Assessment of Function, Structure and Working Memory in Adolescents with a Recent Diagnosis of an Eating Disorder

LINDA SOLSTRAND DAHLBERG
Abstract

Body, weight and shape related obsessions and ruminations are characteristic traits of individuals with eating disorders (ED) that are found to predate the onset of the disorder. Individuals with chronic ED display altered neural activation in response to food stimuli, and are reported to have volumetric differences compared to healthy individuals, which is likely an effect of prolonged starvation. ED individuals are also seen to dispose an attentional bias to food stimuli, even when perceived sub-consciously, which are reported to interfere with cognitive tasks, including working memory (WM). However, whether the differences in neural activation and structure are present in adolescents with a recent ED diagnosis is not known.

In paper I we describe how images of high- and low-calorie foods resulted in greater responses in the prefrontal circuitry in ED adolescents compared to healthy controls (HC). Obsessive-compulsive symptoms in ED individuals were associated with prefrontal circuitry and cerebellar activation, whereas faster reaction times to the WM were associated with greater superior frontal gyrus activity. The findings indicate that ED cognitions may be linked to WM abilities, both of which are associated with frontal cortex functioning. WM performance is examined further in paper II, where we found that the presence of subliminal food images were seen to disrupt WM performance in terms of slower reaction times and less correct responses in ED but not HC. The WM interference was associated with increased activity in the parietal and superior temporal cortex. WM interference caused by subliminal food stimuli may reflect a pre-attentive bias to food in adolescents with ED, which could be a risk factor for further development of an ED.

The structural differences in brain volume between adolescents with ED and HC were examined in paper III. ED symptoms were found to be associated with volume differences in insular cortex and superior temporal gyrus, whereas obsessive-compulsive symptoms were associated with reduced volumes in the putamen and cerebellum. These volumetric differences in regions implicated in restraint, obsessions and WM are likely to precede structural variations caused by starvation as seen in chronic ED’s. Connectivity from these regions, in addition to other regions believed to be implicated in ED, was studied in paper IV. Fronto-parietal regions as well as the insula showed increased connectivity in ED, whereas connectivity from the mesolimbic reward regions did not differ from HC. Regions with increased connectivity in ED are involved with self-awareness, body image and ED related ruminations, connections that could influence how one’s body is perceived.

In conclusion, the studies included in this thesis describes changes in functional activity, connectivity and brain volume in regions involved with ED cognitions, eating behaviour, and body image in adolescents recently diagnosed with an ED.

Keywords: Eating disorders, anorexia nervosa, bulimia nervosa, eating disorders not otherwise specified, fmri

Linda Solstrand Dahlberg, Department of Neuroscience, Functional Pharmacology, Box 593, Uppsala University, SE-75124 Uppsala, Sweden.

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Abbreviations

ACC  Anterior Cingulate Cortex
AN   Anorexia Nervosa
ANCOVA Analysis of Covariance
BIS-11 Barratt Impulsiveness Scale
BMI  Body-mass index
BN   Bulimia Nervosa
DLPFC Dorsolateral prefrontal cortex
DSM  Diagnostic and statistical manual of mental disorders
ED   Eating Disorders
EDE-Q Eating Disorder Examination-Questionnaire
EDNOS Eating disorders not otherwise specified
fMRI Functional magnetic resonance imaging
HC   Healthy Controls
OCD  Obsessive Compulsive Disorder
OCI-R Obsessive-compulsive inventory
PFC  Prefrontal cortex
PMC  Premotor cortex
SMA  Supplementary motor area
TBV  Total brain volume
Eating disorders (ED) are characterized by unhealthy preoccupations in regards to the weight and shape of one’s body, leading to restrictive or compensatory methods with the aim of losing weight. As a diagnostic category in the fourth edition of the diagnostic and statistical manual of mental disorders (DSM) [1], ED includes anorexia nervosa (AN), bulimia nervosa (BN) and eating disorders not otherwise specified (EDNOS). ED has been described as a disorder predominately found in Western societies [2], however recent studies describe increasing prevalence in non-Western countries, potentially caused by the spread of Western beauty standards [3]. ED are also associated with a narrow age of onset, and affects primarily females [4]. There is an increasing prevalence of AN in females between ages 15-19 [5]. It is not clear whether this is due to increased awareness and early detection, or if there is an increasing external pressure in the society to strive for thinness. As a psychiatric disorder, ED is associated with high mortality rates, where some studies have reported a higher standardized mortality ratio in ED compared to any other psychiatric disorder [6]. Mortality is the highest in AN, where the annual mortality rate is reported to be 5 per 1000, person-years, whereas BN with the lowest rate is 1.7 per 1000 person-years, and finally EDNOS is 3 per 1000 person-years [6].

AN and BN are both well-known and frequently studied diagnoses in ED research, however, the most common ED diagnosis is EDNOS, counting up to 60% of the population administered to ED clinics [7]. EDNOS is a wide diagnostic category for ED cases that does not fulfill the specific criteria for AN or BN. Binge-eating disorder (BED) is also included in this diagnosis. Patients with EDNOS may display varied clinical symptoms, similar to that seen in both AN and BN, with comparable severity of psychological and physiological symptoms [8]. Recently diagnosed ED individuals may display a mix of ED behaviours, and fluctuate between sub-diagnoses in the first six months while the disordered ED cognitions remain [9, 10]. Even though it is the biggest diagnostic group, there are currently limited studies including EDNOS patients.

The diagnostic criteria for ED have changed with the most recent edition of the DSM (DSM-V, [11]). AN criterion is now less strict as amenorrhea is no longer included, and BED which was a subcategory of EDNOS, is now a specific diagnosis. With these changes, a substantial proportion of what was previously EDNOS cases (i.e. because of not fulfilling criterion of amenor-
rhea), will now receive a more specific diagnosis of AN or BED [12]. Moreover, the EDNOS category is now replaced with “Other specified feeding or eating disorders” (OSFED), and “Unspecified feeding or eating disorders” (UFED). The first category, OSFED, is for subthreshold cases of AN (i.e. atypical AN), BN (BN of short duration/ low frequency), and BED (BED of short duration/ low frequency) as well as purging disorder and night eating syndrome. UFED is a separate category for cases where there is a lack of information to get a specific ED diagnose and does not fit the criteria for OSFED. Since the studies discussed in the current thesis was carried out before the DSM-V was published, ED diagnoses referred to in the text are in accordance with DSM-IV criteria which are described in Table 1.

Long-standing ED has damaging effects on the body, including cardiovascular problems, loss of bone density and teeth erosion, hair loss, dry skin, but also changes in brain structure and function [13, 14]. Thus early identification is important before the disorder manifests. Identifying early risk factors before disease onset could help intervention, and improve treatment before eventual development of chronic illness. Moreover, it is difficult to determine the consequences of a long-standing ED. Therefore, studying adolescents in the beginning of their ED may provide insight to neural characteristics and behaviour that is not a result of a chronic ED.
Table 1: DSM IV diagnostic criteria for eating disorders [1]

**Anorexia Nervosa**
- A refusal to maintain body weight at or above a minimally normal weight for age and height.
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- In postmenarcheal females, amenorrhea.

**Bulimia Nervosa**
- Recurrent episodes of binge eating.
- Recurrent inappropriate compensatory behaviour in order to prevent weight gain.
- The binge eating and compensatory behaviours both occur, on average, at least twice a week for three months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of Anorexia Nervosa.

**Eating Disorders Not Otherwise Specified (EDNOS)**
- For females, all the criteria for Anorexia Nervosa are met except that the individual has regular menses.
- All the criteria for Anorexia Nervosa are met except, despite significant weight loss, the weight is in the normal range.
- All the criteria for Bulimia Nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for a duration of less than three months.
- The regular use of compensatory behaviour by an individual of normal body weight after eating small amounts of food
- Repeatedly chewing and spitting out, but not swallowing, large amounts of food.
- Binge-eating disorder: recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviours characteristic of Bulimia Nervosa.
Risk factors and traits

EDs are characterized by specific traits that are considered risk factors for disease development. These traits are frequently observed already before disease onset. Individuals who later develop AN tend to have a restrictive personality, obsessions, perfectionism and anxiety which may be considered risk factors [15, 16]. For example, high levels of perfectionism are associated with illness duration, and is a sustaining trait even following reduction of ED symptoms [17]. Along with high self-imposed standards [18], individuals with AN show restriction not only to food intake, but also other hedonic pleasures in life [19]. Restriction of food intake may have a diminishing effect on anxiety [20], another risk factor related to AN. Anxiety during childhood is linked to symptom severity in adults who later develop AN [21, 22]. Moreover, ED is associated with high morbidity, where anxiety disorders are frequently observed in individuals with ED [23]. In particular AN is often comorbid with obsessive-compulsive disorder (OCD) [23-26], which was categorized as an anxiety disorder by the DSM-IV [1]. OCD is in many cases reported to be present already before the onset of an ED [27, 28]. Both obsessions and compulsions are components in the diagnostic picture of AN: patients commonly have obsessions related to food, body and weight, along with compulsive efforts to lose weight. On the other hand, individuals with BN show impulsive traits [29], with frequent binge-eating episodes in combination with a lack of control of food intake. Impulsivity can be defined as performing compulsive acts as response to impulses without considering the following consequences. Impulsive behaviours (i.e. binge-eating, substance abuse) are believed to be linked to reward system deficits [30]. Binge-eating behaviour and over eating, as seen in obesity, may reflect a sensitive reward system leading to increased food intake, similar to the reward sensitivity hypothesis of drug abuse [31, 32].

Attention bias

Attention bias may be another risk factor for ED, as studies show that ED individuals show increased attention towards food and body-related images [33]. It has been suggested that attention bias to disease-salient stimuli may have a role in disease development and preservation as it likely affects how such stimuli are perceived [33]. Attention bias interferes with performance on cognitive tasks, and the amount of interference caused by attention towards the salient stimuli can be used as a measure of attention bias. Attention to stimuli involving food and body shapes interferes with executive function performance in adults with ED, including performance on working
memory tasks [33-35]. This disturbance is not only observed when the stimuli are processed consciously. Attention bias is also present when the stimuli is presented subliminally, i.e. not reaching the threshold of conscious perception [36]. Stimuli can be subliminally perceived by presenting the stimuli for a very short duration, normally with a stimulus onset asynchrony less than 50 ms [37]. Imaging studies have reported activity in subcortical structures such as the amygdala, anterior cingulate cortex, hippocampus, insula and fusiform gyrus in response to arousing subliminal stimuli (i.e. subliminal stimuli with emotional value) [37]. This suggest that certain stimuli can be processed directly without involving the cortex through a “quick and dirty” neural pathway as previously has been suggested by LeDoux (1996) [38]. Since some theories suggest an ineffective reward system in those with ED [39, 40], it is plausible that subliminal stimuli in the form of food images could evoke mesolimbic reward responses that normally may be modulated by prefrontal cognitive control regions [41, 42]. To test this, engaging the prefrontal regions with a cognitive task while presenting subliminal rewarding stimuli may be appropriate. In this way, prefrontal regions may not be able to inhibit appetitive responses to food in ED patients. Working memory is a function of the prefrontal cortex (PFC) [43, 44], and could be a pertinent task to engage this region.

Working Memory

Working memory can be described as a buffer that stores acquired information for a limited time before it is consolidated as long-term memory, or forgotten. This information is used for guiding, planning and executing behaviour [45]. In ED it is likely that working memory is involved in sustaining goal-directed strategies to maintain a restrictive or compensatory eating pattern with the aim to stay thin. Working memory is a function associated with the dorsolateral prefrontal cortex (DLPFC) [43, 44]. Concerns about eating, weight and shape could add increasing load on the DLPFC in ED individuals, and therefore interfere with working memory performance. This is supported by the finding that subliminal food stimuli, but not emotionally exciting or neutral stimuli, interfere with working memory performance in ED [46]. Interestingly, working memory mechanisms is also seen to exert control over arousing stimuli [47], and could therefore interact with reward signals evoked by an attentional bias to food stimuli, which consequently disrupts performance. However, assessment of working memory in ED has provided inconsistent results, with performance to be inferior, superior or the same compared to healthy controls (HC) (see Paper II). Assessment of working memory is conducted through neuropsychological tests. The n-back tasks is one such test [48], and is frequently used in functional magnetic resonance imaging (fMRI) studies as it successfully engages the DLPFC [44]. The
DLPFC is also associated with other cognitive functions, including cognitive control, executive functions and suppression of appetite [49, 50]. It is therefore likely that individuals with restrictive eating behaviours engage this region more in order to suppress appetite, ruminate about food, weight and shape, and use working memory to maintain goal-directed strategies in the strive for thinness.

Neurobiology of ED

Neurobiological studies of ED have reported functional as well as structural abnormalities in the brains of ED individuals. Below, I will discuss evidence from functional imaging studies indicating aberrant activity in the cortico-limbic circuitry, and its functional implications in ED pathology. Next, findings from structural and resting state connectivity studies are reviewed, before a neurobiological model of ED is discussed.

Functional imaging

The most commonly used method to explore neural activity is with fMRI. By studying blood oxygen level dependent (BOLD) signals, one can make inferences on brain regions which show increased activation for example in response to certain stimuli. In adults with chronic AN, food stimuli evokes excessive prefrontal cortex activation, in particular in the DLPFC [51, 52]. The DLPFC is an essential part of the cognitive control network involved with top-down control [53] dealing with regulation and modulation of impulsivity signals from the mesolimbic reward structures [54], including appetite suppression [50]. Increased DLPFC activity is appropriate with regards to excessive worry and rumination in AN [55], and by engaging working memory functions to assert cognitive strategies in order to restrict food intake. Excessive activity in the PFC of AN patients has been discussed in previous reviews [49, 56].

On the other hand, BN is linked to altered activity in reward regions. Increased activity is seen in the striatum in response to food stimuli [51], however, hypofunctioning or the reward system is also likely [57, 58]. Both possibilities accounts for binge-eating behaviour in BN, where in the first instance a heightened sense of reward leads to increased food intake, whereas in the other, a greater amount of food is needed to reach satisfactory levels of reward. An overly active bottom-up reward system, in combination with a less active top-down control system, could lead to impulsive behaviours such as excessive food intake [30].

A common finding in ED studies is aberrant insular activity [15, 59]. The insular cortex works as a connectivity hub in the brain, and receives input from both cortical and subcortical brain regions [42]. The insula is gaining
interest in ED research because of its implications in monitoring of the body state [60], including the digestive system [61], taste perception [62], and regulation of eating and appetite [63]. Thus, the insula is likely to play a prominent role in ED pathology as it integrates information of bodily states with cognitive processes [64, 65]. The anterior cingulate cortex (ACC) together with the insula are essential parts involved with the processing of salient stimuli [66]. The ACC is also implicated in error detection, and relays information on strategic processes to the DLPFC [67]. In ED, this communication may pertain to pursue the right behaviour to achieve the wanted outcome, i.e. avoid food intake in order to stay thin [49].

To sum, ED is associated with aberrant neural activity in regions implicated with cognitive control, reward signaling and somatosensory awareness. Differential activity in these regions is likely to contribute with disordered eating behaviour and faulty body perception as seen in individuals with ED.

Structural imaging

By using MRI, one can implement automatic whole-brain quantification and comparison of brain structure. Both global and regional volumes can be closely examined with voxel-based morphometry (VBM). Such methods have been used in several studies aiming to compare brain structure in ED to controls, however studies are inconclusive. A recent meta-analysis reported findings of a global gray matter and white matter reductions in AN, as well as regional gray matter differences in structures with major implications on feeding and appetite [68]. More specifically, studies have found both reduction and increase in frontal cortex volumes [69, 70], striatal volumes [69, 71], somatosensory areas [68, 70, 72], the cingulate cortex [71, 73], as well as the insula [70, 71]. However, far fewer volumetric studies have included BN. Two studies have reported reduced caudate volumes in BN [72, 74], and one reported increased orbitofrontal cortex and ventral striatum volumes in a region-of-interest (ROI) analysis [75]. However, because most structural imaging studies have been conducted in patients with a long-standing ED, it is not known whether volume alterations are an effect of prolonged starvation and malnourishment. There are only three studies that have examined brain structure in adolescents ED patients. These all included AN patients, where the first study reported gray matter reductions in the cingulate cortex, precuneus and parietal lobes [73], whereas the other two studies examined brain structure in those recovered from AN. The studies report gray matter volumes were normalized after weight restoration [76, 77] (one study reported regional differences in the temporal gyrus and supplementary motor area [76]). Even though brain tissue is seen to return to normal after weight recovery [76-78], early identification and intervention is crucial in order to avoid severe physical effects on the body, including structural brain alterations.
Resting state

Most fMRI studies examine the neural activity in response to behavioural tasks or specific stimuli; however, there is now an increasing interest to know what is happening in the brain during rest. Studying spontaneous neural activity may reveal important information about the intrinsic properties and communication between brain regions [79]. By examining the temporal correlation of activity between regions in the brain, inferences can be made about regions that are functionally connected. Network based approaches study connectivity within and from specific networks in the brain, whereas seed-based analyses are used to examine connections between pre-defined ROIs to either areas in the whole brain or to other ROIs.

A common network of interest is the default mode network (DMN). The DMN is a network of regions that is active during the absence of selective attention or goal-directed cognitions [80]. In ED, studies have reported decreased connectivity in the DMN in patients with AN [81], but increased DMN activity in recovered AN [82]. Also the somatosensory network is found to have altered connectivity in ED compared to controls. Functional connectivity in this network is found to be reduced in BN [83], but increased in AN [84]. This suggests individuals with ED have altered body awareness which likely affects body image and perception of body size [85].

There is only a limited number of studies using seed-based approaches to explore the functional connectivity in ED. Results of these studies report differential connectivity in ED compared to controls, specifically from seeds in the anterior cingulate cortex (ACC) in both AN and BN [86], the putamen in AN [87], the paracentral lobule in BN [83], and the prefrontal cortex in AN [88]. These findings indicate an altered pattern of connectivity in regions involved with reward, cognitive control and somatosensory awareness in ED, which could be contributory to ED symptoms. However, whether differences in connectivity are present even in the early stages of the disorder is not known.

The impulse-control spectrum model of ED

A recent model proposed by Brooks et al. argues for ED conditions and symptoms placed on a single spectrum, instead of categorical classification based on strict diagnostic criteria [10]. Similar to other models [56, 89] it also links underlying neural patterns to the traits and symptoms witnessed in the different ED diagnoses. On one end of the spectrum is the restrictive subtype of AN, associated with restraint, cognitive control and obsessive-compulsiveness. These patients are likely to show excessive frontal cortex activity in response to appetitive stimuli. Further along the spectrum is AN with a binge-purging subtype; patients who show restraint, but sometimes
gives in to impulses leading to episodes of excessive food intake followed by compensatory purging methods. This behaviour may be reflective of an erratic PFC control that sometimes gives way to impulsive reward signals related to food. In the middle of the spectrum are individuals with normal eating behaviours, with more balanced PFC and mesolimbic systems. Towards the opposite end of the spectrum is non-purging BN, with binge-eating tendencies, which does not include compensatory behaviour. Next is BN with a binge-purging subtype, while BED is found at the extreme of the spectrum. The recurrent binge-eating episodes in BN are likely a result of increased bottom-up reward responses from the mesolimbic system, leading to increased arousal and impulsive behaviours (i.e. excessive food intake). In their paper, Brooks et al. supports this model with previous findings from neuroimaging and genetic research conducted with ED patients. It is important to note that the model does not suggest individuals are strictly restrictive or impulsive, but that such responses are warranted by the social and environmental setting in which the individual exists, and is influenced by temperament and genetics [10].

Because of the insula’s widespread connections in the brain which may be instrumental in ED behaviour (see above), the spectrum model describes the insula as a bridge where signals from the PFC and the mesolimbic reward system converge (see Figure 1). An imbalance in either system may cause a rate-limiting defect in the insula that impedes signals, which in turn may lead to symptoms seen in ED. This defect has also been described previously by Nunn et al. [42, 89].

Conversely, a recent study set out to test the impulse-control hypothesis did not find evidence to entirely support the model. In response to food stimuli, patients with AN showed increased PFC activation, which is in accordance to the model, however no reduction in bottom-up regions were observed in AN compared to controls and recovered AN [90]. It could be that AN is not associated with hypofunctioning in the mesolimbic system, but rather a “misplacement” of rewarding signals. Mesolimbic reward signals could in fact be evoked by successfully restricting food as proposed in a model in a recent review paper [91]. The model links AN pathology to that of addicts, proposing AN individuals to be addicted to the rewarding feeling of controlling their appetite. The reward is a product of learnt reward-association following prolonged starvation in the strive for thinness. This habit formation is induced by rewarding signals to behaviours associated with illness (i.e. restriction of food and exercise) [91].

Thus, there are several hypotheses regarding the formation of pathological behaviour in ED, and neurobiological models of ED needs further testing in order to provide a better understanding of neural activity underlying ED pathology.
Figure 1. The impulse-control model suggests converging signals from the PFC or the mesolimbic system causes a rate limiting defect in the insula.

Findings in this thesis are discussed in part within the framework of the impulse-control model, where an additional component is proposed set in the light of the current findings presented in the thesis as well as previous studies in ED patients.
Aims

The overall aim of this thesis is to investigate early neuropathology associated with ED, and how differences in function and structure are linked to core ED traits. Also working memory performance and attention bias was studied as previous research indicates patients with chronic ED show attention bias to disease salient stimuli.

More specifically, the aims in each paper were as follows:

- In paper I, the aim was to investigate the neural responses to food in a sample of newly diagnosed ED patients, and to compare this response to that of controls. Further, we wanted to study how this activity correlates to traits associated with ED, such as restraint, obsession and compulsivity, as well as impulsivity.
- In paper II, attention bias and the effect of subliminal food stimuli on working memory performance were studied, both in terms of behavioural performance and neural activity associated with the interference in ED and HC.
- In paper III, early signs of structural changes in a sample of recently diagnosed ED patients were studied, as well as correlations with ED related cognitions.
- In paper IV, differences in resting state functional connectivity from regions involved with appetite and cognitive control were examined in adolescents with ED compared to HC. Connectivity differences were correlated with traits and cognitions linked to ED.
Materials and Methods

Science is what scientists do, and there are as many scientific methods as there are individual scientists.

-Percy Bridgman, Nobel laureate in physics

The four papers included in this thesis are based on the same sample of participants. Participants completed a selection of questionnaires before they underwent the scanning procedure, in which they conducted a working memory task and were presented with food images (both explicitly and subliminally). Since analyses were conducted continuously while recruitment was still ongoing, the sample size in the papers may vary. Preprocessing of the functional imaging data is the same for paper I, II and IV, whereas in paper III, the data was preprocessed using a toolbox specific for structural imaging data. Statistical methods are described in more detail in the individual papers.

Subjects and ethics statement

The study sample consisted of both patients, i.e. adolescent females recently diagnosed with ED, and age-matched healthy control females. Patients were recruited from the Eating Disorder Unit of the Department of Child and Adolescent Psychiatry at Uppsala Hospital, Sweden. The scanning was performed within two weeks of receiving their diagnosis. The healthy controls were recruited from local schools in Uppsala, Sweden, and screened for psychiatric disorders using a short form of the structured clinical interview for DSM disorders (SCID). Exclusion criteria for both groups were as follows: metallic implants, claustrophobia, left-handedness, co-morbidities, and use of psychotropic medication. All participants and respective guardians signed an informed consent form, and the study was approved by the local ethics committee in Uppsala.

Paper I, II and III are based on the same sample of 15 adolescents recently diagnosed with ED (ages: 13 – 17, mean age: 15). Eleven patients were diagnosed with eating disorders not otherwise specified (EDNOS), three patients were diagnosed with AN, and one with BN according to DSM-IV cri-
teria. In paper IV, eleven patients were included where two were diagnosed with AN, and the rest had an EDNOS diagnosis (ages: 13 – 17, mean age 15). A total of 28 HC participants completed the scanning procedures. Of these, 20 HC participants were included in paper I (ages 13 – 17, mean age: 14.2); twenty-eight healthy controls were included in papers II and III (ages: 13-17, mean age: 14.3), and twenty HC participants were included in paper IV (ages: 13 - 17, mean age: 14.4).

Behavioural Measures

Questionnaire measures
To measure severity of the symptoms associated with eating disorders and specific traits, self-report questionnaires were administered to the subjects. To measure ED symptoms, the participants conducted the eating disorder examination – questionnaire (EDE-Q) consisting of the subscales restraint, as well as concerns about eating, shape and weight [92]. The questionnaire consists of 36 items where answers are indicated on a seven-point scale from 0 (“no days”), to 6 (“every day”).

Obsessive-compulsive symptoms were measured using the obsessive-compulsive inventory - revised (OCI-R). The questionnaire include the following six subscales: neutralizing, hoarding, washing, ordering, checking and obsessing [93]. The 18 items are answered on a five point scale from 0 (“not at all”), to 4 (“extremely”).

To measure the subject’s impulsivity trait, the Barratt impulsiveness scale 11 (BIS-11-11) was conducted. This questionnaire consists of 30 items on a four point scale that ranges from 1 (“never/rarely), to 4 (“almost always/always”) [94]. The scores yield a total score on impulsivity, as well as scores on six subscales: motor, self-control, cognitive complexity, attention, perseverance and cognitive instability.

Working memory task
To assess working memory and its associated neural correlates, a 1-back version of the n-back task was conducted in the scanner [48]. One letter at the time was presented continuously. If a letter was believed to be identical to the preceding letter, the participants were instructed to make a response on a button-press hand controller. The task is illustrated in Figure 2. Accuracy and reaction time (RT) were recorded.
Imaging

Paradigms

Explicit paradigm
In the explicit paradigm, supraliminal food images were presented to the participants. The paradigm consisted of three blocks; high-calorie food stimuli (i.e. images of hamburger, cakes etc. placed on a white plate with a blue background), low-calorie food stimuli (i.e. images of apples, crackers etc. on a white plate with a blue background) and baseline stimuli (a black fixation cross on a gray background). There were five high-calorie blocks, five low-calorie blocks, and ten baseline blocks in-between the food stimuli blocks. Each block consisted of six images and each image was displayed for three seconds. The subjects were instructed to imagine what it would feel like to eat the particular food displayed on the image. Neural responses to the various blocks were recorded and subsequently analyzed.

Subliminal paradigm
The participants carried out the working memory task in the scanner and were presented with a total of 120 letters in six blocks of 20 trials. The letters were displayed to the participants through MRI-compatible goggles for 1077ms, one letter at a time. In half of the trials, a subliminal image of high
caloric food was presented for 23ms immediately before the presentation of the letter. Neural activity to the working memory task with and without the subliminal stimuli were recorded and analyzed. After the scanning procedure, a forced-choice test including the same images presented subliminally in the scanner, accompanied by additional novel food images was administered to the participants. The participants were prompted to answer which of the two images they had encountered during the scanning session. The images were deemed subliminal if performance was worse than chance.

**Image acquisition**

All scans were conducted with a Philips 3-T (Achieva, Philips Healthcare, Best, Netherlands) scanner using a 32-channel standard head coil. Stimuli were presented to the participants in the scanner through MRI-compatible goggles (NordicNeuroLab, Bergen, Norway) attached to the head-coil. T2*-weighted functional images in paper I and II were collected with an echoplanar imaging sequence (EPI) registering 125 volumes in the explicit paradigm, and 250 volumes in the subliminal paradigm. There were 30 slices in each volume (slice thickness: 3 mm; gap: 1 mm; interleaved order; voxel size: $3 \times 3 \times 3$ mm; field-of-view: $230 \times 230$ mm; flip angle: 90° repetition time (TR): 3000 ms; echo time (TE): 35 ms). T1-weighted structural images were registered with 190 slices (voxel size: $1 \times 1 \times 1$ mm; FOV: $240 \times 240$; flip angle: 8°; TR: 8.2 ms; TE: 3.8 ms). The structural images were used for voxel-based morphometry in paper III, and coregistered to the functional images in papers I, II and IV. Resting-state data in paper IV were collected in 180 volumes, including 32 slices (slice thickness: 3 mm; gap: 0.9 mm; interleaved order; voxel size: $3 \times 3 \times 3$ mm; FOV: $192 \times 192$ mm; flip angle: 90°; TR: 20 ms; TE: 30 ms).

**Preprocessing**

Functional data in paper I, II and IV were preprocessed using statistical parametric mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (The Mathworks Inc., 2003). To start, all images were realigned and estimated to correct for movement in the scanner. Each individual’s functional images were coregistered to the participants’ anatomical image. The anatomical images were segmented to remove tissue outside the brain. Adolescent-specific tissue probability maps were used for gray matter, white matter and cerebrospinal fluid (CSF) segmentation. The functional images were normalized to the segmented anatomical image, and finally smoothed to minimize noise in the data.

Structural data for VBM in Paper III was preprocessed with VBM8, a toolbox implemented in SPM8. Segmentation of GM, WM and CSF was
performed with age-representative tissue probability maps for our sample, and smoothed with an 8 mm Gaussian kernel.

Statistical analysis

Differences in questionnaire scores, as well as reaction time (RT) and accuracy to the working memory task between patients and controls were tested using an independent samples t-test in SPSS (IBM SPSS Statistics for Windows, Version 21.0, 2012.). Statistical analyses of imaging data was based on a general linear model (GLM) in SPM8 run in Matlab. A cluster-level significance threshold was set to 0.05 (family-wise error (FWE) corrected), and extent cluster threshold of 10 voxels. However, in paper II we used a cluster threshold of 5 voxels, and reported uncorrected p-values as it is likely that the subliminal presentation of food images did not evoke strong enough activation to survive the FWE-threshold.

In paper I, neural activity in response to high and low-calorie food images were compared between the ED and HC group with a two-sample t-test. Correlations between neural activity and questionnaire measures, as well as general performance on the working memory task, were investigated using multiple regression analysis carried out in SPM.

In paper II, 2 × 2 analysis of covariance (ANCOVA) investigated interactions and main effects of neural responses to subliminal food images and performance on the working memory task in both ED patients and HC participants, with BMI and total brain volume (TBV) as covariates. One ANCOVA was carried out with slow and fast RT to the working memory task (divided by a median split), while a second ANCOVA included low and high numbers of errors in the memory task (divided by a median split). Subsequent post-hoc t-tests to investigate the direction of the effects were masked for the ANCOVA interaction.

In paper III, a one-way ANCOVA tested the effects of the ED and the HC group on brain volume, while correcting for age and TBV. The interaction was used as a mask for post-hoc t-test to look at direction of main effects. Brain volumes in each group were also included in a multiple regression with scores on the EDE-Q, OCI-R and BIS-11 separately.

Resting state functional connectivity in paper IV was analyzed with CONN: functional connectivity toolbox (version 14.p, http://www.nitrc.org/projects/conn, [96]) carried out in Matlab. Before exploring the data with statistical analyses, noise reduction steps were introduced to the data. This included the CompCor method [97]; a principal component based method which maintains the global signal while regressing out noise caused by white matter and CSF. Movement information in six dimensions was also included to control for correlations due to movement. Seed-based functional connectivity was then carried out with eight pre-defined
ROI’s (superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex (ACC), insula, caudate, putamen, pallidum and thalamus) based on a bivariate Pearson correlation analysis. Functional connectivity was explored by temporally correlating activation in the defined seed-regions with activation in other voxel clusters in the brain. A second-level between-groups analysis tested differences in functional connectivity between the ED and HC group. The significance level was set to 0.05 (cluster FWE-corrected). Z-transformed correlation coefficients were extracted for further investigation with clinical variables.

ROI

Based on previous studies and models of the underlying neurocircuitry of ED, we included a priori brain regions in a region-of-interest (ROI) analysis. The ROIs included: the PFC (superior and middle frontal gyrus), the ACC, the insula, and striatal structures (caudate, putamen and pallidum). The thalamus (a limbic structure closely linked to the striatum with suggested implications in food reward [98]) was also included for resting-state connectivity analyses in paper IV.
Results and Discussion

Science never solves a problem without creating ten more.
-George Bernard Shaw

Paper I

ED is associated with traits that may be considered risk factors for disease development. These traits may be correlated with neural responses to food in ED patients. In paper I we examine the neural responses to food in adolescents with ED, and its association with traits linked with ED. To measure ED related traits and symptoms, all participants completed the EDE-Q, OCI-R and BIS-11 questionnaires, in addition to a working memory task in the scanner. ED patients revealed higher scores on all questionnaires compared to the control group, however, average total (RT) on the working memory task was not found to significantly differ between the groups.

Neural responses to food stimuli were recorded in the scanner by measuring activity to both high and low calorie food images. Neural activity in response to food stimuli in the sample of adolescent ED patients was greater in the right medial frontal and left cingulate gyrus compared to HC adolescents, which is similar to findings that have been reported in adult patients with chronic AN [51, 90]. HC individuals did not show any regions with greater activity compared to the ED group.

Obsessive-compulsive traits revealed a clear association with neural activity in response to food stimuli with increased frontal cortex activity (in particular the left DLPFC that correlated with total scores on the OCI-R. The DLPFC is an important component of the top-down control system, and is involved with inhibition of appetitive signals from mesolimbic reward regions [50, 53]. In addition, activity in the left ACC, bilateral cerebellum, bilateral supplementary motor area / pre-motor cortex (SMA/PMC) and the right insula also correlated positively with OCI-R scores in the ED group. Excessive activity in the PFC and ACC is not only described in AN [51, 99], but also in patients with OCD [100, 101], suggesting a common underlying pathology in these disorders. Moreover, the insula and the ACC are identified as two of the main components in the salience system, and works together to identify and evaluate salient stimuli in ones surroundings [66]. The insula is a region with growing interest in ED research because of its wide-
spread connections in the brain, and its role in evaluation of emotional stimuli and integration of somatosensory signals [66, 102]. Activity in the SMA in correlation with OCI-R scores could be due to its suggested role in appetite suppression [103].

Further, reaction times on the working memory task negatively correlated with activity in both right and left superior frontal gyrus in the ED group. Since the PFC (particularly the DLPFC) is implicated in working memory [43, 44], a correlation between faster RT to the working memory task and greater frontal activity may be a result of a “well trained” region involved with obsessions and rumination linked to food, weight and shape of the body.

This study shows that adolescents recently diagnosed with ED show differential neural responses to food stimuli compared to controls of the same age. The results revealing levels of obsessive-compulsiveness predicting DLPFC and insular activity is in line with the impulse-control model as well as other theories regarding insula involvement, where excessive PFC activity causes a rate-limiting defect in the insula [10, 42, 89]. Further in support of this is the finding of no correlation between neural activity to food stimuli and scores on the BIS-11. The lack of correlation with BIS-11 is likely due to our group having more anorexic features, reflected in the correlation between neural activity to food and scores on the OCI-R. Moreover, no correlation was revealed in the HC group, likely due to lower scores on the OCI-R and BIS-11.

**Paper II**

Patients with ED display more attention to disease-salient stimuli. Attentional bias to food causes disrupting effects on cognitive tasks in ED patients. In paper II we show that even subliminal food images were seen to have a detrimental effect on working memory performance in terms of accuracy and RT in adolescents with ED, but not HC. More specifically, the ED group showed longer RTs and fewer correct responses than the HC group during subliminal presentation of food images, while no differences were observed in trials without subliminal food images. This study is the first to investigate the neural correlates of subliminal disruption of working memory. The disruption was found to be associated with right parietal and left superior temporal cortex activation in ED. In particular, ED individuals with the most amounts of error in the working memory task caused by the interference of subliminal food stimuli, compared to ED individuals with the lowest amounts of errors, showed greater activation in the right angular/parietal cortex. The parietal region has in a previous study been found to be engaged with working memory in ED adolescents [104]. Interestingly, fronto-parietal regions are considered the most prone to change in AN [68, 105]. Engage-
ment of this region during the working memory task may be a result of an over-loaded working memory system caused by the presence of subliminal food stimuli that therefore need to employ more resources to work effectively. This activity was not seen in the HC group, suggesting the food stimuli was only interfering in the ED group that likely possess an attentional bias to food. Higher errors in the ED group were also associated with increased activity in the left precentral gyrus, a region implicated in motor signaling. With more omission errors (failing to respond when they should have) than commission errors (responding when they should not have) in ED, such activation could reflect inhibition of motor signals. On the other hand, high amounts of errors in the HC group was associated with greater right superior temporal gyrus and left striatal activity. This striatal activity, linked to appetite and reward signaling, was not seen in the ED patients making high amounts of error, indicating cognitive mechanisms employed in working memory may also have been working to reduce subliminal stimulation of the reward system, and therefore needs to engage other regions (i.e. parietal cortex). However, reduced striatal activity may also be reflective of diminished appetitive signaling to food stimuli in ED.

Subliminal stimuli also caused longer RT in the working memory task in the ED group, which was not seen in the absence of the subliminal food stimuli. ED patients with the slowest compared to the fastest RT, showed increased activity in the left caudate (extending to the temporal lobe). Activity in the caudate, which is a striatal structure, suggests some appetitive response elicited by the subliminal food stimuli. However, striatal responses were only seen in the ED group with the slowest response times, and not in those with the highest amounts of error, which suggest involvement of inhibitory mechanisms to modulate the striatal response. This is further supported when contrasting ED individuals with the longest RT to HC with the shortest RT, which revealed greater activity in regions implicated in working memory; the right inferior prefrontal gyrus, the right superior temporal gyrus, and the right precentral gyrus. The excessive involvement of regions involved with working memory may be a result of trying to cope with pre-attentive bias to subliminal food images in the ED group.

This study demonstrates that a pre-attentive bias towards food exists in recently diagnosed adolescents with ED. Even though the findings did not survive FWE-corrections, the results indicate appetitive responses to subliminal food stimuli may be in conflict with performance on the working memory task.
Previous studies have reported structural differences in the brains of ED patients when compared to controls. However, most of these studies are based on research including AN or BN patients with a long-standing diagnosis. Results may therefore be an effect of starvation and malnourishment. By studying recently diagnosed adolescents with ED, one may gain crucial information about the structural pathology present in the brain before the manifestations of a chronic illness.

In our study, adolescent females in the early stages of an ED showed a trend towards global volume reductions in the left superior temporal lobe in comparison to HC. A recent meta-analysis on VBM studies in AN described the temporal lobe as one of the regions most susceptible to volume decrease in ED [68]. The structural alteration in this area may be in concordance with functional abnormalities linked to ED development.

Volume alterations correlated with ED cognitions in the ED group. Specifically, high scores on the EDE-Q correlated positively with left insular volumes, adding evidence to the notion that the insula is a pivotal region in disordered eating behaviours [42, 59].

Obsessions and compulsions measured by the OCI-R, negatively correlated with left putamen and left cerebellar volumes in the ED group. Also the OCI-R subscale “obsessions” were found to negatively correlate with putamen volumes. The putamen, which is a part of the dorsal striatum, is a main component of the reward system [106]. Our findings suggest that ED patients with high amounts of obsessions and compulsivity have reduced putamen volumes, which perhaps is reflected in a diminished reward response to food. It is believed that the frontal regions, which is involved with obsessions [107], apply cognitive inhibition to modulate striatal responses [54]. Perhaps excessive signaling from the frontal regions during adolescence impinges on the development of striatal structures, leading to reduced appetitive reward response to food. This is in line with the impulse-control model where AN is thought to have a less active reward system, while BN have increased reward activation [10]. However, this not supported by a recent functional imaging study set out to test this model. The study found increased medial frontal cortex activation, but no difference in mesolimbic reward structures in AN compared to HC in response to food stimuli [90]).

OCI-R scores also negatively correlated with cerebellar volumes. The cerebellum a region not only involved with motor skills and balance, but also feeding behaviours [108]. Volume reductions in the cerebellum has previously been reported in adults with long-standing AN, however, no previous study has reported altered cerebellar volumes in adolescents with a recent diagnosis of ED.

This is the first study to assess alterations in brain volume in patients diagnosed with EDNOS, AN and BN of recent onset. Further, we found vol-
volume differences to be associated with ED cognitions and traits. In particular, the findings indicate that volumes in the temporal lobe, insula and striatum are associated with ED pathology in the early stages of the disorder.

**Paper IV**

Because previous fMRI studies have reported aberrant activity in corticolimbic circuits in ED patients, we investigated functional connectivity between these regions in patients with restrictive ED in paper IV. The ED patients showed increased connectivity between a seed in the ACC and the left and right occipital cortex compared to age-matched controls. Since the ACC is an essential component in the salience system, a strong connection between this system and the visual cortex (located in the occipital lobe) could mean that ED patients are more vigilant of disease-relevant stimuli, and further develop an attentional bias to such stimuli.

ED patients also showed increased connectivity between right superior frontal gyrus and the left middle temporal cortex compared to HC. The middle temporal cortex is implicated in body image perception [109]. A strong connectivity between this region and the frontal gyrus, which is involved with obsessions about food, body and weight, could lead to enhancing and maintaining a defective and unhealthy body image. In paper III we fund a trend towards volume reductions in the left temporal cortex in the ED group. Together, these findings are evidence of temporal lobe involvement in ED pathology.

Further, the ED patients showed increased connectivity between the right insula and the left angular gyrus compared to controls. The angular gyrus is located in the inferior parietal lobe (IPL), a region involved with self-awareness [110]. The finding suggests increased connectivity in a network including the insula, IPL (and perhaps ACC) which are all implicated in self-awareness, and thus pertain to increased rumination and concern about the shape of the body in ED compared to HC.

Moreover, greater connectivity between the pallidum and the left and right precuneus was found in the ED group. The pallidum is a part of the basal ganglia, and the ventral pallidum is associated with motivation [111]. The precuneus, located in the parietal lobe, is active when sustaining a mental representation of one-self as well as during self-referential processes [112], suggesting that the strong connectivity in ED patients could reflect recurrent obsessions pertaining to the way their own body is perceived. This is supported by findings from functional imaging studies report increased activity in the parietal cortex as well as the PFC in response to body shapes [113-115]. The results indicate strong involvement of body image perception, perhaps guiding and influencing ED cognitions exerted from the PFC. None of the connections were found to correlate with clinical measures
(EDE-Q, OCI-R, BIS-11), a finding that may in part be due to the early stages of ED in this sample where long-term manifestations is not yet seen to affect connectivity.

This study is the first to investigate functional connectivity in a sample of ED including EDNOS adolescents. The results indicate increased connectivity between regions involved with cognitive control and body image, which could be instrumental in generating a distorted image of the body, with increased obsessions about the weight and shape of the body.
Conclusions

The aim of this thesis was to examine the underlying neurobiology of ED in a sample of recently diagnosed adolescents with ED. Specifically, neural responses to food stimuli, attentional bias and interference of working memory, volume differences and resting state functional connectivity was examined as well as correlations with clinical variables. Paper I is the first to demonstrate that adolescents with ED are associated with aberrant neural activity in response to food. This activity is correlated with levels of obsessions and compulsivity, as well as working memory performance in ED. To conclude, this study shows ED related traits are associated with aberrant neural functioning at an early stage in the disease.

In paper II, neural responses to subliminal food stimuli during a working memory task were examined. We found the food stimuli to have an interfering effect on the working memory task in the ED group. This finding suggests ED patients have an attentional bias to food-related stimuli. Further, fMRI analyses indicate subcortical activity associated with reward in response to subliminal food images, that interact with cortical regions involved with cognitive functioning. In the light of the impulse-control model, it is plausible that appetitive responses to subliminal food stimuli were modulated by the PFC in our sample of patients who show predominately restrictive features. The interference may therefore be a result of the frontal mechanisms trying to modulate appetitive signals, while engaging in the working-memory task. However, the neural activity failed to reach FWE-corrected threshold, thus findings should be considered preliminary.

Structural comparisons of the brains of adolescents with ED to controls are described in paper III. There was an indication towards reduced left superior temporal gyrus volumes in ED patients. ED cognitions correlated with left superior temporal gyrus as well as insular volumes in ED, adding to growing evidence of these regions’ involvement in ED pathology. Levels of obsessive-compulsive symptoms negatively correlated with volumes in the left putamen and cerebellum. This finding fits well within the framework of the impulse-control model which suggests an imbalance in either PFC or mesolimbic circuitry, with excessive activity in one or the other systems leading to pathological eating behaviours. Excessive inhibitory control from the frontal region may have influenced development of the putamen during adolescence, leading to volume reductions. Smaller putamen volumes may consequently have an effect on reward processing.
Finally, paper IV is the first to examine functional connectivity in a sample of adolescents with restrictive ED. Adolescents with ED showed greater connectivity strength between fronto-parietal regions involved in ED cognitions, body image and self-awareness.

The findings presented in this thesis indicate functional, structural and behavioural abnormalities that are evident at an early stage of an ED, as demonstrated in a sample of recently diagnosed adolescents with ED. The results indicate a temporal dynamic of ED, as the findings from this young sample does not match the more severe effects described in other studies on individuals with a long-standing ED. This emphasizes the importance of early identification and treatment of ED. Based on the current findings, screening methods may include measures of obsessive-compulsiveness, attention bias, and body image evaluation to help early identification of ED.
Future perspectives:

The current findings emphasize the involvement of a body image-aspect that the impulse-control model, as well as other neurobiological theories in the field, consider secondary to aberrancies in other neurocircuits [10, 15]. A distorted body image is one of the core symptoms in ED. A body image aspect is supported by the findings of a review which reports the parietal cortex to be consistently involved in functional imaging studies including AN patients [116]. A preliminary neurobiological addition to both the impulse-control model [10] and the more recent reward-centered model [91], may therefore include somatosensory components as suggested in Figure 3, where the component also pertains to the parietal lobes involvement in body image and self-referential processes. The somatosensory regions may also engage in frequent communication with the insula because of its involvement in bodily perception. Aberrant functioning in the insula-parietal regions may thus lead to a faulty interpretation of bodily signals and a distorted body image. A distorted body image as a result of a malfunctioning self-referential system may lead to increased obsessions relating to the shape of the body, and increased reward signals from the mesolimbic region to choose behaviours leading to a thinner body reflected in connectivity strength as seen in Paper IV.
Future research should include more investigation of a body image aspect in ED. A further investigation of the somatosensory system in adolescents with ED using a network based resting state functional connectivity approach might elucidate any aberrant activity in the whole network which might differ from healthy controls. Further, resting state activity in the form of amplitude of low frequency fluctuation and regional homogeneity of resting activity has not been studied in a group of adolescent ED patients before. In contrast to resting state functional connectivity which explores the connections between regions and networks, low frequency fluctuations are thought to provide important information about the intrinsic activity within regions during rest. In a broader perspective, further research should be conducted on OSFED (formerly EDNOS), to study the neurobiology linked to this disorder compared to the more specific disorders AN and BN. Also abilities which are impaired in AN such as interoception [117] and set-shifting [118], as well as impulsivity as seen in BN, should be studied in OSFED. Moreover, linking the abilities and traits with neural activity will elucidate whether or not symptoms seen in ED is in fact due to varying degrees of PFC or mesolimbic dominance as discussed above. Interesting also is the inclusion of a longitudinal aspect to uncover risk factors, traits and abilities that may predict development of OSFED and specific EDs in the future. Moreover, no studies on EDNOS have included genetic analyses. This is pertinent to include as genes are known to have a significant influence on the eating habits in healthy individuals. Thus, genetic studies could reveal important information about the biological predisposition for developing disordered eating behaviour.

Ätstörningar får allvarliga konsekvenser på kroppen men också på hjärnan. Tidigare studier har funnit skillnader i aktivitet, struktur och förbindelser i hjärnan på patienter med långvariga ätstörningar. Däremot så är det svårt att säga om dessa skillnader är orsakade av svält och undernäring till följd av den kroniska ätstörningen eller inte. Att studera unga patienter som nyss blivit diagnosticerade med olika typer av ätstörningar kan hjälpa att upptäcka vilka neurobiologiska faktorer som ligger till grund för ett stört ätbeteende. I denna avhandling beskrivs studier som har undersökt en rad olika parametrar: hjärnans respons till matbilder, arbetsminnet och partiskhet när det kommer till uppmärksamhet av mat, hjärnans struktur samt hjärnans förbindelser i patienter med ätstörningar jämfört med friska kontroller av samma ålder.

I den första studien fann vi mer frontalaktivitet i hjärnan hos de som var diagnosticerade med ätstörningar. Den frontala delen av hjärnan är involverad i kognitiv kontroll och är även med i att inhibera belöningsresponsen till mat. Ökad frontalaktivitet i respons till mat var relaterat till patienternas egen bedömning av deras tvångsmässiga beteende. En enkät som mäter tvångsmässigt beteende kan kanske hjälpa till att identifiera ungdomar som är i risk för att utveckla ett stört ätbeteende.

I den andra studien studerade vi arbetsminnet och hur utförandet av ett arbetsminnestest var påverkat av subliminala bildar på mat. De subliminala matbilderna ledde till en långsammare respons på minnestestet samt färre korrekta svar. Inferensen orsakad av matbilderna på minnestesten var associerad med en ökad aktivitet i parietala och övre delen av temporalloben, något som tyder på att flera resurser behövdes aktiveras för att prestera så bra som möjligt på minnestestet när subliminala matbilder presenterades.
Detta därför att de områden (frontalloben) som vanligtvis är involverade i arbetsminnet, också är involverade i att modulera aptitsignaler, vid detta tillfälle var de i respons till matbilderna trots att de var subliminala. Det kan tänkas att arbetsminnet hos personer med ätstörningar är involverade i tankar som angår vikt, mat och kroppssform, samt upprätthållandet av strategier för att undvika mat. Det är möjligt att hos personer med sådana tankar ofta i minnet, så är frontalloberna hos de med ätstörningar alltid aktiva, och kan på så sett leda till uppmärksamhets bias när det kommer till mat. Denna snedfördelning av uppmärksamhet till mat kan vara en indikator på stört ät beteendet.

Det finns även strukturella skillnader i hjärnan mellan ungdomar med ätstörningar och friska kontroller. I den tredje studien hittade vi en indikation till mindre hjärnvolym i den vänstra temporalloben i patienterna. Vi fann också ett samband mellan volym i vänstra insula och temporalloben hos personer med ätstörningar gällande restriktion, bekymmer om vikt, mat och kroppssform. Dessa resultat överensstämmer även med tidigare evidens som pekar mot insulas involverande i symptom som man ser hos individer med ätstörningar. I ätstörningspatienterna sågs också en korrelation mellan tvångsbeteende och storleken på putamen, en belöningsstruktur, och volymen på cerebellum hjärnan. Dessa strukturer är involverade i födointag, något som pekar mot ett födonätverk i hjärnan som inte är i balans. Att strukturella skillnader finns allaredan hos ungdomar som nyss har fått en ätstörningsdiagnos är mycket oroväckande och betonar vikten av att så tidigt som möjligt identifiera dessa personer för att undvika att sjukdomen får utvecklas.

I den sista studien utforskade vi konnektiviteten mellan områden i hjärnan som är involverad i födointag, belönning och kognitiv kontroll. Resultaten visade att det fanns en starkare konnektivitet mellan områden involverade i mentala representationer av en själv och sin kropp, samt ätstörda tankar i patienterna jämfört med kontrollerna. Dessa förbindelserna kan betyda att patienterna tänker oftare på hur deras kropp ser ut, kanske till och med får en förvrängd bild av hur den ser ut, vilket leder till mer bekymmer om kroppssform, vikt och mat i denna grupp.

De resultat som presenteras i denna avhandling visar till funktionella och strukturella skillnader i hjärnan på ungdomar med ätstörningar som fanns även före en långvarig sjukdom. Det är svårt att säga om detta är en orsak till sjukdomen, men det gör det inte mindre intressant att de redan fanns där början av sjukdomstiden. Dessa resultat visar att det är viktigt med tidig identifiering och behandling, före sjukdomsbilden och att patienterna förvärras.
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References

Part of this thesis, including Figure 2 on page 18, has been presented previously in the licentiate thesis *Neural activation in response to food stimuli in adolescents with a recent diagnosis of eating disorders*, L Solstrand Dahlberg (2015).


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