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EATING, CHEWING AND THE MIND

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To my parents, Foteini, Ingrid and Leander

"The consequences of an act affect the probability of its occurring again"
-B.F.Skinner

ABSTRACT

The need for detailed description of eating behavior has become relevant by the limited success of simplified models in genetics and neuroscience to explain and predict eating behavior in humans. Failure of cognitive interventions, combined with the success of treatments normalising eating styles in obesity and eating disorders, demonstrates the central role of eating in dealing with these problems. In continuous recording of eating behavior and satiety over the course of a meal, women have been found to eat either at a decelerated or a constant rate. Linear eaters, unlike decelerated ones, are unable to control their food intake when the rate of eating is experimentally increased or decreased and their rating of satiety become disassociated from the actual food intake. Their responses to these experimental challenges simulate the eating patterns and the satiation ratings of anorexic and binge eating disorder patients. The development of an improved methodology for the analysis of single meals, combining video derived and intake data, allows for the analysis of the distinct behavioral elements of the meal over time. Semi-automation, high validity and reliability make this procedure ideal for comparing eating patterns among different groups of individuals. The chewing frequency, the distribution of chews within the chewing sequences and the pauses between mouthfuls remain stable across the meal both in decelerated and linear eaters. The weight of the mouthfuls decreases and the duration of the chewing sequences increases over time in the decelerated eaters, but not the linear ones, clarifying the nature of deceleration. Additionally, the default chewing frequency, quantified by the use of chewing gum, is lower in linear than in decelerated eaters, indicating that there is a baseline difference in the default chewing frequency between the two groups. It is suggested that linear eating is a behavioral risk factor for the development of disordered eating and it is hypothesized that while repeated disordered eating is the cause of eating disorders, the accompanying chewing characteristics might be the mediator of the emotional profile that characterizes patients with eating disorders.

LIST OF PUBLICATIONS

I. Zandian, M., Ioakimidis, I., Bergh, C., Brodin, U., & Södersten, P. (2009). Decelerated and linear eaters: effect of eating rate on food intake and satiety. *Physiology & Behavior, 96*(2), 270-275.

II. Ioakimidis, I., Zandian, M., Bergh, C., & Södersten, P. (2009). A method for the control of eating rate: a potential intervention in eating disorders. *Behavior Research Methods, 41*(3), 755-760.

III. Ioakimidis, I., Zandian, M., Eriksson-Marklund, L., Bergh, C., Grigoriadis, A., & Södersten, P. (2011). Description of chewing and food intake over the course of a meal. *Physiology & Behavior, 104*(5), 761-769.

IV. Ioakimidis, I., Zandian, M., Ulbl, F., Åhlund, C., Bergh, C., & Södersten, P. (2011). Food intake and chewing in women. *Journal of Integrated Neuroscience,* (Accepted for publication).

CONTENTS

LIST OF ABBREVIATIONS

AN	Anorexia Nervosa
BED	Binge Eating Disorder
BMI	Body Mass Index
BN	Bulimia Nervosa
CIC	Cumulative Intake Curve
DEB-Q	The Dutch Eating Behaviour Questionnaire
DEC	Decelerated eaters (Figures)
ER+	Increased Eating Rate
ER-	Decreased Eating Rate
LIN	Linear eaters (Figures)
SSRIs	Selective Serotonin Reuptake Inhibitors
STAI-T	State-Trait Anxiety Inventory -Trait
STAI-S	State-Trait Anxiety Inventory -State
TFEQ-R21	21-item Three Factor Eating Questionnaire

INTRODUCTION

The background for research on eating behavior and associated clinical problems will be outlined. Eating behavior is used as an intervention to improve the situation of under- and overweight patients; a translational approach has been found valid in two randomized controlled trials (Bergh, Brodin, Lindberg & Södersten, 2002; Ford et al., 2010). This preliminary success encouraged us to look into eating behavior in further detail.

Thesis framework

The focus on the ever-increasing problem of obesity in our times has led to a corresponding increase of research on every aspect of eating. Great advances have been made in describing the neurobiological, genetic and sociological elements of obesity, each accompanied by various proposed solutions to the problem. Nevertheless, little has been achieved to halt the progress of the so-called "obesity epidemic" (Dietz, 2011). Present demographical data and predictions for the occurrence of obesity in the future are bleak and the sheer prevalence of the problem defies its characterization as a disease or an epidemic (Södersten, Bergh, Zandian & Ioakimidis, 2011). Effective obesity drugs, based upon simplified neurobiological models, inferring direct brain control over eating behavior expressed some time ago (e.g., Bray & Tartaglia, 2000), have proven enormously difficult to develop and even pharmaceutical companies now admit that a "change of fortune may require a change of strategy" (Ledford, 2010). On the other hand, combinations of lifestyle interventions seem to have somewhat positive results, especially in children, even though the reported effects can hardly be generalized due to their dependence on sociological circumstances (Oude Luttikhuis et al., 2009). Finally, surgical interventions, although effective in some cases, are accompanied by various undesirable side effects and the inherent risks of any invasive surgical procedure (Encinosa, Bernard, Du & Steiner, 2009). Hence, they are currently regarded as mere compliments rather than replacements of less invasive interventions (Dixon, Straznicky, Lambert, Schlaich & Lambert, 2011).

The emergence of eating disorders as an important problem afflicting mostly young women and its high profile in western societies (Treasure, Claudino & Zucker, 2010) has not lead to a similar increase of research on the main elements of these disorders, i.e., disordered eating and increased physical activity (Södersten, Bergh & Zandian, 2006). On the contrary, the targeted symptoms for the "mainstream" research concerning Anorexia (AN) and Bulimia Nervosa (BN), i.e., depression, enhanced anxiety and an unspecified, pre-existing mental pathology, might not even be causally related to the disorders (Ioakimidis, Zandian, Ulbl, Bergh, Leon & Södersten, 2011). For this and other reasons (e.g., diagnostic and remission criteria of questionable validity), many interventions have less than satisfying results (Striegel-Moore & Bulik, 2007; Treasure et al., 2010) and high levels of relapse (Berkman, Lohr & Bulik, 2007; Steinhausen, 2002). While the need for the development of a behavioral intervention for eating disorders, based on eating itself, was proposed early on (Bergh, Eklund, Eriksson, Lindberg & Södersten, 1996), its importance is only now starting to be discussed by the rest of the field (Treasure, Cardi & Kan, 2011; Walsh, 2011).

While the connection between obesity and eating disorders have been proposed many times in the past (Kissileff, 1989), the precise relationship of the two conditions remains unclear. Potential underlying elements range from addiction (Wilson, 2010) and reward mechanisms (Berridge, Ho, Richard & DiFeliceantonio, 2010) to various cognitive "progresses" (Riva, 2011). Still, it is noted that the obvious shared characteristic among obese individuals and patients with eating disorders is the development of disordered eating (Day, Ternouth & Collier, 2009). A strong argument for the importance of eating itself in these conditions is the success of interventions based on normalization of the eating pattern through in-meal training (Zandian, Ioakimidis, Bergh & Södersten, 2007). Training patients to eat in a non-pathological way has been proven beneficial both in eating disorders (Bergh et al., 2002) and obesity (Ford, et al., 2010).

The failure of simplified models in genetics and neuroscience to explain and modulate eating regulation and behavior, the obvious relationship between obesity and eating disorders and the subsequent lack of success of cognitive interventions, combined with the success of behaviorally based treatments, suggest that eating behavior itself is of paramount interest. There can be no doubt that excessive over- and under- eating emerge from specific behavioral patterns observed in normal weight individuals (Zandian et al., 2007). Hence, detailed information on eating behavior is required in order to comprehend the eating patterns described in obesity and eating disorders. Better understanding of the specific behavioral elements of human meals might shed light on the underlying relationship between brain and eating and provide the necessary behavioral evidence for the development of a framework bridging the gap between the neurobiological and behavioral substrates of eating disorders (Ioakimidis et al., 2011).

This thesis attempts to thoroughly describe previously reported discrete eating patterns during single meals in normal-weight women and to compare them with eating patterns observed in AN and Binge Eating Disorder (BED) patients. In the meantime, it deals with methodological issues encountered during the collection and the assessment of behavioral data from single meals. Thus, it provides a tool simplifying the collection of information on human eating behavior. Based on the findings of this thesis and supplementary work from our group, the development of a hypothetical model providing insights on the brain-eating relationship is also attempted on a theoretical level.

Microstructural meal analysis

In animals, there is a long history of detailed analysis of eating and drinking, going back at least as far as Skinner (1938). The limitations of simple, cumulative measurements around meals (Davis & Smith, 1992) resulted in the development of more comprehensive methods for the detailed quantification of the microstructural characteristics of the meal.

In 1927, Richter pointed out that behavior is displayed in bouts (Richter, 1927). For example, in rats, drinking is organized in bursts of licking separated by pauses (Hill & Stellar, 1951; Stellar & Hill, 1952) and further organized into clusters when rats are fed with a sugar loaded liquid diet (Davis, 1973; Davis & Smith, 1992). While the duration of bursts and pauses were shown to be fairly constant during similar measuring sessions (Davis, 1973; Stellar & Hill, 1952), they can be modulated by different experimental manipulations (e.g., water deprivation and variation in the concentration of sugar), pointing to the direct control of licking initiation and termination by meal specific characteristics (Berridge & Fentress, 1986; Davis, 1996). Further research has since revealed that licking and mouth movement frequency during the bursts are affected by taste (Berridge, 2000; Smith 2000). Finally, the relationship (Fitzsimons & Le Magnen, 1969; Kissileff,

1969) and the pattern similarities (Hill & Stellar, 1951; Jordan, Wieland, Zebley, Stellar & Stunkard, 1966; Stellar, 1967) between drinking and eating in rats have been described in detail.

In humans, meals have long been recognized as the unit of intake (Woods & Strubbe, 1994) and a lot of research has focused on factors that affect their occurrence, initiation and termination (Strubbe & Woods, 2004; Woods, Schwartz, Baskin & Seeley, 2000). By further dissecting meals into their behavioral components, the study of the progression of the meal (Davis, 1989; Kissileff, 2000) has proven useful in providing information about different aspects of the ingestion of food. Various electromyographic and other oral sensor techniques have offered information about the behavioral details of the meal (Bellisle & Le Magnen, 1980; Stellar & Shrager, 1985) and insights into eating patterns of obese and lean individuals (Bellisle & Le Magnen, 1981; Spiegel, Kaplan, Tomassini & Stellar, 1993), including the effect of food deprivation (Bellisle, Lucas, Amrani & Le Magnen, 1984). However, the invasive nature of the equipment has been a concern (Hennequin et al., 2005) and in many cases, video recording is a better alternative for collecting the data (Bellisle, Guy-Grand & Le Magnen, 2000; Hill, 1974; Llewellyn, Van Jaarsveld, Boniface, Carnell &Wardle, 2008).

Cumulative intake curve

A method for the analysis of single meals in humans was inspired by the research on rats' drinking (Stellar & Hill, 1952). Thus, the "Drinkometer" (Figure 1A) was developed for continuous recording of fluid intake in humans under a variety of experimental conditions (Jordan, et al., 1966; Stellar, 1967). Meyer & Pudel (1972) used a modified version of the same equipment to describe the eating patterns of obese and lean individuals and associated the differences with satiation, being the first to suggest that the cumulative intake curve (CIC) could be modeled by a quadratic equation. Thus the CIC is mathematically expressed as $y=kx^2+lx$, where y is the amount of food ingested, x is the time and the k-coefficient is related to the change of the speed of eating over the course of the meal and the l-coefficient is related to the initial speed of eating.

The procedure and the equipment was refined by Kissileff and his colleagues (Figure 1B), who adapted the machine to solid food diets, renaming it the "Universal Eating Monitor" (Kissileff, Klingsberg &Van Itallie, 1980). They formalized the modeling of intake over time by the use of quadratic equations (Kissileff et al., 1980; Kissileff, Thornton & Becker, 1982), theorizing about the relationship among the equation's coefficients and biological processes. Subsequent variants of the same equipment include the "VIKTOR" (Barkeling, Rössner & Björvell, 1990) and the "Sussex meal pattern monitor" (Yeomans, 1996). The development of the Mandometer® (Figure 2), build on the same principles, added mobility and support for real-time feedback to the user, allowing experimental manipulation of the pattern of the meal (see Materials and Methods).

Hubel and colleagues (Hubel, Laessle, Lehrke & Jass, 2006) have shown that quadratic equations reliably model intake across the meal. Their results, combined with other reports, reveal that curve characteristics are stable across an individual's meals (Barkeling, Rössner & Sjöberg, 1995; Westerterp-Plantenga, 2000). However the rate of deceleration varies among different groups of individuals and across conditions (see below). Thus, the adaptability of the CIC makes it a valuable tool for the analysis of meals (Westerterp-Plantenga, 2000).

In other studies, the l-coefficient has been related to the "eating drive", activated by oral stimulation at the beginning of the meal (Davis & Levine, 1977), or alternatively by the "desire to

eat" (Yeomans, 1996; Yeomans, Gray, Mitchell & True, 1997), which depends on palatability (Bobroff & Kissileff, 1986). Also, the eating pattern and, thus, the CIC is affected by the type of the served food, with liquid meals characterized by more linear CICs than solid meals (Guss & Kissileff, 2002). Preparatory and satiety-related components of a meal are affected by smell conditioning (Yeomans, 2006), while meal termination is accelerated by increased retro-nasal aroma release (Ruijschop et al., 2011). Besides, eating rate has been proposed to be a helpful phenotype for the prediction of fat adiposity in children, where higher eating speed was correlated with higher Body Mass Index (BMI; Llewellyn et al., 2008). Furthermore, we have reported sex differences in the CIC characteristics, men being more decelerated than women (Zandian, Ioakimidis, Bergh, Leon & Södersten, 2011; see also Barkeling et al., 1995). Finally, food deprivation prior to the meal affects its CIC characteristics, women eating more linearly and men less so (Zandian et al., 2011).
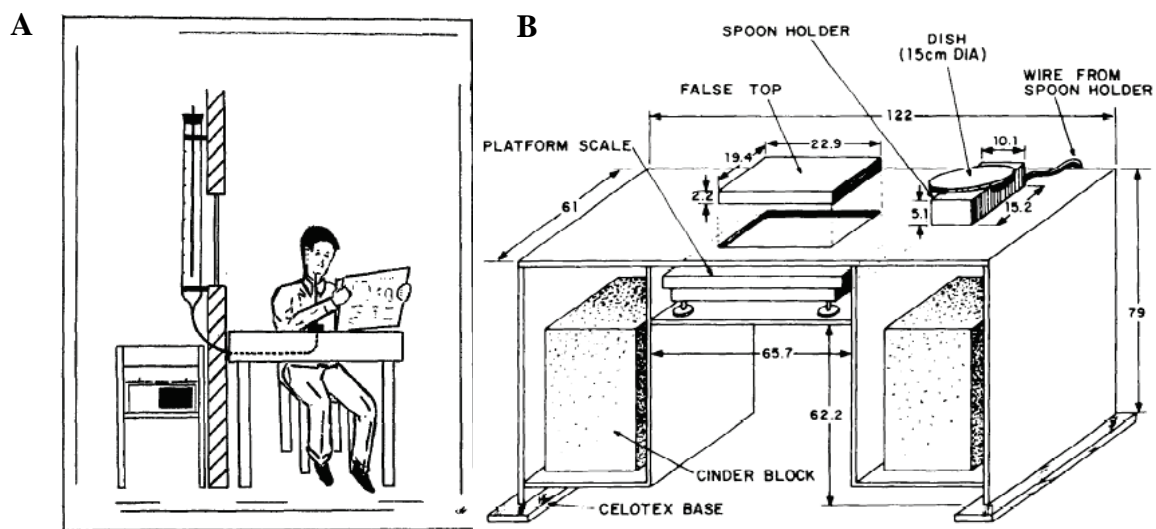

Figure 1. The Drinkometer (A) for analysis of intake of liquid diets and the Universal Eating Monitor (B) for analysis of intake of liquid and solid diets.

Eating styles

The first to describe two different types of CIC were Meyer & Pudel (1972). In normal, underweight and obese individuals the rate of eating remained stable across the meal in one group of subjects, whereas in another there was a reduction in the speed of ingestion towards the end of the meal. Hence, the speed of eating is constant in the first group and decelerated in the second.

The authors linked the decelerated model with the "biological satiation curve", associated linear eating with a disturbed perception of satiation and noted a higher percentage of linearity among the over- and underweight. (We use satiation for the feeling of fullness that develops during the meal. This is in contrast to satiety, which denoted the feeling of fullness between meals.) Although these findings have been replicated (e.g., Adams, Ferguson, Stunkard & Agras, 1978; Barkeling, Ekman & Rössner, 1992; Bellisle & Le Magnen, 1981; Kaplan, 1980; Lindgren et al., 2000), they were not confirmed by a number of other studies (Barkeling et al., 1995; Laessle, Lehrke & Duckers, 2007; Llewellyn et al., 2008; Westerterp, Nicolson, Boots, Mordant &

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Westerterp, 1988; Westerterp-Plantenga, Wouters & Ten Hoor, 1990; Zijlstra et al., 2011). Westerterp-Plantenga and colleagues (1988; 1990) suggested that those eating at a decelerated speed should be referred to as Decelerate Eaters and those eating at a constant speed should be referred to as Linear Eaters and reported a correlation between linearity of eating and the cognitive restraint parameter. Dietary restraint is a cognitive process expressed as a drive to control body weight by limiting food intake (Polivy & Herman, 1985). It does not strictly relate to the way a person eats, but refers to the attitude towards food and has even, and surprisingly, been suggested to be outside of physiological control (Bryant, King & Blundell, 2008; see discussion in: Zandian, Ioakimidis, Bergh & Södersten, 2009). Interestingly, cognitive restraint is significantly reduced once Linear Eaters have practiced eating and adopted the decelerated pattern of eating pattern (Zandian et al., 2009), raising questions about the cause-and-effect relationship between eating behavior and cognitive restraint. Although both eating styles appear in normal-weight individuals, it is possible that obese patients, e.g., patients with BED, are Linear Eaters (Westerterp et al., 1988). Reviewing cumulative meal data for BED patients, Walsh & Boudreau (2003) noted that disturbed eating is not limited on binge eating episodes, but spreads across all the patients' meals. However, there is a lack of detailed information on eating styles in this group of patients (Walsh, 2011).

Unlike obesity, there are only a few reports concerning the eating style of eating disorder patients (Walsh, 2011). While there are numerous reports of eating parameters based on external questionnaires (e.g., Wardle, 1987; Wardle et al., 1992), few efforts have been made to describe the eating behavior of these patients. Meyer & Pudel (1972) initially referred to an underweight group of subjects, including mainly anorexic patients, but provided no information about the individuals and did not report details of the pattern of their eating. Hadigan and colleagues (2000) reported that anorexic patients had cumulative intake with fewer calories than controls upon admission to the clinic but no other details. Differences in cumulative intake of AN patients before and after standard treatment have been reported (Mayer, Schebendach, Bodell, Shingleton & Walsh, 2011; Sysko, Walsh, Schebendach & Wilson, 2005). Thus, the total intake increased after the treatment, but it remained lower than intake in the control groups. An attempt to predict the one year outcome in weight-restored AN patients by examining their dietary habits upon weight restoration reported a lower risk of relapse in patients with normalized dietary habits on remission (Schebendach et al., 2008; 2011). By teaching AN patients to eat using Mandometer[®], we have normalized their eating behavior, restored their health and prevented relapse over a five year period of follow-up (Zandian et al., 2007).

Chewing, mouthfuls and pauses

While chewing is an important part of the ingestion of food, it has received limited attention in studies of the microstructure of meals, most likely because of technical constraints. Bellisle & Le Magnen (1980;1981) analyzed meals using the "Edograms", i.e., oscillographic recordings of chewing for subjects consuming food items of predefined shape/size and varied palatability (white bread pieces with different tasting pastes) and noted the occurrence of chewing bouts, followed by swallowing and a short pause before the intake of the next food unit (Bellisle et al., 2000). The authors reported an increase of chewing time (but not an increase in "chewing movements") per food unit and an increase of the interval between mouthfuls at the end of the meal, irrespective of palatability. In another two studies based on consumption of standardized bread-based food items,

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chewing was analyzed using electromyography, but no chewing results across meals were reported (Spiegel, 2000; Spiegel et al., 1993). On average, in meals with smaller food units, the subjects chewed the food longer at an increased frequency, while the size of the food units did not affect the pauses between bites (Spiegel et al., 1993) and the total consumption in the meal. Elsewhere, experimental prolongation of the pauses between bites only marginally affected the size of a meal, but inconsistencies in data reporting and small sample size make these results difficult to evaluate (Kaplan, 1980).

By contrast, Zijlstra and colleagues (Zijlstra, De Wijk, Mars, Stafleu & de Graaf, 2009) reported clear effects of mouthful size and oral processing on the amount of food ingested; lower weight and longer processing time per mouthful result in smaller meals of a semi-liquid, chocolate based drink. Additionally, the size of the mouthfuls decreased over the course of the meal. Westerterp et al. (1980; 1988) reported "chewing time per bite" per individual over the course of the meal using a concealed camera they but did not present data on the progression of this variable across the meals. Mouthful size was stable across meal quarters among linear eaters, decreasing across time among decelerated eaters, while the mouthful frequency remained stable for both groups. In all these studies, the results indicate intra-individual stability of chewing frequency, even across meals with different kinds of food. The size of the mouthful has been examined in people of different body weights with mixed results (Laessle et al., 2007; Llewellyn et al., 2008; Zjilstra et al., 2011). Higher viscosity for liquid food reduces bite size (De Wijk, Zijlstra, Mars, de Graaf & Prinz, 2008) and it has been shown that easily ingested food the total energy intake is higher (Viskaal-van Dongen, Kok &de Graaf, 2011). As whole, methodological differences, diverse groups of participants, a wide variety of test foods and incomplete data reports make conclusions about the relationship among cumulative food intake, mouthful sizes, chewing patterns and pause duration difficult.

Chewing

Mastication is an important issue in dentistry (Soboļeva, Lauriņa & Slaidiņa, 2005A; 2005B). Studies in this field are concerned with chewing movements (rather than meals) and use diverse, usually invasive, techniques with high resolution to describe chewing. These studies use both natural (e.g., Agrawal, Lucas, Bruce & Prinz, 1998) and model foods (e.g., Grigoriadis, Johansson &Trulsson, 2011). The characteristics of chewing sequences have been described thoroughly in animals (e.g., Ootaki et al., 2004; Schwartz, Enomoto, Valiquette & Lund, 1989). Similarly, in humans, chewing can be divided into functional phases based upon characteristic jaw movements, recorded electromyographically (Hiiemae, et al., 1996). These movements adapt depending upon the characteristics of the food (Woda, Mishellany & Peyron, 2006; Wintergerst, Throckmorton & Buschang, 2008) and the subject (Woda, Foster, Mishellany & Peyron, 2006). Thus, the hardness and rheological characteristics of the food and the size of the bolus of the food affect chewing. In the future, development of less invasive equipment with high resolution might allow analysis of chewing in a real-life setting in further detail. For instance, chewing cycles can be recorded based on the sounds of mastication (Amft, Kusserow &Tröster, 2007).

Neurobiology of chewing and mood

It is widely accepted that the rhythmic jaw movements of chewing and licking are controlled by a pattern generator located in the hindbrain (Dellow & Lund, 1971), between the caudal facial nucleus and the trigeminal motor nucleus (Kogo, Funk & Chandler, 1996; Lund & Kotla, 2006; Travers, Herman & Travers, 2010). It is clear that the behavioral expression of the pattern generator is affected by peripheral sensory feedback, probably mediated via adjacent areas such as the serotonin cells in raphe nuclei (Hornung, 2003; Kogo et al., 2006; Stephenson, Hunt, Topple & McGregor, 1999). The activation of chewing according to the sensory characteristics of the food, facilitated by the pre-activation of the masticatory area of the cerebral cortex (Lund & Kotla, 2006; Masuda et al., 1997; Ootaki et al., 2004), suggests the existence of a neural network that is engaged in eating (reviewed in Ioakimidis et al., 2011). For example, during chewing gum use the ventral part of the prefrontal cortex is activated (Kamiya et al., 2010), and experimental activation of that area has been shown to evoke increased activity in the serotonin cell groups in the raphe nuclei (Celada, Puig, Casanovas, Guillazo & Artigas, 2001). Because the raphe nuclei are engaged in a variety of cognitive and emotional processes (Cools, Roberts & Robbins, 2008; Fumoto et al., 2010; Ögren et al., 2008), we have hypothesized that chewing can cause mood changes (Ioakimidis et al., 2011). Supporting evidence is provided by the well known calming effect of breast-feeding in infants (Febo, Numan & Ferris, 2005), the early observation that chewing is relaxing in adults (Hollingworth, 1939) and the more recent report of reduced anxiety after the use of chewing gum to buffer the effect of an acute experimental stress (Scholey et al., 2009). In addition, the rate of chewing affects salivary cortisol levels in a "dose-dependent" manner (Tasaka, Tahara, Sugiyama & Sakurai, 2008). Interestingly, military personnel and professional athletes report high chewing gum use in stressful situations (Wrigley Athlete Study, 2008). The US military forces have been equipped with chewing gum since the first World War (Koehler, 1958) and chewing gum is part of the modern military meal (www.mreinfo.com/us/mre/mres.html). Conversely, the negative effects on mood after disturbances in parts of the chewing network (Stephenson et al., 1999) and the comorbidity of bruxism and mood (Manfredini, Ciapparelli, Dell'Osso & Bosco, 2005) and eating disorders (Vetrugno et al., 2006), support the possible association between chewing and negative mood as well.

Summary

From these introductory considerations it is clear that eating behavior has been studied for a considerable period of time and that humans can be divided into Decelerated and Linear Eaters on the basis of the CIC. Linear Eaters are clinically interesting because they may be at risk of losing control over food intake and, therefore, over body weight. Eating behavior, however, is chewing and swallowing and rather than measuring these, the CIC is a model of cumulative food intake based on information on weight loss from a scale. Previous attempts to measure both chewing and cumulative intake have yielded inconsistent results and in view of the possible role of chewing, not only in food intake but in emotional and cognitive functions, comprehensive study of eating behavior is of interest.

This thesis has studied eating behavior in women because our aim is to understand and treat eating disorders, which mainly affect women. Based on the hypothesis that eating behavior has an important role in the development of disordered eating the thesis has the following aims.

Aims

1. To describe decelerated and linear eating in detail

2. To examine the effect of increasing or decreasing the speed of eating on eating behavior

3. To examine the eating behavior of AN and BED patients

4. To synchronize data on food intake with chewing

5. To analyze chewing in Decelerated and Linear Eaters

6. To formulate a theoretical model for the relationship among eating, chewing and the brain

MATERIALS AND METHODS

Participants

Paper I

Forty-seven normal-weight women (age = 21.2 [19.5-23.1] years; median [range]) with a BMI = 22.2 [20.2-24.3] kg/m2 were recruited by advertisement on a nearby college campus. They completed a health questionnaire to ensure that they were healthy, without a history of eating and anxiety disorders, non-smokers, without food related allergies. Pregnant and lactating women, vegetarians and athletes were excluded. An additional group of thirty women matched for age and body weight was used to test the reliability of the method.

Paper II

Twenty-nine normal-weight women were recruited from a nearby college campus as described above. They were screened according to their rate of deceleration in a control test and sixteen were selected for further testing (age = 19.8 [17.8-24.3] years, BMI = 21.7 [18.5-24.6] kg/m^2).

Sixteen women with AN (age = 14.6 [12.3-26.7] years, BMI = 15.3 [13.4-16.9] kg/m^2, time since diagnosis = 2.6 [0.3-9.5] years, number of previous treatments = 1.5 [0-4]) who were consecutive referrals to our clinic during a period of 6 months were included in the study.

Twelve women with BED (age = 32.2 [17.3-63.3] years; BMI = 39.5 [31.2–62.8] kg/m^2, time since diagnosis = 15.1 [2.2-45.5] years, number of previous treatments = 3 [0-6]) were similarly recruited.

Both patient groups were diagnosed using DSM-IV criteria.

Paper III

Six normal-weight women (age = 24.2 [23.2-24.7] years, BMI = 23.5 [21.2-24.5] kg/m^2) were recruited as described above to participate in the procedure for the validation of the video quantification of the chewing. The participants were visually inspected by a trained dentist for the absence of any outstanding dental conditions.

A similarly selected, matched group of eleven women (age = 22.3 [18.1-24.8] years, BMI = 22.3 [18.6-24.7] kg/m^2) participated in the second experiment. In addition to the previously presented inclusion criteria, all women had a good dental health (self reported absence of dental problems and regular dental controls). They were selected for having k coefficients around -0.25 in the CIC, i.e., between decelerated and linear eaters.

Paper IV

Eighteen normal-weight women were recruited as above (including good dental health). The women were divided into decelerated (n = 9, age = 24.2 [20.7-24.8] years, BMI = 21.5 [20.6-

24.5] kg/m^2, k<-0.3) and linear (n =9, age = 23.9 [20.2-25] years, BMI = 21.1 [19.5-24.2] kg/m^2, k>-0.2) eaters.

A matched sample of 21 normal-weight women was also recruited. They were grouped as decelerated (n = 10, age = 23.6 [19.6-24.6] years, BMI = 20.9 [18.5-24.5] kg/m^2, k<-0.3) and Linear Eaters (n = 11, age = 22.8 [19.5-24.3] years, BMI = 21.4 [19.9-23.7] kg/m^2, k>-0.2) as above.

Food

Food was precooked and reheated before the test meals. Papers I, II and the second group in Paper IV, used a homogenous mix of grilled chicken fillet in cubes (maximum size of the pieces: 2.2 g) with curry-rise and vegetables pieces ("*Nasigoreng*", Findus AB, Bjuv, Sweden: 400 kJ, 4.5 g protein, 15 g carbohydrate and 18 g fat/100 g). Paper III and the first group in the Paper IV used a homogenous mix of grilled chicken fillet and vegetable pieces (maximum weight per piece: 2.6g and 1.2 respectively; "Grönsakspytt med kyckling", Findus AB, Bjuv, Sweden: 426 kJ, 10.7 g protein, 8 g carbohydrate and 2.5 g fat/100 g). The food was selected based on availability, mechanical characteristics (low itemization, small size of components, homogeneity and moderate hardness) and palatability (relatively blunt with acceptable taste).

Mandometer[®]

Figure 2. Mandometer[®], a personal computer connected to a scale recording the weight loss of a plate during the meal. Feedback on how to eat can be provided on the touch screen.

The Mandometer[®] is a scale connected to a portable computer (Figure 2). It is used for the detailed analysis of single meals, based upon principles first developed in research on rats (Hill & Stellar, 1951) and adapted for research of drinking (Jordan et al., 1966; Stellar & Hill, 1952) and eating in humans (Kissileff et al., 1980; Meyer & Pudel, 1972).

The user places a plate on the scale and puts food on the plate. During the meal, the weight loss on the plate is recorded by the computer every second. A quadratic equation is fitted on the generated weight-loss data series, producing the CIC in real time.

Mandometer® has two modes of operation. During control meals, the user receives no feedback (i.e., empty screen) and the device is used for recording. In test meals, real time feedback, in the form of a weight-loss/time graph is provided to the user. A CIC of predetermined weight/time (i.e., a training curve) is presented on the screen and the user adapts her/his eating behavior to the proposed meal pattern (Figure 3). Deviations >15% from the training curve cause voice and text alerts from the computer, urging the user to eat faster or slower.
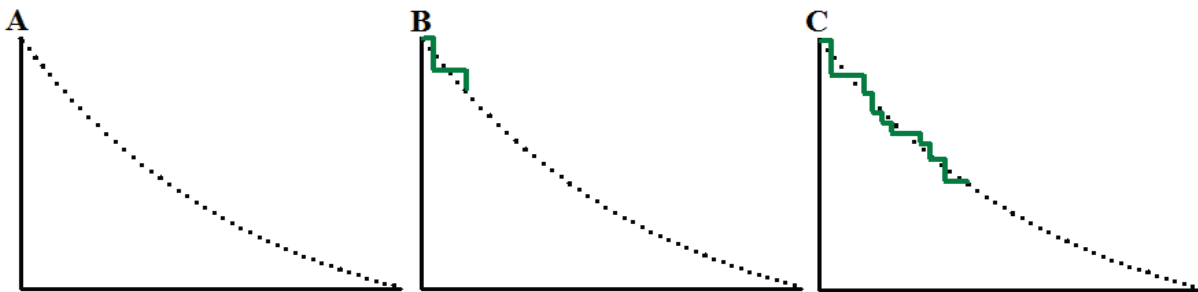

Figure 3. Progression of a meal (green line), following a CIC (dashed curve) on Mandometer®.

Additionally, the Mandometer® features a revised Borg scale (Borg, 1982) and users are asked to rate their satiation on the scale form 0 (nothing at all) to 100 (maximal satiation), which is displayed on the touch screen.

Experimental procedure

Eating

All the meals were served between 11:30 and 13:00 (i.e., typical "lunch" time in Sweden). The women agreed to a certain time of breakfast the morning before the test meals. The ingested amount and the type of food were agreed upon at the beginning of the studies (subject-specific arrangements) and remained stable through consecutive tests. Afterwards, the participants agreed to abstain from eating and drinking, except water. The patients went through a similar procedure.

The recording mode on Mandometer® was used in all Papers to assess the baseline eating pattern and for "Short" and "Interrupt" meals in Paper I. The "Short" meals were reduced by 40%, compared to the control meals. The "Interrupt" meals included one-minute pauses for every 60g of intake. In Papers I and II meals with predefined training curves had individually increased (ER+) or decreased (ER-) rates of eating. The model CICs were preprogrammed with the same duration and 40% more (ER+) or 30% less (ER-) food, compared with the individual's baseline meals. The experimental conditions are summarized in Table 1.

Table 1. Experimental conditions

Meal type	Time	Amount of food	Satiety ratings	Food	Special features
Paper I					
Healthy women					
Control	Unlimited	Unlimited	1 min intervals	Chicken & rice	None
Short	Limited (Control-40%)	"	"	"	External alarm
ER+	Limited (same as Control)	Limited (Control+40%)	"	"	Training curve
ER-	"	Limited (Control-30%)	"	"	"
Interrupt	Unlimited	Unlimited	"	"	1 min pause / 60g
Paper II					
Healthy women					
Control	Unlimited	Unlimited	1 min intervals	Chicken & rice	None
ER+	Limited (same as Control)	Limited (Control+40%)	"	"	Training curve
ER-	"	Limited (Control-30%)	"	"	"
AN/BED patients					
Control	Unlimited	Unlimited	Before/after meal	Restaurant food	None
Paper III					
Healthy women					
Control	Unlimited	Unlimited	Before/after meal	Chicken & vegetables	External cameras
Paper IV					
Healthy women - Group 1					
Control	Unlimited	Unlimited	Before/after meal	Chicken & vegetables	External cameras
Healthy women - Group 2					
Control	Unlimited	Unlimited	Before/after meal	Chicken & rice	None

On admission, the healthy women and the patients were escorted to a secluded room, without windows. The external stimuli were minimized; use of mobile phones, reading and listening to music were not allowed. The appropriate questionnaires were presented on the dining table before and after the meals. For meals requiring a sense of *ad libitum* availability of food, the food was served on a big serving tray (1.2 to 2 kg depending on the study) and the participants were asked to freely transfer food to a plate placed on the Mandometer[®]. During control meals, subjects were instructed to eat as much as they wished and they were allowed to transfer extra food to their plate during the meal as many times as they saw fit. No time limitations were set on control meals and the women were allowed to conclude their meal irrespectively of the amount of food left on the tray and the plate on the Mandometer[®]. In meals requiring a prearranged amount of food (i.e., ER+ and ER-), the food was presented on the plate that was placed on the Mandometer®. Time limitations were enforced either indirectly through the presented training curves (ER+ and ER- meals), or with an external alarm clock (i.e., in the "Short" meal). The participants were informed that while they were eating they should try hard to follow the presented curve, but it was also made clear that they were free to quit the meal at any given moment (i.e., when the procedure became "uncomfortable"). In all studies the surface temperature of the food was around 50^oC. Care was taken in keeping the composition, preparation, and presentation of the food constant.

In Papers III and IV, two digital video cameras (DigitalCam, Samsung, Seoul, South Korea) were placed inside the dining room in obvious positions, 2 to 2.5 meters away from the subject, facing the plate (i.e., "*plate video*") and the maxillary-mandibular area of the subject (i.e., "*chewing video*"), respectively. In Papers I and II, the meals after "Control" were presented in random order. During all meals, the subjects were eating alone, after the researcher exited the room. Before the initiation of every study, the participants were familiarized with the procedure and the surroundings in a mock session, during which no data were collected.

Chewing

In Paper III, the participants were escorted into an electrically and magnetically shielded room and they were asked to sit on a specially modified dentist chair. An array of magnetic sensors (Umeå University, Physiology Section, IMB, Umeå, Sweden) was attached on the head of the subject, without limiting movement and a small magnet was attached to the labial surfaces of the mandibular incisors. Magnetic signals were recorded by a microcomputer system operated by a researcher inside the chamber. Inside the room, a digital video camera, pointed to the maxillary-mandibular area of the subject (i.e., "*face*" video), was used to record three consecutive sessions of chewing in random order. Chewing gum (Wrigley Scandinavia AB, Stockholm, Sweden; one piece) with peppermint flavor was used, and every session was 20 sec long. The sessions included one session of unrestraint chewing (i.e., *natural* chewing speed) and two sessions with predetermined chewing frequencies (0.5 and 0.75 Hz), realized with the use of an external metronome. These frequencies were selected to be significantly lower than previously reported natural chewing speeds (e.g., Bellisle, Guy-Grand & Le Magnen, 2000).

In Paper IV, subjects in group 2 participated in two five-minute long chewing sessions. The chewing sessions had no restraints on chewing speed (i.e., *natural* chewing speed), took place in the same room as the eating sessions and were filmed as described above.

Subjective measurements

In the first two papers, the satiation scale was presented to the participants once every minute of the meal using the Mandometer®. In Papers III and IV ratings were collected only before and after the meals, using an external visual analogue scale (Torrance, Feeny & Furlong, 2001), also generating scores from 0 to 100.

In addition, a variety of questionnaires were used for screening individuals. Another set of subjective measurements was collected repeatedly during the studies, before and after each eating session. Questionnaires that were administered only one time per study included the Dutch Eating Behaviour Questionnaire (DEB-Q; Van Strien, 2002), the 21-item, Three Factor Eating Questionnaire (TFEQ-R21; Stunkard & Messick ,1985; Tholin, Rasmussen, Tynelius, & Karlsson, 2005), the State-Trait Anxiety Inventory -Trait (STAI-T; Spielberger, Edwards, Gorsuch & Lushene, 1970) and one custom-made questionnaire concerning the structured meal habits of each individual. The repeated measurements included STAI - State (STAI-S; Spielberger, et al., 1970) and a list of questions in visual analogue scale format (Torrance, Feeny & Furlong, 2001), dealing with the general emotional state and the hunger profile of each subject around a meal. Other questions dealt with the food presentation and palatability. The above results were not treated as outcome measures (unless otherwise specified), but were used as session-specific screening material, in order to identify methodological or state inconsistencies across sessions (e.g., sudden drop in the quality of the food and abnormally high anxiety, respectively).

Data analysis

Video recordings

The video recordings of eating (*plate* and *face* videos) and chewing sessions (*chewing* video) were transferred to a PC for analysis. The recordings were played back in half speed and were manually timestamped for target behaviors, using a custom-made macro for Excel 2007 (Microsoft, Redmond, Washington, USA), recording the time occurrence with millisecond accuracy. The *plate* videos were timestamped for occurrences of food removal from the plate (i.e., *spoonfuls*). The *face* videos were timestamped for occurrences of food entering the mouth (i.e., *mouthfuls*), for obvious occurrences of completed *chewing cycles* or *chews* (i.e., opening of the maxillary-mandibular area and subsequent occlusion) and for rare behaviors, e.g., *double mouthfuls* originating from the same spoonful. In a similar fashion, the chewing videos were timestamped for occurrences of *chewing cycles* during chewing gum use.

Eating behavior recordings

The ratings of satiation collected during the meals were fitted with a two-parameter sigmoid curve: $y = 100/(1 + e - (\chi_0)/\beta)$, with χ_0 = the time when satiation has reached 50 (i.e., the mid-point of the scale, or the inflection point of the curve) and β the steepness of the curve.

Weight-loss data recorded by the Mandometers® were transferred to a PC and corrected before they were fitted with CICs. The correction was manual, with a trained researcher visually inspecting each meal's weight-loss data series. Obvious mistakes (e.g., exclusion of weight increases on the scale due to pressure or placement of a utensil on the scale) and target behaviors (e.g., food additions during the meal) were corrected by hand (Figure 4). A partially automatic program was developed in Matlab (The MathWorks, Natick, Massachusetts, USA), for the correction of the weight-loss series, dealing with the same kind of mistakes as described above. The included algorithms require limited user input, mainly for the manual marking of the beginning and the end of the meal, the points of food additions and for suspected errors in the automatic correction. For the initial screening of individuals in Papers III and IV and the analysis of the meals of the second group in Paper IV, a similar, revised version of the program was developed for Excel 2007 (Microsoft, Redmond, Washington, USA).
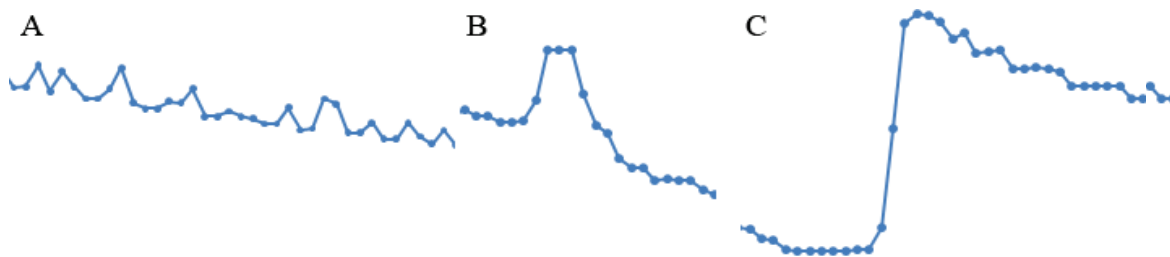
Figure 4. Errors in weight-loss data series. Repeated instances of pressure exerted on the plate due to manipulation of food (A), utensil placed on plate (B) and addition of food (C).

In Papers III and IV (group 1), the Mandometer® weight-loss data series was corrected with the help of the *spoonful* and *mouthful* data series, with a semi-automated procedure. In summary, the *spoonful* and *mouthful* series were synchronized, wiping out discrepancies due to time latency and rare behaviors (i.e., *double mouthfuls*). The derived mouthful occurrences were then used as "anchor" points, around which the weight-loss data were corrected with the use of successive sliding-window filtering, in an adapted format of convolution algorithms. The *chewing sequences* and *pauses* included into the chewing data series were indentified automatically. A *chewing sequence* is an uninterrupted sequence of chews (pauses ≤2 sec) that includes 95% of the chews in the time period between two *mouthfuls*, while a *pause* is the remaining time till the following *mouthful*. Finally, the *chewing sequences* with eight or more *chewing cycles*, were further divided into four temporal quarters, to estimate the distribution of *chewing cycles* over time inside the *chewing sequence*. The corrected weight-loss and mouthful series were synchronized further with the chewing data series, producing a comprehensive representation of the meal (Figure 5). Meals were further divided into thirds in order to describe the behavioral measures over the course of a meal, across groups.
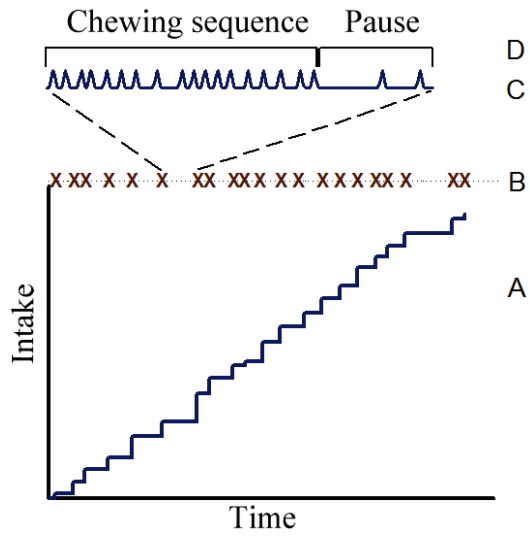
Figure 5. Schematic representation of Cumulative food intake (A), *Mouthfuls* (X) (B), a *Chewing cycle* (C) and a *Chewing sequence* and *Pause* in an *Inter-mouthful interval* (D).

RESULTS

Paper I: Linear Eaters lose control after experimental challenges

After analysis of their eating behavior in the Control meals, the women were divided according to the average value of the k-coefficient of their CICs. Women with negative k-coefficients were dubbed "Decelerated Eaters", and those with k-coefficients close to zero were dubbed "Linear Eaters".

Thus, in Decelerated Eaters, the speed of eating speed decreased gradually through the meal, while Linear Eaters retained a steady eating speed throughout the meals. Decelerated Eaters had a higher initial speed of eating than Linear Eaters but they consumed a similar amount of food, even though the duration of the meals tended to be longer among the linear eaters (Figure 6).
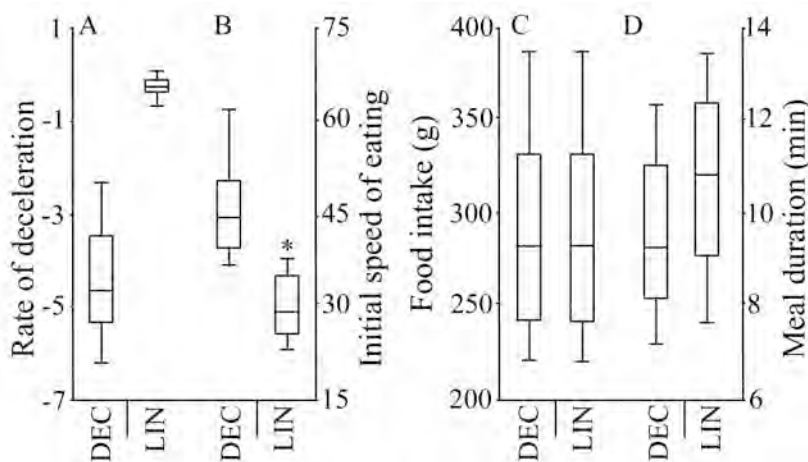
Figure 6. Rate of deceleration (A), initial speed of eating (B), food intake (C) and meal duration (D) in Decelerated (DEC) and Linear Eaters (LIN). * Significantly different from DEC.

When the two groups of eaters were challenged, differences in their food intake were observed. Thus, in the Short and ER+ meals, Decelerated Eaters ingested less food than in the control meal, while the Linear Eaters ate more food. In the ER- and Interrupt meals, the intake was not altered in the Decelerated Eaters, but the Linear Eaters ate less and more food respectively in these conditions (Figure 7A).

The two types of eaters also rated their satiety differently at the end of meals (Figure 7B). For example, after their control meals, Linear Eaters reported significantly less satiety than the Decelerated ones. Interestingly, they rated their satiety higher than in the control meal after the ER-meal, despite eating less food. Conversely, although they ate more food after the ER+ meal, their estimation satiety after the meal did not increase.

These results suggest that Linear Eaters, unlike Decelerated Eaters, have difficulty maintaining their intake and rating their satiation when the speed of eating is changed or when the pattern of eating is disrupted.
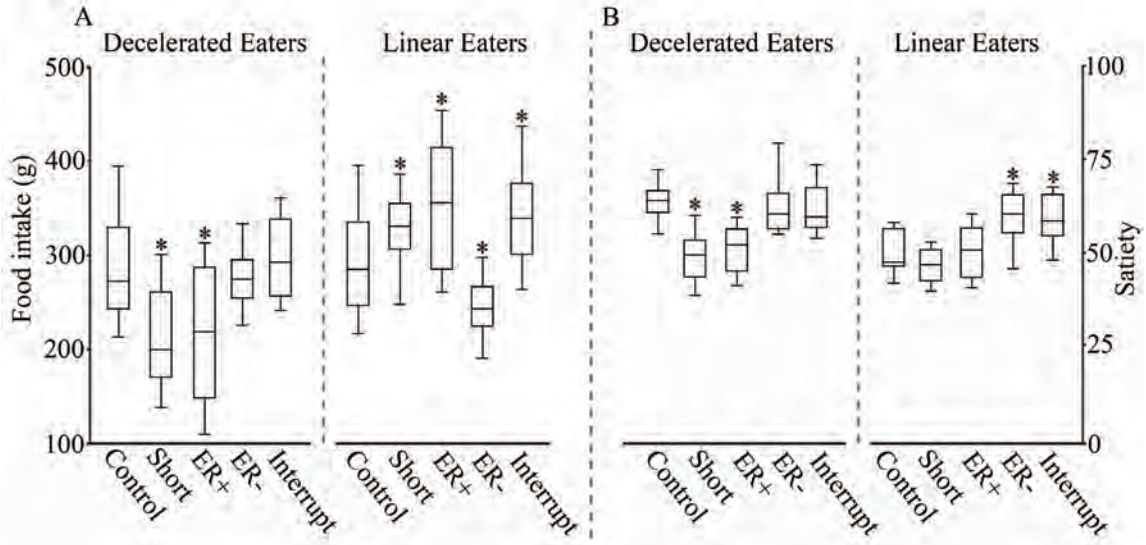
Figure 7. Food intake (A) and satiety (B) in Decelerated and Linear Eaters after the Control meals, and an experimentally shortened meal (Short), after increasing (ER+) or decreasing (ER-) the speed of eating or interrupting the meal (Interrupt).
* Significantly different from Control meal.

Paper II: Linear Eaters adopt AN and BED eating patterns

Next, we described the eating pattern of AN and BED patients and compared them to that of Linear Eaters.

Both patient groups displayed a linear pattern of eating
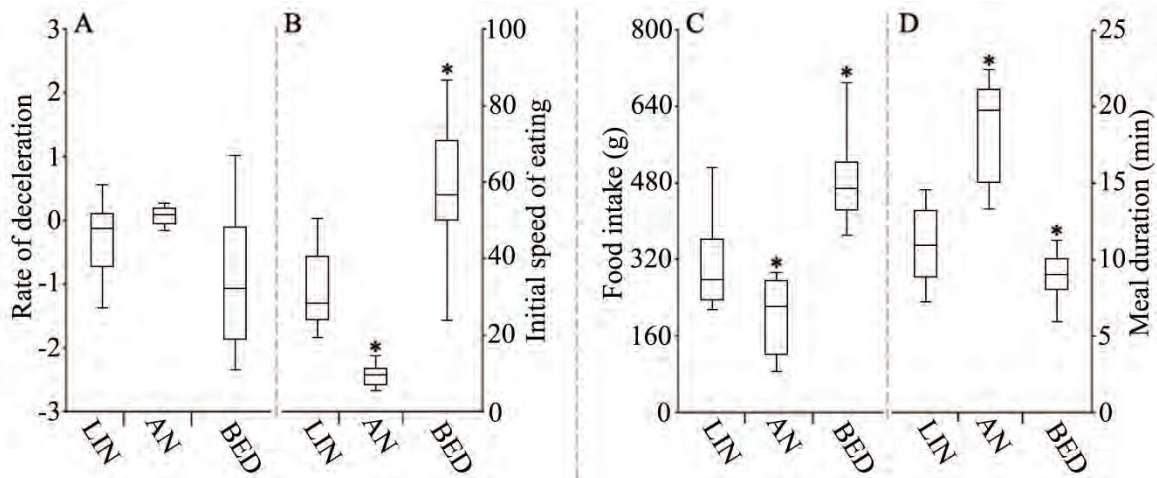
Figure 8. Rate of deceleration (A), initial speed of eating (B), food intake (C) and meal duration (D) in Linear Eaters (LIN) and in patients with Anorexia Nervosa (AN) or Binge Eating Disorder (BED). * Significantly different from LIN.

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Figure 8 shows that AN and BED patients differed in that AN were Linear Eaters, their k-values were close to 0, but BED patients had variable k-values. AN patients started eating at a low speed, but the initial speed of eating among the BED patients was high. As expected, AN patients ate only little food, while BED patients ate much more. Conversely, the duration of the meal was much longer among AN than BED patients. The results from Linear Eaters were in between the AN and the BED patients (Figure 8).

Interestingly, the Linear Eaters simulated the pattern of the AN patients when the speed of eating was experimentally decreased and the pattern of the BED patients when the speed of eating was experimentally increased (Figure 9A).

As expected, AN patients rated their satiety high after the meal and BED patients rated their satiety low. The Linear Eaters rated their satiety in between the patient groups. As with food intake, the Linear Eaters' rating of satiety approached that of the AN patients when the speed of eating was experimentally decreased and it approached that of the BED patients when the speed of eating was experimentally increased (Figure 9B).
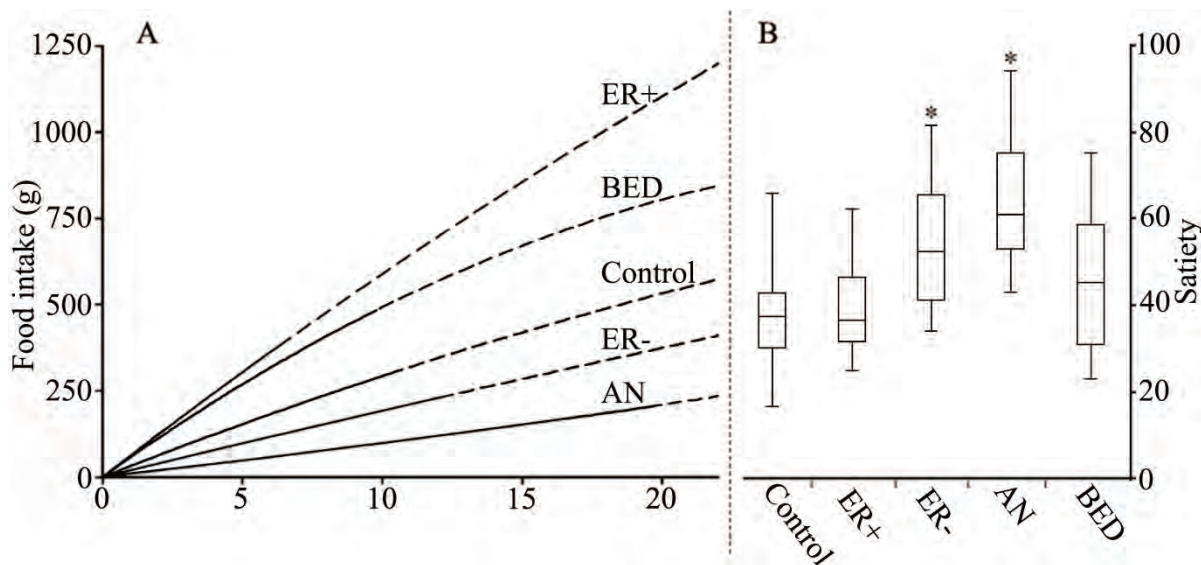

Figure 9. Schematic representation of food intake (A) and satiety ratings (B) in Linear Eaters eating without constraints (Control). When eating at a decreased (ER-) or increased (ER+) speed Linear Eaters adopt a pattern of eating similar to that of patients with Anorexia Nervosa (AN) and Binge Eating Disorder (BED). * Significantly different from Control.

It is noteworthy that the eating pattern and the satiation ratings of the Linear Eaters are similar to those reported above (Figure 6).

These results show that Linear Eaters exhibit disordered eating and satiation similar to AN and BED patients when their speed of eating is experimentally decreased and increased respectively.

Paper III: Synchronizing food intake and chewing

The CIC is a measure of the removal of food from a plate during eating, but eating, of course, is chewing and swallowing. Hence, we aimed at a method for measuring both of these in the next study using Mandometer®and video recording.

Video recording of chewing yielded very similar results as magnetic recording of jaw displacement (Paper III, Figure 2) both at chewing with no constraints and at several different frequencies maintained through external control. Hence, video analysis produces valid results of chewing.

Similarly, Mandometer® weight loss data were corrected by use of video derived data and found to be valid, providing evidence for the reliability the semi-automatic procedure.

Women took about 50 mouthfuls followed by one chewing sequence most of which included 8 to 20 chewing cycles (Figure 10A). More mouthfuls occurred during the first and the last thirds of the meal (Figure 10B), while the weight of separate mouthfuls decreased in the last third of the meal (Figure 10C). Irrespective of the mouthful weight, the chewing cycles per sequence, the chewing frequency and the duration of the chewing sequences did not change across the meal (Figure 10D), inferring stability in chewing patterns across meals. Finally, the pauses between chewing sequences and the subsequent mouthfuls were significantly longer in the middle of the meal, corresponding to a drop in the number of mouthfuls (Figure 10E).
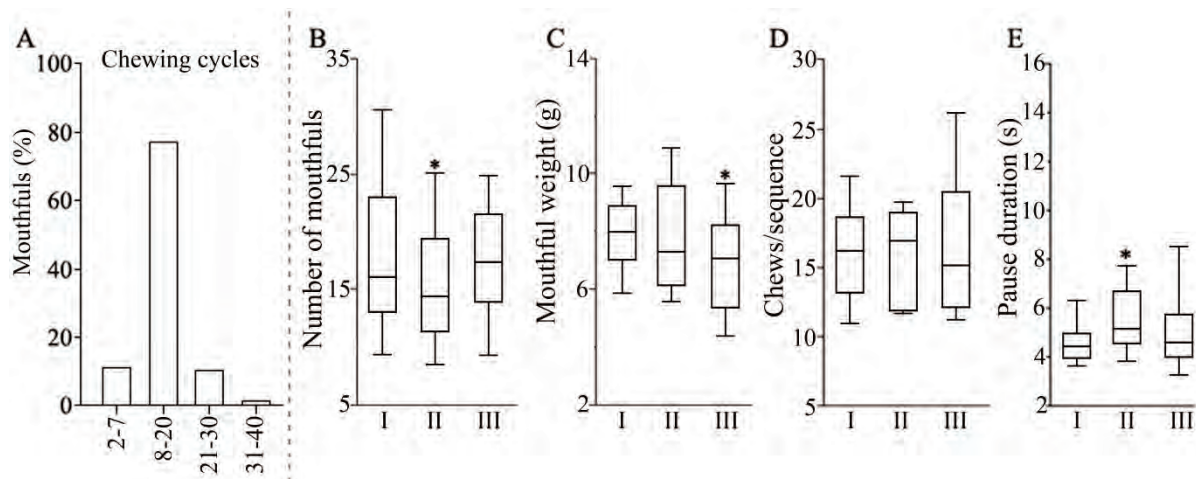

Figure 10. Number of chewing cycle per mouthful (%) (A), number (B) and weight (C) of mouthfuls, chewing cycles per chewing sequence (D) and duration of pauses between mouthfuls (E) in eleven women. The meal was divided into thirds (I-III).
* Significantly different from I.

The second and last quartile of each mouthful had more chewing cycles, indicating the stereotypic character of human chewing behavior (Figure 11).
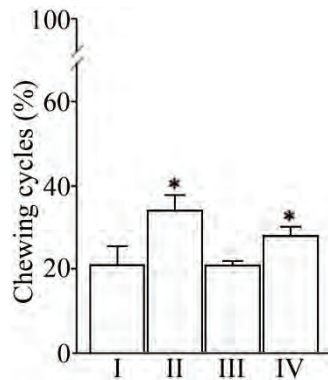

Figure 11. Distribution of chewing cycles within quartiles (I-IV) of the chewing sequences of a meal. * Significantly different from I.

Interestingly, the chewing frequency for a piece of chewing gum was markedly lower than that for food (0.95 [0.9-1.05] vs 1.75 [1.41-2.16] chews/s).

These results validate our error-correcting and chewing quantification procedures, proving the reliability of our data collection methodology. Analysis of the data provides details about the changes in eating behavior during a meal.

Paper IV: Deceleration equals smaller mouthfuls, longer chewing sequences and shorter pauses by the end of the meal

Having developed a method for detailed analysis of eating behavior, we examined food intake and chewing in Decelerated and Linear Eaters.

Two groups of Decelerated Eaters differed from the Linear Eaters in the manner described in Figure 6, despite the fact that somewhat different food was served; the results are therefore not repeated here (Paper IV, Figure 1). The only and slight difference was that the tendency of a longer meal amongst the Linear Eaters (Figure 6) was statistically significant.

More interestingly, while Decelerated Eaters took fewer mouthfuls of lower weight during the last third of the meal, Linear Eaters distributed their mouthfuls evenly across the meal. The two groups had similar chewing frequencies across the meals, but the length of the chewing sequences among Decelerated Eaters was significantly greater during the third part of the meal, an effect not seen among Linear Eaters. Finally, during the second third of the meal, Linear Eaters took significantly longer pauses between chewing sequences.

Figure 12 gives a schematic representation of the difference in mouthfuls and chewing pattern between decelerated and linear eaters. While Decelerated Eaters take mouthfuls of progressively lower weight and display more chewing sequences by the end of the meal, the eating behavior of the Linear Eaters remains stable over the course of the meal.

During the videotaped sessions with a chewing gum the other group of Decelerated Eaters had higher chewing frequency than the Linear Eaters (Figure 13A). Confirming the findings in Paper

III, frequencies with the chewing gum were significantly lower than the chewing frequencies during the meals for the respective groups. A strong correlation was shown between the chewing frequency with a piece of gum and the initial speed of eating for the meals of each individual (Figure 13B).

Combining the findings from the eating and the chewing sessions from the two groups of eaters, it was proposed that the well established (Kissileff, et al., 1980; Westerterp-Plantenga et al, 1990) difference in the initial speed of eating between Decelerated and Linear Eaters may be an expression of a difference in the baseline chewing frequency among those individuals

This paper adds information about the differences between the decelerated and linear eating styles and shows that Decelerated and Linear Eaters display differences in their baseline chewing characteristics.
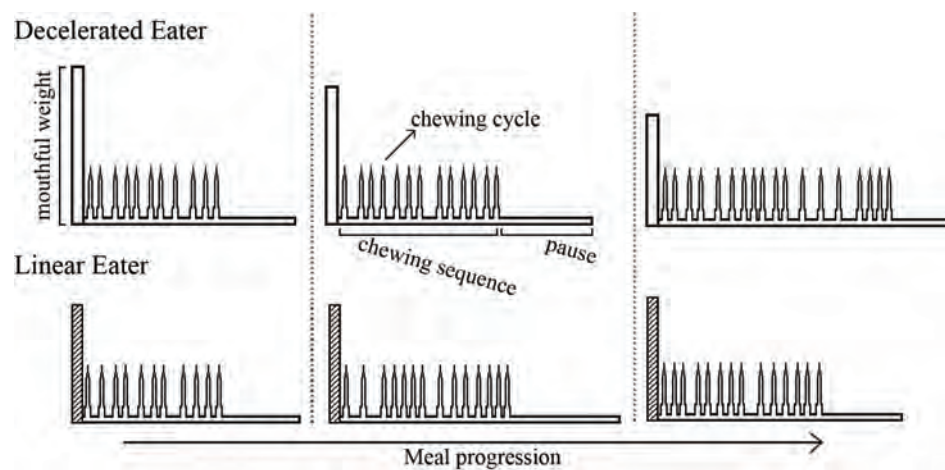

Figure 12. Schematic outline of the weight of mouthfuls and the pattern of chewing over the course of a meal in a Decelerated and a Linear Eater.
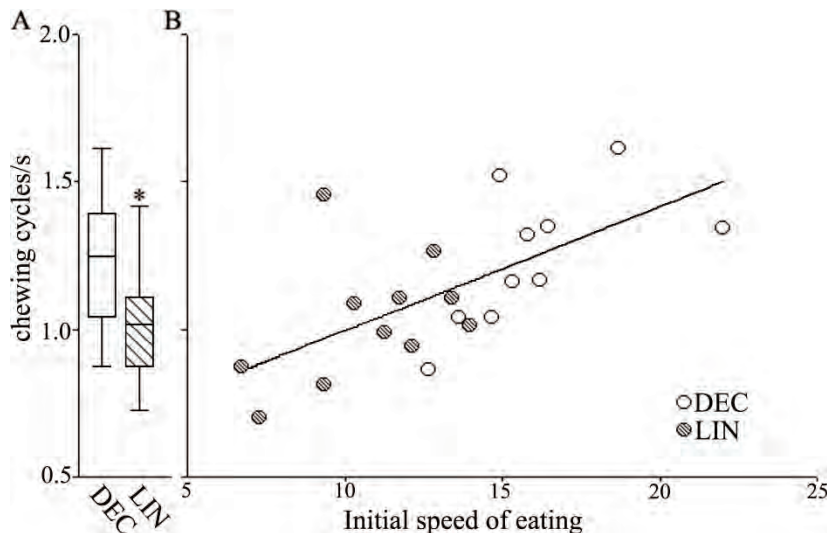

Figure 13. Chewing frequency with a piece of chewing gum in Decelerated (DEC) and Linear (LIN) Eaters (A) and correlation between this frequency and the initial speed of eating food (B).
* Significantly different from DEC.

DISCUSSION

The research presented in this thesis aims at improving the treatment of eating disorders and obesity in collaboration with the Mandometer and Mandolean clinics and relates to relevant animal research that we have performed (reviewed in Södersten et al., 2008). Thus, while the main focus of the covered papers is on the analysis of eating behavior of normal weight women (Papers I, II and IV), Paper II is touching on the comparison between normal eating behavior and the eating patterns of underweight and obese patients and there lies the scope of the work.

Theoretical and clinical background

Anorexia nervosa has a long history in literature. Apart from a wide variety of descriptions in non-medical literature, deriving from the identification of eating disorders as an important western society issue (Treasure et al., 2010), Gull provided a comprehensive description of the disorder as early as 1874 (see Gull, 1894). Hypothermia and hyperactivity were identified as the main symptoms of the anorexic patients and favorable clinical effects were reported by treating these symptoms (Gull, 1894). Since then, the focus of clinical interventions has shifted, targeting various mental (often not well defined) characteristics of the patients, including, but not limited to: anxiety, depression, obsession, temperamental vulnerabilities and cognitive deficits (Kaye, Fudge, Wagner & Paulus, 2011; Klump, Bulik, Kaye, Treasure & Tyson, 2009). Despite its popularity and its longevity, it is widely accepted that this perspective has not yielded satisfying clinical results in anorexia (Striegel-Moore & Bulik, 2007; Treasure et al., 2010). Similarly, current interventions have proven ineffective in dealing with the ever increasing problem of obesity (Ledford, 2010), despite the excessive allocation of funds to support research on this field (Loveman et al., 2011). Recently, it has been recognized that "reversing the tide of obesity" cannot be based upon a "miracle" pharmacological intervention and that, instead, more attention should be paid to alternative interventions targeting the improvement of dietary intake and the increase of physical activity (Dietz, 2011).

The poor outcome of mainstream clinical interventions for eating disorders and obesity dictates the development of new theoretical perspectives and clinical strategies to deal with the problems of under- and over-eating. We have reviewed the theoretical background, the outcome and the treatment in AN many times (Ioakimidis et al., 2011; Zandian et al., 2007). Recently we have also presented our view of the problem of obesity (Södersten et al., 2011). Briefly, we argue that eating is controlled by external factors, mainly the physical and economic prize of food. If that price is high, individuals are able to maintain a low healthy body weight. Once the price is reduced, people gain weight "passively" as the result of a phenotype that evolved to eat whenever provided with the chance. Evolution has not encouraged mechanisms of satiation since starvation has been the human condition and those who can eat a lot have been favored. Thus, obesity evolves without protection from endogenous mechanisms (Södersten et al., 2011). This view has recently been shared by others (Swinburn et al., 2011). Anorexic patients are able to manage starvation, i.e., they have a phenotype that resists the shortage of food, our main evolutionary threat. They are captured in their starved condition through neural mechanisms of conditioning, which we have described in detail (Södersten et al., 2008). For these reasons, our clinical starting point is that both under- and

overweight patents need external support to regain and maintain a healthy body weight. The role of the brain is permissive rather than controlling.

The effectiveness of interventions focusing on the normalization of eating behavior in both AN and obesity (Bergh at al., 1996; 2002; Ford et al., 2010) was a strong motive to investigate the eating patterns of normal individuals in detail, in order to identify behavioral risks that potentially lead to disordered eating. Once this goal was accomplished, we tried to dissect eating behavior into its basic behavioral elements in order to gather additional information about the different eating styles. The final step was to try and associate our findings with the existing knowledge about the neurobiological aspect of eating and formulate a theoretical framework that might guide future research.

Describing a meal with CICs

The CIC has been used extensively in studies on eating behavior in humans, but there are very few descriptions of changes in its characteristics in patients and the effect of pharmacological and other interventions has been studied only occasionally (see discussion in Zandian et al., 2011). Here, we attempted a systematic study of the parameters of the CIC in two previously defined types of eaters: Decelerated and Linear.

Modeling intake over time

The CIC was used to describe food intake over time, i.e., as a model of the meal, the basic unit of eating behavior (Woods & Strubbe, 1994). First proposed by Meyer & Pudel (1972) and replicated by Kissileff et al. (1980), a quadratic curve is fitted to the change in intake over time. The CIC is useful for the description of an individual's eating style, the coefficients are measures of the initial speed of eating (the l-coefficient) and the rate at which intake changes over time (the k-coefficient) (Kissileff et al., 1982). All CIC characteristics have a high test-to-test repeatability under similar circumstances (Hubel et al., 2006), pointing to the stable nature of human eating behavior (Martin et al., 2005). The high values of the intra-class correlation coefficients in Papers I and III confirm the above finding.

However, it has also been shown that the CIC is modified by taste, texture and smell (Kissileff et al., 1982; Yeomans, 2006; Zijlstra et al., 2010; 2011), preload (Spiegel, Shrager & Stellar, 1989; Yeomans, Lartamo, Procter, Lee & Gray, 2001), pharmacological agents (Yeomans & Gray, 1997) and food deprivation (Kissileff et al., 1980; Spiegel et al., 1989; Zandian et al., 2011). Yet, despite all the effort, there is no evidence that any of the parameters of the CIC can be clearly related to a biological factor (see Zandian et al., 2011).

In order to minimize the influence of external factors, we have standardized our experimental procedures. Thus, the inclusion criteria, e.g., gender, age, BMI and diet habits, were similar in all studies. We took care in screening participants for medical conditions including the use of drugs, resulting in homogenous, readily comparable, groups. To further minimize external influences, all meals were served during lunch hours in a secluded room without windows and subjects had no reading materials, music or mobile phones. Subjects participated in an introductory meal to get familiar with the procedure. AN and BED patients were already familiar with the procedure as they had enrolled in the Mandometer and Mandolean clinical programs. Additionally, the timing and content of breakfast were standardized and the participants were asked to refrain from snacking

before the test meal, in an effort to standardize satiety levels at the beginning of the meals. Subjective measurements on self-report questionnaires were collected around the meals, allowing us to identify methodological and state session-specific inconsistencies. Mandometer® was used in all studies, video-cameras were added in some and in order to facilitate comparison, the food was carefully selected. Constraints in the availability of the food forced us to change from "Nasigoreng" to "Grönsakspytt med kyckling" in some of the studies (see Materials and methods). However, food intake and the meal durations remained about the same after this minor culinary shift. Also, the other characteristics of the CIC remained unchanged suggesting that "Nasigoreng" and "Grönsakspytt med kyckling" were perceived in a similar manner. In addition, Decelerated and Linear Eaters displayed very similar CICs' characteristics in the control meals suggesting successful methodological standardization. By contrast, AN and BED patients ate restaurant foods, as part of their clinical program. However, as their foods had a comparable macronutrient composition and caloric density, this methodological weakness is probably a minor one.

CIC characteristics

Decelerated and Linear Eaters. Normal weight women were identified as Decelerated and Linear Eaters, as was first done by Meyer & Pudel (1972), and using the terminology introduced by Westerterp-Plantenga (1988; 1990; 2000). The groups differ in that Decelerated Eaters have a high initial speed of eating which decreases over the course of the meal, while the Linear Eaters have a lower, stable speed of eating throughout the meal. Both groups eat about the same amount of food but Linear Eaters take more time to complete their meal. Our behavioral results partly agree with previously reported results (Westerterp-Plantenga, 2000), confirming the usefulness of the CIC for the identification of an individuals' eating pattern. Unlike previous reports, eating behavior was the main outcome, avoiding questionnaire scores. This is because DEBQ scores did not correlate with the cumulative food intake (Paper I, Table 3, Appendix). Interestingly, we found that when Linear Eaters are trained to eat in a decelerated fashion, there is a significant reduction in their restrained eating scores, suggesting that eating behavior causes cognitive changes rather than the other way around (Zandian et al., 2009). These findings indicate the importance of eating behavior over cognitive processes and constitute the main reason why our work concentrates on the analysis of eating behavior itself.

One should note the difference in the range of values for the rate of deceleration (the k-coefficient) between the first and the last two papers. This difference is the result of the methodological refinements of the way the CIC was fitted to the intake data (time series in seconds instead of minutes), rather than a real change in behavior; the actual rate of deceleration remained unchanged.

Effect of experimental changes in the speed of eating. In addition to recording intake over time using Mandometer®, we experimentally changed the conditions by displaying real-time feedback on the computer screen (also see Zandian et al., 2009). We found that Linear Eaters ate more food when directed to eat at an increased speed (ER+) and less food when directed to eat at a decreased speed (ER-). By contrast, Decelerated Eaters ate less food in the ER+ and the same amount in the ER- condition. In Paper II these results were replicated in the Linear Eaters. Additionally, Linear Eaters ate significantly more in the two other experimental conditions, i.e., the Short and Interrupt, supporting the notion that they are sensitive to external changes. The Interrupt condition was tested as it has been suggested that taking breaks within a meal may affect food intake and even be used to control body weight in the obese (e.g., Brownell, 2000); our results corroborate those of others

(Yeomans et al., 1997), but, interestingly enough, only for Linear Eaters. Thus, our results do not agree with the popular idea that interruptions during a meal reduces food intake (Brownell, 2000).

In order to explain the differences among eaters, we hypothesized that decelerated eating is the default eating style, described in children from 4 to 6 years of age (Jung, 1973), following the patterns of many other behaviors, reported long ago (Skinner, 1938). Conversely, we suggested that linear eating is a behavioral risk factor for disordered eating that emerges from dieting and a high level of physical activity, the main causes of eating disorders (Zandian et al., 2009). Our recent report that Linear Eaters are less able to compensate by eating more food after fasting than Decelerated Eaters, verifies the hypothesis (Zandian et al., 2011).

Satiety in the Decelerated and Linear Eaters. Estimates of satiation collected during meals were modeled differently than proposed in the past (e.g., Yeomans, 2000), by use of a sigmoid rather than quadratic model. Decelerated Eaters experienced higher levels of satiation after the control meal Linear Eaters. More interesting, Linear Eaters estimated their satiation higher after eating at an experimentally decreased rate, despite eating less food. Conversely, they estimated their satiation lower when eating at an experimentally decreased rate, yet they ate more food. The Decelerated Eaters resisted these experimental challenges and they estimated their satiation in accord with the amount of food that they consumed. These observations again indicate that the linear pattern of eating may be a behavioral risk factor for loss of control over food intake and body weight as food intake gets uncoupled from the experience of satiation as soon as there is a shift in the speed of eating among these subjects.

AN and BED patients. Our findings that BED patients ate quicker, consumed more food and had shorter meals than the Linear Eaters agree with previous reports (Walsh & Boudreau, 2003). Even though the recorded meals were not binge eating episodes, the main characteristics of disordered eating persist (Walsh, 2011). The recorded differences from the control group contradict the results in a number of studies that were unable to find cumulative meal differences between lean and obese individuals (Barkeling et al., 1995; Laessle et al., 2007; Llewellyn et al., 2008; Zijlstra et al., 2011). This disagreement can possibly be attributed to the homogeneity of our sample that included only hospitalized patients. While the eating style in the BED group was linear they displayed a large variation in CIC characteristics. That points to a wider range of eating patterns in this group than in the AN patients, whose linear eating style is very pronounced (Figure 8). The reported characteristics of the anorexic eating pattern are novel and complement our previous report concerning the cumulative meal characteristics in a similar group of patients (Zandian et al., 2007). Also, they fit with the clinical impression that AN patients eat slowly and with the slow eating of men in experimental starvation (Keys at al., 1950)

Similarities among patient groups and Linear Eaters. When the eating speed of the Linear Eaters was experimentally decreased and increased, they assumed a pattern of eating behavior strikingly similar to that of the AN and the BED patients, respectively, and more similarities were found in the reported satiety after the meals (Figure 9). These results demonstrate that normal-weight, Linear Eaters have the potential to simulate the disordered eating patterns displayed by eating disorder patients, unlike the Decelerated Eaters, and therefore support our hypothesis that the linear eating is a behavioral risk for the development of disordered eating. Independently, these findings do not reveal the precise causal relationship between eating style and the development of eating disorders, neither do they explain how and why does the linearity develops in some individuals and not in others. However, our recent finding that short-term fasting increases linearity of eating in women (Zandian et al., 2011) suggests that dieting might be the cause of linear eating.

From CICs to mouthfuls and chewing

Synchronizing food intake and chewing. The need to describe the behavioral elements affecting the shape of the CIC and the early work on curves of cumulative drinking in rats (e.g., Stellar & Hill, 1952), led us to develop a method for analyzing chewing during meals in tandem with the CIC. For this we used the Mandometer® during video recorded meals and we developed a semi-automatic procedure for the analysis of the results.

Probably because it is technically difficult there are few successful attempts to relate chewing and food intake over the course of a meal. Bellisle & Le Magnen (1980; 1981) used invasive equipment (Bellisle at al., 2000) and served artificial food items as did Spiegel and colleagues (1993; 2000), who recorded chewing using electromyography. Semi-liquid food was used in another study that found a direct relationship between oral processing time (but not chewing) with total intake (Zijlstra et al., 2009). Unfortunately, in the studies that examined the problem using realistic food, the results were presented in an unclear manner (Westerterp-Plantenga et al., 1980; 1988). Videotaped meals have been analyzed before (Llewellyn et al., 2008), but not associated with an analysis of food intake. However, the studies concerning the mechanisms of mastication in animals and humans (see Introduction) have provided detailed information on the specifics of the chewing mechanism, but as a rule, a fixed number of mouthfuls/chewing episodes were analyzed, rather than the chewing over the meal.

Video recording of chewing has already been validated against electromyography (Hennequin et al., 2005), a finding that we confirmed by comparing video recording with magnetic recording of jaw displacement, a method with high resolution considered the "golden standard" (Grigoriadis et al., 2011; Soboļeva et al., 2005A; 2005B). The comparison showed that while video analysis of chewing does not differentiate among types of chewing, it is adequate for the quantification of the chewing cycles regardless of frequency.

In addition to chewing cycles, video recordings were coded for the occurrence of spoonfuls and mouthfuls, which were also outcome measures across the meals. Our familiarity with the nature of the data recorded by Mandometers® allowed us to develop a computerized procedure for the correction of the recorded data series, using the coded mouthfuls as objective anchor points. The validity of our correctional technique was assessed by comparison with two separate manual corrections performed by trained researchers. The introduction of this semi-automatic procedure enables faster, systematic analysis of food intake and chewing, and it is ideal for use in comparisons of group characteristics amongst Decelerated against Linear Eaters. The combination of our technique with a fully automatic method of chewing and mouthful quantification (e.g., Amft et al., 2007) might prove even more powerful for the study of eating behavior in humans.

Food intake and chewing. The method was developed on women eating with a rate of deceleration between that of Decelerated and Linear Eaters.

In these "Intermediate" eaters, the average number of mouthfuls per meal was in the lower range reported by Bellisle and colleagues (2000), while it was somewhat higher than the bite number reported for a control group by Zijlstra and colleagues (2011). Such differences can be expected from differences in the foods used (See Introduction). In the Intermediate and the Decelerated Eaters there was a decrease in the weight of the mouthfuls over the course of the meal. By contrast, no such change occurred among Linear Eaters. These results agree with previous

results for these groups (Westerterp-Plantenga et al.,1990). The changes in mouthful weights over time, reveal the weaknesses of studies that use food items of standard size (e.g., Bellisle & Le Magnen 1980; 1981), or that calculate average mouthful sizes by dividing total food intake with the number of observed mouthfuls (e.g., Burger, Fisher & Johnson, 2011).

The stable chewing frequency across the meal in all groups and the similarities in the distribution of chews in the chewing sequences suggest that the human chewing during meals is relatively stereotyped. The chewing frequency (1.7 chews/s) was higher than what has been reported before (1.25 and 1.44 chews/s) (Bellisle & Le Magnen, 1981; Spiegel, 2000). Although the chewing frequency did not change for different foods in the previous studies (palatability, but not texture, varied in Bellisle & Le Magnen, 1981), we suspect that the chewing pattern depends on the sensory characteristics of the food (Grigoriadis et al., 2011; Wintergerst et al., 2008; Woda et al., 2006).

The observed differences in the duration of the chewing sequences over time complete the description of the differences between Decelerated and Linear Eaters. Thus, deceleration appears to be the result of decreased amount of food, chewed for longer time towards the end of the meal, while the chewing frequency and chewing sequence are stable (Figure 12).

Default chewing rhythm. The rate of chewing a piece of chewing gum was lower than that of chewing food and agrees with previously reported values (Brandini, Benson, Nicholas, Murray & Peck, 2011). The blunt characteristics of the chewing gum compared with the food may explain the difference (Woda et al., 2006). However, feedback for ingested food may obviously contribute to this difference. Use of chewing gum provides a test in which such feedback is minimal or at least reduced and it is tempting, therefore to suggest that such a test reveals the "default" chewing rhythm.

Interestingly, there was a strong correlation between chewing rate with a piece of chewing gum and the initial speed of eating food, i.e., the behavioral difference that reliably differentiates between the Decelerated and Linear Eaters. Hence, there might be baseline differences in chewing rhythm amongst Decelerated and Linear Eaters.

An extended framework for eating disorders

Our group has pointed out that the two risk factors for AN are dieting and increased physical activity (Bergh & Södersten, 1996; Södersten et al., 2008). Dopamine is released in mesolimbic terminals as a consequence, hence reward mechanisms are activated by the risk factors of AN (Bergh & Södersten 1996; Scheurink, Boersma, Nergårdh & Södersten, 2010). Recently, the notion that reward system has a role in anorexia has gained popularity (e.g., Wagner et al., 2007), but the cause-effect relationship between dopamine and AN remains unclear because most patients remain symptomatic when studied (Cowdrey, Park, Harmer & McCabe, 2011). On our perspective, the initial dieting or enhanced physical activity is rewarding, sensitizing the reward system which is then conditioned to the rewarding stimuli, through activation of the noradrenalin attention network (Bergh & Södersten 1996; Ioakimidis et al., 2011; Södersten et al., 2008). There is no need to postulate dysfunction in any neural system, however, only engagement (Bergh & Södersten, 1996). The definite test of our hypothesis is the examination of patients who had AN but are free of symptoms. No such group of patients has been studied.

Chewing on the mind. One weakness of our early model was the neglect of the emotional profile that characterizes eating disorder patients. The results from Papers III and IV encouraged us to develop an extended version of our model that bridges eating behavior to mood changes, at the level of the brain (Ioakimidis et al., 2011). Our finding that normal-weight individuals can be grouped into clearly defined eating styles and that Linear Eaters have the potential to simulate the disordered eating behavior and the discovery that the two groups of eaters have different default chewing rhythms, yields the hypothesis that slowing of this motor rhythm causes changes in mood.

It has been shown that the serotonin cells in raphe nuclei, which are related to prefrontal cortex areas activated during chewing (Bordukalo-Niksic et al., 2010; Celada et al., 2001; Kamiya et al., 2010) are targeted by selective serotonin reuptake inhibitors (SSRIs), used for treating depression and anxiety (Ipser, Stein, Hawkridge, & Hoppe, 2009; Savitz, Lucki & Drevets, 2009). Interestingly, SSRIs have been shown to cause bruxism (Gerber & Lynd, 1998), and they remain ineffective in treating eating disorders (Kaye, Fudge & Paulus, 2009). Early life exposure to SSRIs results in emotional alterations (Ansorge, Zhou, Lira, Hen & Gingrich, 2004) and locomotor rhythm disruptions in mice and other animal models (Airhart et al., 2007; Dunbar, Tran, & Whelan, 2010). These behavioral effects of SSRIs are conspicuously similar to the effects caused by long term starvation in humans (Keys et al., 1950). The subjects participating in the study on starvation used lots of chewing gum and ate their meals very slowly. It is tempting to speculate that there is a relationship between the slowing of the eating rhythms in AN and human starvation and the emotional changes that occur in these condition.

The proposed relationship between the chewing rhythm and emotion needs further verification. Interestingly, however, psychomotor slowing is conspicuous in human depression (Salamone, Correa, Farrar & Mingote , 2007; Schrijvers et al., 2009). Whether this finding can be extended to chewing is an open question.

No one knows what accounts for the marked gender differences in the prevalence of eating disorders, which contrast to the situation in obesity. Interestingly, Zandian et al. (2011) found that men responds differently to fasting than women; adopting a more decelerated pattern of eating. However, no known sex difference in endocrine and metabolic parameters can, as yet, be related to the reported sex difference in eating behavior (Zandian et al., 2011).

Also, the role of physical activity for the CIC and eating behavior should be explored. In ongoing experiments we find that physical activity is enhanced in AN, but that the patterns of activity over the day is normal and that in obesity physical activity is at an expected reduced level. Because evolution has acted on one aspect of physical activity, foraging for food (Södersten, Nergårdh, Bergh, Zandian & Scheurink, 2008) and because the high level of physical activity is a main clinical problem associated with AN, exploration of the cause - effect relationship between physical activity and eating behavior is a research priority that is likely to yield clinically important results.

CONCLUSIONS

1. Women display an either decelerated or constant speed of eating. The two types of eaters ingest a similar amount of food, but Linear Eaters take more time to eat.

2. When Linear Eaters are challenged to eat experimentally manipulated meals, they are at risk of losing control over their food intake. That is not the case for Decelerated Eaters.

3. Satiety estimations after the meals are dissociated from the actual food intake in Linear, but not in Decelerated Eaters.

4. Linear Eaters respond to experimentally accelerated or decelerated meals in striking similarity to BED and AN patients, respectively. Thus, linear eating may be a behavioral risk for the development of disordered eating.

5. Simultaneous analysis of chewing and food intake over the course of a meal is suitable for the investigation of the behavioral elements of eating in humans.

6. Deceleration of food intake over a meal occurs due to the decreasing weight of the mouthfuls and the increasing duration of the subsequent chewing sequences. In Linear Eaters these characteristics remain stable across the meal.

7. The chewing frequency, the distribution of chewing within the chewing sequences and the length of the inter-mouthful pauses is relatively stable for both types of eaters.

8. The default chewing frequency is higher in Decelerated than in Linear eaters.

9. The observed eating and chewing pattern in Linear Eaters might be related to the changes in mood observed in eating disorders.

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