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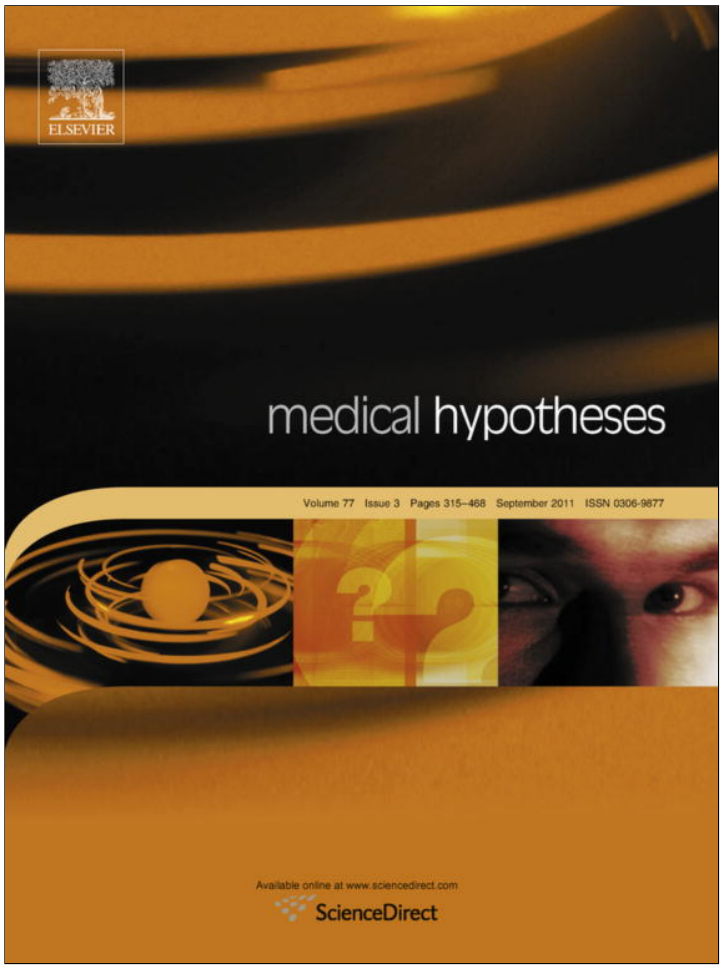

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Obesity and the brain ☆

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ABSTRACT

The world-wide increase in obesity has markedly stimulated research on the possibility that its cause can be found the brain. However, this research has produced little that can be used to treat obesity. The reason for the limited success of this approach may be that it relies on the hypothesis that the brain controls behavior. We suggest that this hypothesis is an artefact of the powerful tools used in behavioral neuroscience and that the brain has a permissive rather than causal role in eating behavior. Drugs affecting brain function are largely ineffective in treating obesity and may remain ineffective. Instead, we hypothesize that humans need external support to control body weight because they have evolved to pay a high physical price for food and are able to eat large amounts of food without constraints when that price is minimal. Two randomized controlled trials verify the hypothesis that support on how to eat normally and how to feel a normal level of fullness by use of on-line, real time feedback on a computer screen enables under- as well as overweight patients to adjust their eating behavior and improve their health.

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The rise and decline of hypothalamic homeostasis

In 1901, Fröhlich [1] reported that a patient with a pituitary tumor was obese and three years later Erdheim [2] suggested that the obesity was caused by damage to adjacent hypothalamic tissue. Soon afterward, technical developments made it possible to manipulate selected regions in the brain of experimental animals and after 50 years of research a theory of hypothalamic control of eating behavior had emerged [3]. Physiologists had already suggested that the body strives to maintain equilibrium and in line with this it was argued that body weight is kept stable because eating behavior is controlled by excitatory and inhibitory centers in the hypothalamus. The hypothalamic theory of body weight homeostasis remained essentially the same after another 50 years of research [4]. The difference is merely that while hypothalamic excitation and inhibition were previously studied as anatomically distinct phenomena, they are now thought to be chemically mediated and to some extent anatomically overlapping.

It is estimated that as many as 30% of the American people have become obese, i.e., they have a body mass index > 30 kg/m^2, over a period of about 30 years. By 2050 obesity is predicted to affect 60% of adult men, 50% of adult women and 25% of children [5]. This situation is obviously inconsistent with the existence of hypothalamic centers that keep body weight constant. Yet research on hypothalamic homeostasis continues. Obesity genes have now been found and as the associated gene products are expressed in the hypothalamus and in a few extrahypothalamic sites obesity is considered a "hypothalamic disease", a "complex genetic disease", an "epidemic disease" and "a product of life style choice" [4]. While this theory was expressed more clearly a few years ago [4], than it is today: "Many ... genes are expressed ... in the hypothalamus ... known to play a major role in susceptibility to obesity" [6], it remains the same theory. Sadly, the theory has offered virtually nothing that can be used to manage the problem of obesity; an authority recently stated: "The obesity problem is unsolved, and looks like it's going to stay that way for quite some time", and fewer drugs are available for treatment today than five years ago [7].

The failure of neuroscience to explain the problem of obesity begs the question why? We will attempt an answer and launch an alternative hypothesis and a method for how problems of body weight can be treated.

Obesity: disease, epidemic or life style?

A disease can be defined as an impairment of normal physiological function affecting part or all of an organism [8]. It seems unlikely if at all possible, that as many as 100 million people in the USA have developed a hypothalamic disease at a rate which matches the development of obesity in this country. An increase in a brain disease at such a rate has not occurred in the history of neurology. There is probably nothing wrong with the brain of obese people and it is unlikely that there are genes that have caused a third of the population of the USA to develop a disease in a decade or two.

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An epidemic is often thought of as an infectious disease, one that develops and spreads rapidly among people through a specific kind of contact [8]. On this definition, it is obviously incorrect to say that there is an obesity epidemic. There are many examples of rapidly spreading infectious diseases but a phenomenon should not be labeled an epidemic simply because it increases quickly.

Some philosophers may disagree, but it is generally assumed that people use their free will in selecting a life style that reflects their values and attitudes [8]. It makes no sense to say that 100 million Americans have recently chosen to eat so much food that they get obese and that they value being obese.

Viewing obesity as an epidemic brain disease or a life style violates semantic conventions. Also, these labels offer little in the way of explanation.

If our brain is unable to control how we eat, how did the idea that the brain controls behavior develop?

Brain control

The thought that different functions are localized to different parts of the body paved the way for mechanistic physiology in the seventeenth century [9]. For example, Descartes wrote: "I postulate that the body be nothing other than a machine ... all the parts necessary for it to walk, eat, breath ... can be imagined to proceed from matter, and to depend only on the arrangement of the organs" [9]. As a result, machine models of eating behavior appeared (Fig. 1).

Behavioral neuroscience, the study of brain and behavior, also started at this time. Parts of the central nervous system were experimentally removed and loss of function and alterations in physiology and behavior were observed. The results were startling. The heart continued to beat for hours and animals were able to walk after removal of the brain but not the medulla. The analysis of such results could read: "The immediate *cause* (italics added) of muscular contraction ... appears evidently to be lodged in the brain" [9].

The idea that the brain controls behavior was born long ago and has remained the preferred interpretation in behavioral neuroscience. Hence, the clinical observation that an obese patient had hypothalamic damage associated with a pituitary tumor and the finding that a rat with an experimentally induced lesion in the corresponding area of the brain overeats until it has doubled its body weight provided evidence for the existence of a hypothalamic center that controls satiety [3]. The list of such compelling experimental results continues to grow today with reports that mice get twice as big as normal if their hypothalamic eating center has been genetically modified [4]. It has even been suggested that the cause of the entire scenario of the metabolic consequences in human obesity is lodged in the brain [10].

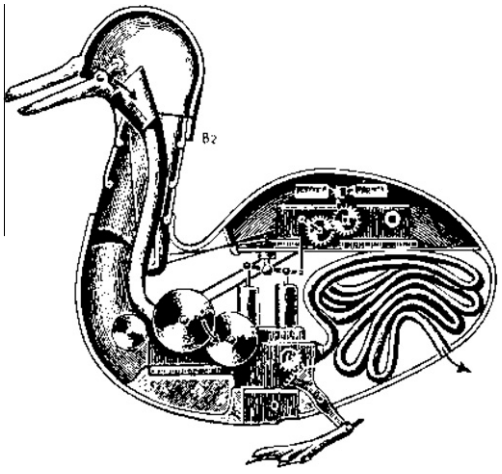

Fig. 1. The mechanical duck, a machine that eats, digests and excretes food. The brain was not included in this model [15].

The dramatic findings in behavioral neuroscience over many years have enforced the view that the brain *controls* behavior, i.e., that the *cause* of a change in behavior can be found in the brain.

But what is cause and effect in behavioral neuroscience?

Causation

David Hume outlined the relationship between cause and effect in the middle of the eighteenth century. Two events are causally related if the first event occurs before the second and if they always occur together and are located closely together in time and space. Bertrand Russell and others added some details, but Hume's analysis of causation holds true even today.

None of Hume's three conditions for causality is fulfilled for the relationship between brain function and eating behavior as studied by behavioral neuroscientists. Some events may take place in the brain and elsewhere in the body before and after eating, but these are no more likely causes than effects of eating [11,12]. In fact, no-one knows why we start to eat. The only necessary condition is the presence of food. For example, a rat offered a diet rich in fat and carbohydrate eats and gains as much weight as a rat with a hypothalamic lesion [13]. The role of the brain in this situation is obviously to allow excessive eating and whatever has happened in the brain once the rat is obese is the result, not the cause, of all the eating.

It has been suggested that those with the greatest capacity to eat when food is abundant are best fitted to survive ensuing periods of food shortage and that human evolution has been dominated by marked fluctuations in the availability of food, including long periods of starvation [14]. This phenotype is, however, normally combined with a high physical price for food, i.e., humans are able to maintain a low healthy body weight only if they have to work hard to obtain food. Once they obtain the food, no diets, genes or hypothalamic satiety centers prevent them from eating; evolution has not favoured the development of mechanisms of satiation [14]. Under such conditions, the best brain is one that allows us to eat under a variety of circumstances rather than one that strives to keep our body weight constant. What is the best design for such a brain?

Neural plasticity

"The brain happens to be a meat machine" – Marvin Minsky [15].

Ramon y Cajal, a founder of neuroscience, believed that we can all become scientists. Such is the plasticity of our brain that if we just engage in scientific work it will gradually adapt and one day it will be indistinguishable from the brain of scientists [16]. The idea that the brain is modified by experience is an old one but, due to technical constraints, it was verified only recently. We now know that the brain responds to various types of experience by growing new neurons and re-arranging its anatomical and chemical connections [17]. Previous orthodox theories of "brain control" of behavior have been gradually replaced by much more flexible models emerging from discoveries of neural plasticity: "The brain of adult homeothermic vertebrates exhibits a higher degree of morphological neuroplasticity than previously thought" [18], "the adult brain is much more resilient and adaptable than previously believed" [19]; with plasticity extending even across different sensory modalities and their neural coding [20].

The discovery of neural plasticity, perhaps the "meat" part of Marvin Minsky's machine brain, has generated a, somewhat less

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charismatic, view of the brain as a "liquid state machine" [21]. By contrast, attempts to construct eating machines, such as the mechanical duck (Fig. 1) or the neural machine made up by hypothalamic centers have not taken the "meat" or "liquid" part of the machine into consideration. The view of the brain as a controller of eating behavior is outdated and will probably continue to generate results that offer little help in understanding and treating obesity.

However, it is long known that neurosecretory cells of the hypothalamus are structurally rearranged in response to the hormonal secretions of lactation [22]. This observation was confirmed more recently by the finding that hypothalamic neurons that are engaged in body weight regulation also adapt to what goes on. Thus, in the presence of the hormones associated with eating, hypothalamic neurons alter their morphology and secretions [4]. It is likely that this plasticity allows adaptation to changing conditions, an obvious advantage for someone who must eat in a world with marked fluctuations in the availability of food at a high physical price for the food.

Hypothesis

As the physical price of food approaches zero, humans eat progressively more food, and with no inhibitory brain mechanisms, body weight increases as a simple epiphenomenon of a phenotype that evolved under circumstances which were very different from the current conditions. Today, therefore, humans cannot manage a healthy body weight, they need external support.

Treating obesity

"We should begin by finding ways of dealing with the growing problem of obesity. How can we change the eating habits of today's children" – Sydney Brenner [23].

The brain may be viewed as a flexible mediator between food and eating behavior. Evolution rewards flexibility. On the present hypothesis, obesity is simply the consequence of the continuous presence of too much food at a too low price. And manipulation of brain function is at best marginally effective in reversing obesity [7,24], because of the versatility of the neural and genetic mechanisms engaged in eating [6,25].

Humans have long used technical devices to navigate in the world and build models of the world [15]. The computer is obviously one of the most impressive and can be used for virtually anything, including assisting us in thinking [15]. Long ago, it was argued that humans are unable to navigate among too much information; we need a machine to help us thinking [26]. We hypothesize that today, with too much food available at a low physical price, we need a machine to help us eating. Hence, we are using computer support to teach under- and overweight adolescents how to eat [27,28] in an attempt to answer Sydney Brenner's question how we can change the eating habits of today's children [23]. In view of the possibility that calorie restriction, such as in anorexia, may be the opposite end of calorie abundance, such as in obesity [29] both under- and overweight patients are provided with online, real time feedback on how much and how quickly to eat on a computer screen and, at the same time, feedback on how to estimate the feeling of fullness [30]. Two randomized controlled trials have shown that this method works in under- as well as overweight patients [27,28]. Thus, the present hypothesis has been partially verified already, but a challenge remains: how do we understand the engagement of a flexible brain mediating between external variations in food resources and eating behavior?

Conflict of interest

P. Södersten and C. Bergh own stock in Mando Group AB and the patent right of Mandometer® a medical device used to treat patients with body weight problems.

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