. The method according to claim 4, wherein the target region is at the border of a dorsomedial and ventromedial nucleus of the hypothalamus.

8. The method according to any of claims 5-7, wherein the electrode is positioned in a ventricle proximate to said ventromedial or dorsomedial nucleus of the hypothalamus.

9. The method according to any of claims 6-8, wherein the electrical lead is positioned at an angle of about 45° to the midline of the brain.

10. The method according to any of claims 1-9, wherein the electrical stimulation is applied intermittently to said electrical lead.
11. The method according to any of claims 1-9, wherein the electrical stimulation is applied continuously to said electrical lead.

12. The method according to any of claims 1-9, wherein the electrical stimulation is applied alternatively to two or more electrical leads positioned in target regions of the subject's brain.

13. The method according to any of claims 1-9, wherein the electrical stimulation is applied concurrently to two or more electrical leads in target regions of the subject's brain.

14. The method according to any of claims 11-13, wherein the electrical stimulation is of low frequency.

15. The method of any of claims 11-14, wherein the voltage of the electrical stimulation is between about 1.0 and 5.0 mA.

16. A method of treatment for a weight disorder, comprising:
   (a) positioning an electrical lead in the brain of a subject having a weight disorder, wherein said lead is positioned within a target region of said brain associated with appetite or eating; and
   (b) applying electrical stimulation to said electrical lead under conditions suitable to cause a desired change in the weight in the subject, thereby treating the weight disorder.

17. The method according to claim 16, wherein the weight disorder is refractory to conventional therapy to promote the desired weight change.

18. The method according to claim 16, wherein the desired change is a loss of weight in the subject.

19. The method according to claim 16, wherein the desired change is a gain of weight in the subject.

20. The method according to claim 18, wherein the weight disorder is obesity.

21. The method according to claim 19, wherein the weight disorder is selected from the group consisting of anorexia nervosa, bulimia nervosa and binge-eating disorder.
22. The method according any of claims 16-21, wherein an electrical lead is positioned in two anatomically or physiologically comparable target regions situated on the left and right sides of the brain.

23. The method according any of claims 16-21, wherein an electrical lead is positioned within two or more anatomically or physiologically distinct target regions of said brain.

24. The method according to any of claims 16-23, wherein the target region of the brain is the hypothalamus.

25. The method according to claim 24, wherein the target region is a ventromedial nucleus of the hypothalamus.

26. The method according to claim 25, wherein the target region is a dorsomedial nucleus of the hypothalamus.

27. The method according to claim 24, wherein the target region is at the border of a dorsomedial and ventromedial nucleus of the hypothalamus.

28. The method according to any of claims 24-27, wherein the electrode is positioned in a ventricle proximate to said ventromedial or dorsomedial nucleus of the hypothalamus.

29. The method according to any of claims 23-28, wherein the electrical lead is positioned at an angle of about 45° to the midline of the brain.

30. The method according to any of claims 16-29, wherein the electrical stimulation is applied intermittently to said electrical lead.

31. The method according to any of claims 16-29, wherein the electrical stimulation is applied continuously to said electrical lead.

32. The method according to any of claims 16-29, wherein electrical stimulation is applied alternatively to two or more electrical leads positioned in target regions of the subject’s brain.

33. The method according to any of claims 16-29, wherein the electrical stimulation is applied concurrently to two or more electrical leads in target regions of the subject’s brain.
34. The method according to any of claims 16-29, wherein the electrical stimulation is of low frequency.

35. The method according to any of claims 16-34, wherein the voltage of the electrical stimulation is between about 1.0 and 5.0 mA.
FIG. 8