THE ROLE OF SET-SHIFTING AND CENTRAL COHERENCE IN DIFFERENTIATING THE RESTRICTIVE AND BINGEING/PURGING SUBTYPES OF ANOREXIA NERVOSA

Evidence from neuropsychological and neurobiological studies

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Abbreviations

AN: anorexia nervosa

AN-R: anorexia nervosa, restrictive subtype

AN-BP: anorexia nervosa, bingeing/purging subtype

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

General introduction

Anorexia nervosa

Anorexia nervosa is a severe psychiatric disorder, mostly affecting females in their early adolescence (Smink, van Hoeken, Hoek, 2012). Next to a wide range of adverse psychological and social consequences (National Institute of Mental Health, 2014), anorexia nervosa has high rates of comorbid psychiatric disorders (e.g. depression, substance abuse, or anxiety disorders). In contrast to most other mental health disorders, anorexia nervosa has a high prevalence of concomitant somatic complications (e.g. hypotension, bradycardia, infertility, osteoporosis, constipation, dry skin, respiratory failure, …) (Mehler & Brown, 2015). The core symptoms can become life-threatening, which is reflected by anorexia nervosa being associated with the highest mortality rate of any psychiatric disorder (National Institute of Mental Health, 2014).

Anorexia nervosa is one of three broad diagnostic categories that are delineated in the section 'Eating Disorders' of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), next to bulimia nervosa and eating disorder not otherwise specified (EDNOS)[1] (American Psychiatric Association, 1994). According to the diagnostic criteria of DSM-IV, anorexia nervosa is characterised by an extreme low body weight, an intense fear of gaining weight, a disturbance in the way in which

[1] Next to anorexia nervosa, bulimia nervosa and eating disorder not otherwise specified are described in DSM-IV. To be diagnosed with *bulimia nervosa*, recurrent episodes of bingeing and purging must occur at least twice weekly over a period of three months and these must be combined with inappropriate compensatory mechanisms. The *eating disorder not otherwise specified* is a residual category for those who exhibit pathological disordered eating behaviours but who do not meet the full criteria for anorexia nervosa or bulimia nervosa as stipulated in the DSM-IV (American Psychiatric Association, 1994).

one's body weight or shape is experienced and the absence of at least three or more consecutive menstrual cycles (amenorrhea) (American Psychiatric Association, 1994). In the fifth and latest edition of the DSM (DSM-5)[2], the core diagnostic criteria for anorexia nervosa are conceptually unchanged compared to DSM-IV, with one exception: the requirement for amenorrhea has been eliminated (American Psychiatric Association, 2013). In this thesis, the DSM-IV-criteria have been applied for the diagnosis of anorexia nervosa.

Epidemiologic research shows an estimated life time prevalence of 1% in Belgium (Preti et al., 2009). The remission rates reported in (international) follow-up studies vary from 29% (after 2,5 years of follow-up) to 84% (after a 16 years period) (Keel & Brown, 2010). Despite its serious course, little is known about the pathophysiological mechanisms that account for the development and persistence of anorexia nervosa (Jauregui-Lobera, 2013), and up to now the evidence for effective treatment is rather weak (Watson & Bulik, 2013).

Pathophysiological mechanisms in anorexia nervosa: the role of cognitive factors

The aetiology of anorexia nervosa is regarded to be multi-factorial, considering that social, genetic and psychological factors appear to be involved in its onset and maintenance (Rikani et al., 2013). Several study groups focused on the possible presence of cognitive disturbances associated with anorexia nervosa (Aspen, Darcy, & Lock, 2013; Lang, Lopez, Stahl, Tchanturia, & Treasure, 2014; Brooks, Rask-Andersen, Benedict, & Schioth, 2012). Indeed, in recent explanatory models of anorexia

[2] The nosologic classifications of dysfunctional eating behaviour in the DSM-5 list the following diagnoses: pica, rumination disorder, avoidant/restrictive food intake disorder, anorexia nervosa, bulimia nervosa, binge eating disorder, other specified feeding or eating disorder and unspecified feeding or eating disorder (American Psychiatric Association, 2013).

nervosa, biases in information processing are propounded as core elements in the development and maintenance of anorexia nervosa (Hatch et al., 2010; Treasure & Schmidt, 2013; Herpertz-Dahlmann, Seitz, & Konrad, 2011). Biases in both illness-related (food and body shape) and non-illness-related information processing are detected (Treasure, Claudino, & Zucker, 2010): next to the attentional, interpretation and memory biases towards food and body shape, some more general impairments in cognitive processing include difficulties in decision making, reduced cognitive flexibility, a bias towards focusing on detail at the expense of seeing the general picture, problems in social cognition and dysfunctional emotional regulation (Adan & Kaye, 2011; Tuschen-Caffier et al., 2015; Martinez, Cook-Darzens, Chaste, Mouren, & Doyen, 2014; Lang et al., 2014).

In the 'Cognitive-interpersonal maintenance model' for anorexia nervosa proposed by Treasure and Schmidt (Schmidt & Treasure, 2006; Treasure & Schmidt, 2013) cognitive factors are described to act, together with socio-emotional and interpersonal elements, to both cause and maintain anorexia nervosa. Specifically, *weak central coherence* and *weak set-shifting* are described as important vulnerabilities to anorexia nervosa: i.e. respectively, the tendency to over-focus on detail with problems integrating elements appropriately, and inflexibility of people with anorexia nervosa in adapting to changing demands.

In this thesis, the role of these two domains in the information processing in anorexia nervosa will be further examined. In the next part, we will define central coherence and set-shifting and discuss the current knowledge concerning their role in the pathogenesis of anorexia nervosa.

Central coherence

Central coherence can be described as the drive for coherence, seen in typical development that integrates pieces of information in a congruent and meaningful unit (Frith, 1989). This focus on the 'gestalt' form is supposedly at the expense of the attention to details and the memory for details (Happe & Frith, 2006). *Weak central coherence*, first appointed in the domain of autism spectrum disorders, is defined as the tendency to process information in parts rather than a whole, with a relative difficulty in global or integrative thinking (Happe & Frith, 2006). Originally, in the 'weak central coherence theory' it was claimed that children with autism have problems integrating incoming information, and *consequently* tend to rely on piecemeal processing (Frith, 1989, 2003). Later, the original theory was modified in such a way that the reduced global processing was appointed to as, possibly, a *secondary effect* of superior local processing (Happe & Booth, 2008).

A weak central coherence is supposed to underlie the clinical observation that patients tend to focus on detail, neglecting the larger picture, also referred to as 'not seeing the wood for the trees' (Kidd & Steinglass, 2012). For instance, patients with anorexia nervosa are known to focus, more than the general population, on the size of separate body parts (Tchanturia, Campbell, Morris, & Treasure, 2005).

Weak central coherence is reflected in *superior task performance* when the ability to process featural information is advantageous and/or inferior performance when a global processing is advantageous. Classic examples include the superior performance on the Embedded Figures Task (which requires identification of a simple part within a complex and camouflaging whole), and on the Block Design Test (which benefits from an ability to see the whole design in terms of its constituent parts), or worse performance on the Object Assembly (construction of a whole from certain parts requiring global processing strategies) (Wechsler, 1981; Witkin, Oltman, Raskin, & Karp, 1971).

In a meta-analysis about central coherence in eating disorders, published in 2008, it was concluded that the weak central coherence hypothesis remained unresolved: there seemed a consistency about lower global processing in anorexia nervosa but the hypothesised superiority in local processing, was less clear (Lopez, Tchanturia, Stahl, & Treasure, 2008). In an updated meta-analysis of the same group, however, it was concluded that both elements of the weak central coherence theory could be supported (Lang et al., 2014).

Set-shifting

Set-shifting, also referred to as 'mental flexibility', can be defined as the ability to switch between tasks, operations and mental sets (Miyake et al., 2000). It has also been defined as the ability to be flexible with one's mind set in adapting to new task demands or changes in situations (Roberts, Tchanturia, & Treasure, 2011). Set-shifting is a fundamental component of cognitive ("executive") control together with inhibition, planning, attentional control, and working memory (Friederich & Herzog, 2011). A bias in set-shifting may manifest in cognitive and behavioural inflexibility, rigid approaches in problem solving, fixation with routines or specific rules, perseverative or stereotyped behaviours (Bulik et al., 2007; Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007).

This process of set-shifting has often been studied using neuropsychological tasks in which participants are asked to adapt their behaviour in response to changes in the task demands, e.g. the Wisconsin Card Sorting Test, Trail Making Task, Brixton Test (Lezak, 1995; Reitan, 1958; Burgess & Shallice, 1997). Further, experimental set-shifting paradigms have been developed to operationalize the process of set-shifting (Kiesel et al., 2010; Vandierendonck, Liefooghe, & Verbruggen, 2010). In

general, people seem to be slower when switching between tasks than when repeating them. This performance difference is called the 'switch-cost' (Jersild, 1927).

Problems in set-shifting are assumed to play a role in anorexia nervosa. A meta-analysis containing 15 studies confirms the presence of set-shifting inefficiencies (Roberts et al., 2007). Problems in set-shifting are expected to be one possible factor hampering the possible effects of psychotherapeutic treatments that place emphasis on the adaptation of essential cognitions and behaviours (Lock et al., 2013).

Neurobiological correlates of anorexia nervosa

Insights into the underlying mechanisms of anorexia nervosa have been growing, using advanced technologies that measure brain structure and function. In what follows, a brief introduction is given into the evidence from brain imaging research in anorexia nervosa.

First, *structural brain imaging studies*, revealed a significant decrease in global grey and white matter volumes, with concomitant increases in cerebrospinal fluid, comparing subjects with anorexia nervosa with healthy participants (Titova, Hjorth, Schioth, & Brooks, 2013). Further, regional decreases in grey matter volume were demonstrated in the hypothalamus, left inferior parietal lobe, right lentiform nucleus and right caudate (Titova et al., 2013) and in the frontoparietal-cingulate network, including the precuneus (Bar, de la Cruz, Berger, Schultz, & Wagner, 2015). Also cortical thickness, which is thought to be a more specific and biologically significant measurement of brain structure compared to brain volume, is found to be reduced in patients with anorexia nervosa in fronto-cingulate and parietal regions compared to controls (Bar et al., 2015).

Further, findings from *functional imaging* suggest disturbances in prefrontal cortical areas (i.e. the dorsolateral prefrontal, the medial prefrontal, and the orbitofrontal), anterior cingulate (dorsal and ventral), inferior parietal and insular cortices (Pietrini et al., 2011; van Kuyck et al., 2009; Brooks et al., 2012). The majority of these functional brain imaging studies evaluate the neuronal processes of subjects at rest or the brain responsiveness to visual stimulation with body or food images. Brain functioning related to the neuropsychological inefficiencies found in anorexia nervosa has been less studied up till now. Interestingly, two studies reported similar neural alterations in patients with anorexia nervosa as compared to healthy participants, although the one study used a set-shifting paradigm during functional brain imaging and the second applied a reward paradigm (Wagner et al., 2007; Friederich & Herzog, 2011). In both, hypoactivations at different levels (thalamus, ventral striatum, rostral anterior cingulate cortex) of the fronto-striato-thalamic network were reported, combined with preserved neural metabolism in the right ventral frontoparietal network.

Based on this growing knowledge about neurobiological alterations in anorexia nervosa, several *neural systems* are considered to be implicated in the aetiology of anorexia nervosa, including those associated with hunger regulation, cognitive self-regulatory control and reward processing (Kaye, Frank, Bailer, & Henry, 2005; Nunn, Frampton, Fuglset, Torzsok-Sonnevend, & Lask, 2011; O'Hara, Campbell, & Schmidt, 2015; Kaye et al., 2013; Kaye, Wagner, Fudge, & Paulus, 2011). A core aspect of these models is a *'top-down'* versus *'bottom-up'* element in which top-down modulatory mechanisms reflect prefrontal cognitive control, while bottom-up limbic and interoceptive processes reflect the integration of input from systems that regulate homeostatic need, responses to reward, and motivational drive. Several groups have reported on alterations in top-down cortical structures versus bottom-up subcortical structures (Brooks et al., 2012; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Kaye, Fudge, & Paulus, 2009; Wierenga et al., 2014). They propose that, in anorexia nervosa, hyperactivation of top-down cognitive control networks dominates bottom-up appetitive responses, and that, at a symptomatic level, this emerges as a pathological desire to be

thin, as high anticipatory anxiety when exposed to food and as behavioural rigidity including excessive control over food intake (Kaye et al., 2009).

Starvation and the brain

Any quest to identify underlying neuropsychological or neurobiological mechanisms in anorexia nervosa is hampered by the unsolved dilemma of whether the alterations in these domains are the cause or the result of prolonged starvation (Bar et al., 2015; Kaye et al., 2013). It is known that around 20% of the caloric intake is used in the brain, and therefore, in addition to the specific effect of starvation on the appetite system, poor nutrition can have a general effect on brain functioning (Treasure et al., 2010). These effects of starvation are most likely significant confounding factors in the research to the underlying eating disorder psychophysiology (Frank, 2015). As food deprivation is inevitably correlated with AN, it is hard to disentangle whether such a bias is a core feature of AN, a side-effect of short-term starvation, related to more chronic undernourishment, or a combination of the three (Pender, Gilbert, & Serpell, 2014).

The evidence for the relationship between body mass index (BMI) and *task performance* is however inconsistent: in various studies a significant relation could be established (Andres-Perpina et al., 2011), but this was contradicted in other studies (Fowler et al., 2006; Roberts, Tchanturia, & Treasure, 2010; Wilsdon & Wade, 2006).

Study results concerning the relation between alterations in the brain and BMI seem conflicting as well. E.g., one study could show that different indicators of disease severity of anorexia nervosa (i.e. pain thresholds, symptom severity and illness duration) were correlated with *structural alterations* in the brain (i.e. grey matter loss, reduced cortical thickness), while a relation with BMI could not be

established (Bar et al., 2015). Another study however showed a significant correlation between BMI and cortical thickness in patients with anorexia nervosa (Lavagnino et al., 2015). This seems in line with the results from a recent meta-analysis showing that white and grey matter losses in anorexia nervosa were nearly normalized after remission of anorexia nervosa (Seitz et al., 2014).

Diagnostic subcategories in anorexia nervosa

In DSM-IV and DSM-5, two subtypes of anorexia nervosa are described: the restricting type of anorexia nervosa (AN-R) in which the person has not regularly engaged in binge-eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics or enemas) during the current episode, and secondly, the binge-eating/purging type (AN-BP) in which the person has regularly engaged in binge-eating or purging behaviour (American Psychiatric Association, 1994; American Psychiatric Association, 2013).

Although many studies do not differentiate between AN-R and AN-BP (e.g. Kaye et al., 2013), there is growing evidence for the relevance of these subcategories. Next to common personality features such as high perfectionism, high harm avoidance, low self-directedness and low cooperativeness (Cassin & von Ranson, 2005; Degortes, Zanetti, Tenconi, Santonastaso, & Favaro, 2014; Vervaet, Van Heeringen, & Audenaert, 2004), there is consistent evidence for differences between eating disorder patients who exhibit bingeing and/or purging behaviours and patients who do not binge/purge. AN-BP seems more related with impulsive traits, lower behavioural inhibition and a higher reward sensitivity while AN-R seems to be associated with a higher compulsiveness and higher self-directedness (Claes, Robinson, Muehlenkamp, Vandereycken, & Bijttebier, 2010; Claes, Vandereyeken, & Vertommen, 2002; Vervaet et al., 2004; Matton, Goossens, Vervaet, & Braet, 2015).

Further, some authors focused on variations in features in the information processing that might be associated with different behavioural presentations in the subtypes of anorexia nervosa. Findings from these studies will be described in the following part.

Diagnostic subcategories in anorexia nervosa: differences on the neuropsychological level

Concerning similarities and differences between the neuropsychological profiles of AN-R and AN-BP, little is known up to now. In the current literature on central coherence and set-shifting in anorexia nervosa, most authors do not mention results of a comparative examination between subtypes although they give a description of the subtypology of the included anorexia nervosa subjects in the method section of their work (Andres-Perpina et al., 2011; Danner et al., 2012; Fowler et al., 2006; Giel et al., 2012; Konstantakopoulos, Tchanturia, Surguladze, & David, 2011; Nakazato et al., 2008; Sarrar et al., 2011; Urgesi et al., 2012; Zastrow et al., 2009). Other studies only include AN-R patients (Abbate-Daga et al., 2011; Fassino et al., 2002) and in a third group of studies, the typology of the included anorexia nervosa patients is not mentioned (Hatch et al., 2010; Kim, Kim, & Kim, 2010; Murphy, Nutzinger, Paul, & Leplow, 2002; Ruiz, De Leon, & Diaz, 2008; Southgate, Tchanturia, & Treasure, 2008; Steinglass, Walsh, & Stern, 2006; Tchanturia et al., 2012; Tenconi et al., 2010). The few available studies about differences across anorexia nervosa subtypes are inconsistent. Some authors report set-shifting problems at a higher rate in patients with AN-BP than in patients with AN-R (Claes, Mitchell, & Vandereycken, 2012; Roberts et al., 2010) whereas other authors could not find any significant difference (Tchanturia et al., 2004a; Tchanturia et al., 2004b). On central coherence measures, there is, as far as we know, only one study, where subtypes are compared using one central coherence task, the Matching Familiar Figures Task. With this task, in which a detail-focused

style is assumed to benefit performance, a difference in reaction times between patients with AN-R and patients with AN-BP could not been found (Toner, Garfinkel, & Garner, 1987).

Diagnostic subcategories in anorexia nervosa: differences on the neurobiological level

It has been argued that eating disorders are transdiagnostic at the neuronal level finding similar disturbances in different eating disorder categories (e.g., Uher et al., 2004). However, as mentioned by Collier and Treasure (2004), some study results suggest a differential biological bias for anorexia nervosa subtypes. Most of these findings are based on the comparison of each anorexia nervosa subtype with a healthy control sample, without a direct comparison being made between both subtypes (except for Sato et al. (2013), see below). In a review on functional brain imaging in anorexia nervosa, results were organized on a diagnostic subtype basis if available and, if not, were presented for the total anorexia nervosa sample (Pietrini et al., 2011). It has been noted that some of the established alterations in the cerebral functioning found in AN-R (as compared to healthy subjects) were not found when the clinical distinction (AN-R, AN-BP) was not made (Pietrini et al., 2011). A more recent study that clearly distinguished between anorexia nervosa subtypes performing a set-shifting task showed an increased activation in response to shifting in the putamen, insula and caudate head in the AN-R group compared to healthy controls. These increased activations were not found in the AN-BP group when compared to healthy controls (Sato et al., 2013). No significant differences could be shown by making a direct comparison between anorexia nervosa subtypes. However, this study was not designed to evaluate possible differences between AN-R and AN-BP. Consequently, the small samples make it difficult to draw any firm conclusions.

Thus, the current studies about the comparison between the restrictive and bingeing/purging subtypes of anorexia nervosa on a neuropsychological and/or neurobiological basis are scarce and results are inconsistent.

In sum

According to DSM-IV and DSM-5, within the diagnosis of anorexia nervosa a subtype should be specified depending on the presence or absence of bingeing and/or purging behaviours (American Psychiatric Association, 1993; 2013). The study of *underlying features* of anorexia nervosa might contribute to the understanding of the differences in behavioural presentation in these two patient groups. Concerning possible underlying *temperamental* features, both similarities and differences between eating disorder diagnostic categories have been found. One might assume that the study of *variations in the information processing* and *associated neurobiological processes* may provide additional insight into the symptomatic variations in anorexia nervosa and, subsequently in our understanding about what specific treatment is indicated for whom.

In this PhD, the included studies have the goal to further explore central coherence and set-shifting in the restrictive and bingeing/purging subtypes of anorexia nervosa.

Outline included studies in this thesis

In this thesis, the following studies are included:

1. A systematic review was conducted aiming to give a state of the art synthesis of the available studies comparing patients with AN-R and AN-BP in respect of behavioural measures of central coherence or set-shifting (**chapter I**).
2. A neuropsychological study was carried out aiming to investigate central coherence and set-shifting in the acute phase of anorexia nervosa, in comparison with a healthy control groups, with special attention to possible differences between AN-R and AN-BP (**chapter II**).
3. A computerised set-shifting task was performed during functional brain imaging (fMRI). Possible group difference (between AN-R, AN-BP, healthy controls) in neural correlates of set-shifting were examined (**chapter III**).
4. An Embedded Figures Task was used during fMRI to explore the possible differences (between AN-R, AN-BP, healthy controls) in neural correlates of detail-focussed processing (**chapter IV**).

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Chapter I. Are there differences in central coherence and set-shifting across the subtypes of anorexia nervosa? A systematic review[3]

Anorexia nervosa (AN) has been associated with weaknesses in central coherence and set shifting. In this line, it has been proposed to directly address these neuropsychological features in treatment (e.g., cognitive remediation therapy). It is not clear, however, whether the 2 subtypes of AN, the restricting (AN-R) and bingeing/purging (AN-BP) type, have the same amount of problems in these domains. A systematic search of the literature was conducted, using the databases Web of Science and PubMed, looking for studies on the comparison of AN-R and AN-BP in performing central coherence/ set-shifting tasks. Notably, very few authors describe the results of a direct comparison of the performance of patients with AN-R and AN-BP. In summary, the available indications for possible group differences are not strong enough to draw definitive conclusions.

[3] Van Autreve, S., Vervaet, M. (2015). Are there differences in central coherence and set shifting across the subtypes of anorexia nervosa? A systematic review. *The Journal of Nervous and Mental Disease, 203*, 774-780.

Introduction

Anorexia nervosa (AN) is an important medical health problem, with a serious nature, a high comorbidity and considerable rates of relapse and chronicity (Ben-Tovim et al., 2001; Birmingham et al., 2005; Steinhausen, 2009). Despite this, the evidence for AN treatment is weak (Bulik et al., 2007a), and little is known about the pathophysiologic mechanisms that account for its development and persistence (Jauregui-Lobera, 2013).

Alterations in neuropsychological functioning are assumed to be important in understanding AN, including problems in central coherence and set shifting (Holliday et al., 2005; Kidd and Steinglass, 2012; Lena et al., 2004; Roberts et al., 2010; Tenconi et al., 2010). Weak central coherence can be defined as the tendency to process information in parts rather than a whole, with a relative difficulty in global or integrative thinking (Happé and Booth, 2008). The central coherence theory, first mentioned in relation to autism, is explaining both a superior processing of featural and local information as well as a disordered "global" processing. A weak central coherence is supposed to underlie the clinical observation that patients with AN tend to focus on detail neglecting the larger picture (Kidd and Steinglass, 2012). A systematic review of central coherence in patients with AN shows consistency concerning a deficit in global processing across studies, but the expected superiority in detail processing could not be confirmed in each study (Lopez et al., 2008).

Furthermore, problems in set shifting are assumed to play a role in AN, thereby contributing to cognitive and behavioural inflexibility (Bulik et al., 2007b). Problems in set shifting may manifest in rigid approaches in problem solving, fixation with routines or specific rules, perseverative or stereotyped behaviors (Roberts et al., 2007; Tchanturia et al., 2014). This process can be operationalized in set-shifting tasks, where participants are asked to adapt their behavior in response to changes in the task demands. In a meta-analysis of set shifting in eating disorders, a consistent deficit in set-shifting ability was found (Roberts et al., 2007).

According to the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM 5), 2 subtypes of AN can be described (American Psychiatric Association, 2000; American Psychiatric Association, 2013). Subjects with the restricting type of AN (AN-R) have, during the current episode, not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). In contrast, subjects with the bingeing/purging type of AN (AN-BP) have regularly engaged in binge-eating or purging behavior.

The study of personality traits in patients with AN gives evidence for some shared as well as distinct features in the restrictive and bingeing/ purging subtypes. Different eating disorder diagnostic categories seem to share increased levels of harm avoidance and perfectionism (Bardone Cone et al., 2007; Fassino et al., 2009). However, comparing patients with AN-R and AN-BP, patients with AN-BP seem to show more impulsive traits, a higher novelty seeking, a higher emotional dysregulation, and a higher extravagance. Patients with AN-R seem to show a higher self-directedness, a higher compulsiveness, and a higher conscientiousness (Claes et al., 2002; Claes et al., 2010; Diaz-Marsa et al., 2008; Tasca et al., 2009; Vervaet et al., 2003). On the level of neuropsychological functioning, up to now, little is known about the similarities and differences between the 2 subtypes of AN (Roberts et al., 2013).

Finding a variation in underlying features across diagnostic subtypes might lead to the question whether a single (not differentiated) treatment approach for patients with and without bingeing/purging behaviors is appropriate. There is growing evidence that the processing biases in central coherence and set shifting might be interesting targets for cognitive remediation strategies (Tchanturia et al., 2013). These strategies aim to systematically train disturbed cognitive processes by using neuropsychological test materials. No information is as yet available on the specific indications for these approaches.

This study systematically reviews the literature that compares patients with AN-R and AN-BP (in the acute phase of the illness) in respect of central coherence and/or set-shifting measures.

Review

Inclusion Criteria

Studies that include a comparison of the performance of restrictive and bingeing/purging types of AN on one or more cognitive task(s) assumed to assess central coherence, a part of central coherence, or set shifting were selected. All the included patients fulfilled the criteria of AN-R or AN-BP according to the DSM-III, DSM-IV, International Classification of Diseases, Ninth Revision, or International Classification of Diseases, Tenth Revision and were in the acute phase of the illness while tested (follow-up measures were excluded) (American Psychiatric Association, 1980, 2000; World Health Organization, 1978; World Health Organization, 1992). The performance of patient groups was compared mutually and with a healthy control sample (HC). Only original studies published in peer-reviewed journals and written in English were considered. Case studies and conference abstracts were excluded.

Information sources were the electronic databases Web of Science and PubMed. The following search terms and Boolean operators were used: (central coherence OR set shifting OR neuropsych* OR mental flexibility) AND (anorexia). In addition, reference lists of previous reviews were scanned to find eligible studies. Articles published between January 1985 and June 2014 were considered.

Study Selection

Figure 1 gives an overview of the study selection process. Using the electronic databases Web of Science and PubMed and the reference lists of relevant records, 1,021 papers were identified. After the screening on the basis of title and, if appropriate, on the content of the abstract (n = 218) and the full text (n = 131), 67 studies were found that met the inclusion criteria except for the presence of

data on the comparison between AN-R and AN-BP. Among these, another 57 papers were excluded because they were exclusively based on AN-R (n = 8); no information was available about the subtypology of the AN (n = 26) or because the results of a comparative analysis (AN-R vs AN-BP) were not described (n = 23). The remaining studies (n = 10) were subsequently included in this systematic review.

We like to note that one study (Toner et al., 1987) was published before the DSM-IV criteriawere published. The descriptionoftheir “bulimic anorexia nervosa” group is however very similar to the AN-BP subtype defined in DSM-IV (American Psychiatric Association, 2000). Furthermore, we have chosen to include a study (Claes et al., 2012) in which a general “bingeing/purging eating disorder group” was compared to AN-R (including patients with AN-BP, bulimia nervosa, and eating disorder not otherwise specified with bingeing/purging behaviors).

Description of the Measures

In the studies that have been included, the following tasks were used to assess (parts of) central coherence.

Rey-Osterrieth Complex Figure Task

In this task, the participant is asked to copy a complex figure (Osterrieth, 1944). The experimenter tracks the order of figure completion. Based on Booth (2006), a central coherence index (scored between zero and 2) is calculated by combining order and style indices. The order index is a quantitative representation of whether the construction of the drawing begins with more detailed elements or more global elements. The style index is a quantitative representation of whether 6 key global elements were constructed in a continuous (score 2) or fragmented (score 0) fashion (where a

partially fragmented element scores 1). The coherence index is a weighted average of order and style indices, where a low coherence index indicates a more detailed and fragmented processing style.

Group-Embedded Figures Task

This perceptual test measures the time taken to locate and trace 18 simple shapes embedded in complex designs (Witkin et al., 2002). The main outcome is the time taken to locate the hidden shapes. The Group-Embedded Figures Task is assumed to investigate detail processing skills.

Fragmented Pictures Task

In this task (Snodgrass et al., 1987; Witkin et al., 2002), a series of pictures is presented to the participant, from their most fragmented form to their most complete form. The participant is instructed to identify each figure as quickly as possible. The items are all commonly known items (e.g. a pig, an apple, a chair). The central coherence measure is the mean frame at which the participant accurately labels the pictures across all trials, with a higher score and therefore a lower level of fragmentation relating to poorer global integration abilities.

The Matching Familiar Figures Test

This test involves simultaneous presentation of a figure (e.g., a boat) with eight different facsimiles (Kagan et al., 1964). For each of the items, the participant is asked to select the one that exactly matches the standard. Outcome measures include the total number of errors and the average time to the first response. This task is assumed to require detail processing.

Block Design

This task is a subtest of the revised Wechsler Adult Intelligence Scale (Wechsler, 1981). In this test, the participant is asked to produce complex geometric figures using colored cubes to replicate a

displayed figure. A total score is calculated on the basis of reaction times and accuracy. A detail-focused processing style is assumed to benefit performance.

Object Assembly

This task is also a subtest of the revised Wechsler Adult Intelligence Scale (Wechsler, 1981). In this task, the subject must compose a logic figure (elephant, house, body, face, or butterfly) from pieces of a puzzle. A higher score suggests a better ability to create an integrated global representation.

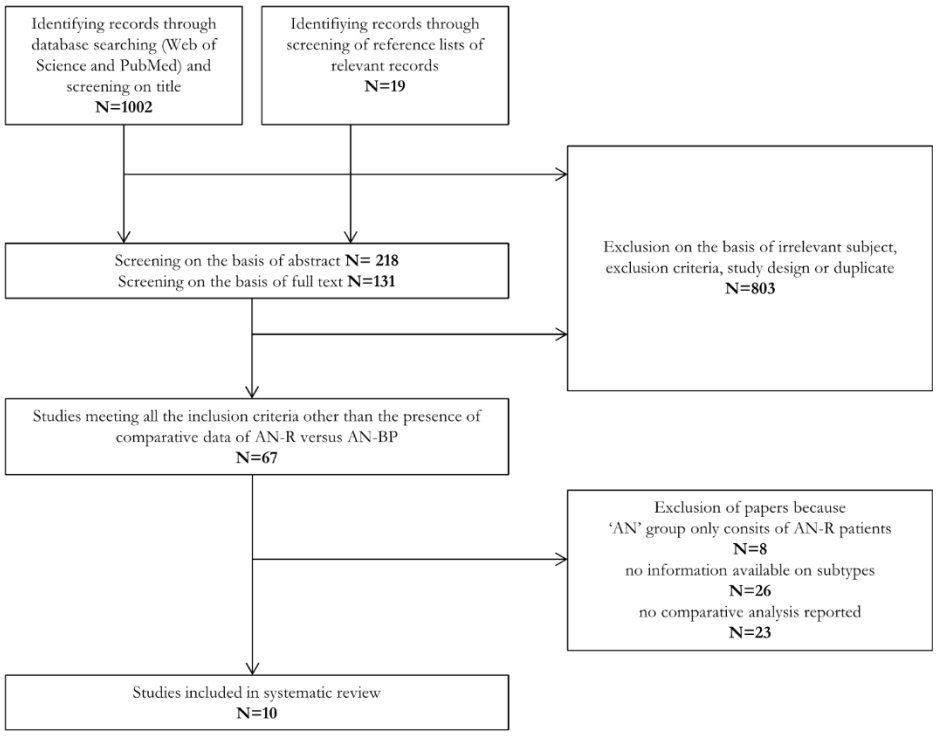

Figure 1. Flow chart systematic review.

The following measures were used to assess set-shifting abilities.

Trail-Making Test

This task consists of a first part (trail A) in which the subject is asked to connect numbered circles in the right order and a second part (trail B) in which the subject needs to link circles alternating numbers and letters (1–A–2–B–3–C–. . .) (Reitan, 1958). The time taken to complete each part of the test is registered. A longer time to complete part B or a greater ratio of part A and part B (B minus A or B divided by A) are assumed to indicate a weaker set-shifting ability.

Intradimensional/Extradimensional Shift Task, From Cambridge Neuropsychological Test Automated Battery

In this task, the participant needs to induce a rule through computer feedback (Robbins et al., 1998). The rule changes after a certain number of correct answers. Measures of the ability to shift set are the number of stages completed, the number of errors, and the total number of trials to complete the exercise.

Wisconsin Card Sorting Test

This test consists of geometric figure cards with specific features (color, shape, and number) (Berg, 1948). The subject needs to match one card at a time to 1 of 4 models using a “matching rule” based on color, shape, or number. The participant receives feedback on his matching by which he can learn the underlying rule. In the course of the test, the matching rule changes unannounced. A higher number of perseverative errors are indicative of an impairment of set shifting abilities.

Brixton Task

This task requires the participant to predict the movement of a blue circle across 10 circles presented in a grid (Burgess and Shallice, 1997). The pattern changes throughout the task and needs to be detected through trial and error. The number of incorrect predictions is a measure of set shifting.

Haptic Illusion

In this task (Tchanturia et al., 2004a), participants are asked to judge the relative size of wooden balls placed into each hand while their eyes are closed. First, 2 different sized balls are held in the hands (habituation phase). Next, 2 balls of the same size are introduced. The same-sized balls are perceived as having different sizes (perceptual illusion). The number of perceptual illusions is considered to be a set shifting measure.

Picture Set Test

In this task (adapted by Tchanturia et al., 2004a from the Set Flexibility Test (Surguladze, 1995)), the participant is shown 4 objects on a computer screen. They have to determine which is the odd one out by applying a sorting rule. The sorting rule changes after a number of trials. The total number of errors comprises the set-shifting measure.

The Verbal Fluency Task

This task(Controlled Oral Word Association, FAS;Lezak, 1983) requires the participant to vocalize as many words as possible in 1 minute beginning with the letters f, a, and s without repetition and excluding proper nouns, numbers, and sequences. The number of perseverative responses is assumed to be a set-shifting measure.

The Cat Bat Task

The participant is asked to fill in missing letters in a written short story (Eliava, 1964). In the first part of the test, the subject is primed to reconstruct one particular word, and in the second part of the task, the subject needs to adjust his cognitive set to the changes in the context. The number of errors (perseverations) and the time taken to complete the task are measures of set shifting.

An Adapted Task Switching Paradigm

In this task, adapted for one specific study (Van Autreve et al., 2013), participants have to switch between 2 easy tasks. Participants need to judge whether a presented number (from 1 to 9) is odd or even or whether the number is smaller or larger than 5. Before the presentation of the number, a geometric figure is presented to indicate which task to perform. Weak set-shifting abilities are linked with larger differences in response time and accuracy between task switch and task repetition trials, so-called switch costs.

Summary of the Results Concerning Central Coherence

Four studies on central coherence met the inclusion criteria. Fora brief summary, see Table 1. If central coherence is considered to be comprised of 2 parts, global integration and local information processing, as defined by Happé and Frith (2006), the results can be organized as follows.

TABLE 1. Studies Comparing AN-R and AN-BP on Central Coherence Tasks

Authors		Groups (N)	Tasks	AN-R Versus AN-BP?	Comments
1.	(Harrison et al., 2011)	AN-R (35) AN-BP (15) ANrec (35) BN (48) HC (89)	RCFT, GEFT, FPT	No difference	
2.	(Roberts et al., 2013)	AN-R (35) AN-BP (33) BN (30) ANrec (30) Sis (50) HC (88)	RCFT, GEFT	No difference	AN-R performs significantly better than HC, AN-BP does not
3.	(Toner et al., 1987)	AN-R (23) AN-BP (21) HC (24)	MFFT	No difference	AN-BP made more errors than AN-R
4.	(Van Autreve et al., 2013)	AN-R (31) AN-BP (20) HC (26)	Block design, Object assembly	AN-R < AN-BP	AN-R performs significantly worse than AN-BP and HC (latter do not differ)

ANrec indicates recovered AN; BN, bulimia nervosa; FPT, Fragmented Pictures Task; GEFT, Group-Embedded Figures Task; HC, healthy controls; MFFT, Matching Familiar Figures Test; RCFT, Rey-Osterrieth Complex Figure Task; Sis, healthy sisters.

Global Integration

Two studies included tasks assumed to require good global integration abilities. In one study, which used the Object Assembly Task (Van Autreve et al., 2013), a significant difference between AN subtypes was found, with AN-R performing worse than AN-BP. This could not, however, be shown in an earlier study using the Fragmented Pictures Task (Harrison et al., 2011).

In both studies, patients with AN (as a group on the whole) are shown to perform worse when compared to HC. However, a difference between AN-BP and HC could not be established in one of these studies (Van Autreve et al., 2013).

Detail Processing

In 2 studies, which used the Rey-Osterrieth Complex Figure Task and the Group-Embedded Figures Task, statistically significant differences between AN-R and AN-BP could not be shown (Harrison et al., 2011; Roberts et al., 2013). However, in an earlier study, which used the Matching Familiar Figures

Test (Toner et al., 1987), patients with AN-BP were found to make significantly more errors than restrictive patients. In a more recent study, a significantly worse performance was observed in AN-R compared to AN-BP, using the Block Design Task (Van Autreve et al., 2013).

When comparingAN to HC participants, the superiority in detail processing of both AN groups was confirmed (Harrison et al., 2011; Van Autreve et al., 2013), but not in each study or with each measure (Roberts et al., 2013; Toner et al., 1987).

Weak Central Coherence

In one study (Roberts et al., 2013), all participants were divided into 4 groups, based on the outcome measures of 2 tasks and a comparison with HC: good/poor detailed processing and good/poor global processing. Weak central coherence (good detail processing combined with poor global processing) was found in 41% of AN-R participants and 42% of AN-BP participants. This was significantly higher than the 18% of HC showing this neurocognitive profile.

Summary of the Results Concerning Set Shifting

Table 2 presents the 8 selected studies regarding set shifting across AN subtypes. In 6 of these studies, no significant difference was established between the AN subtypes using a range of different measures (Galimberti et al., 2012; Galimberti et al., 2013; Sato et al., 2013; Tchanturia et al., 2004a; Tchanturia et al., 2004b; Van Autreve et al., 2013). Galimberti et al. (2012) could not even find differences within a HC group.

TABLE 2. Studies Comparing AN-R and AN-BP on Set-Shifting Tasks

Authors	Groups (N)	Tasks	AN-R Versus AN-BP?
1. (Claes et al., 2012)	AN-R (23) ED-BP (25)	TMT-B	ED-BP < AN-R
2. (Galimberti et al., 2012)	AN-R (24) AN-BP (12) BN (16) HC (40)	ID/ED task	No differences
3. (Galimberti et al., 2013)	AN-R (14) AN-BP (15) AN rel (29) HC (29) HC rel (29)	WCST	No differences
4. (Roberts et al., 2010)	AN-R (35) AN-BP (33) ANrec (30) BN (30) Sis (50) HC (88)	TMT, WCST, Brixton, HIT	AN-BP < AN-R
5. (Sato et al., 2013)	AN-R (9) AN-BP (6) HC (15)	WCST	No differences
6. (Tchanturia et al., 2004a)	AN-R (20) AN-BP (14) BN (19) HC (35)	TMT, Brixton, PST, VFT, CBT, HIT	No differences
7. (Tchanturia et al., 2004b)	AN-R (20) ANrec (18) HC (36) AN-BP (14)	VFT, CBT, HIT, TMT, Brixton, PST	No differences
8. (Van Autreve et al., 2013)	AN-R (31) AN-BP (20) HC (26)	TMT, CST, TSP	No differences

AN rel indicates relatives of patients with AN (unaffected); Brixton, Brixton Test; CBT, Cat Bat Task; ED-BP, bingeing/purging eating disorder (AN-BP, or bulimia nervosa or EDNOS with B/P behaviour); HC rel; relatives of HC participants (unaffected); HIT, the Haptic Illusion Task; ID/ED task, Intradimensional/ Extradimensional Task from Cambridge Neuropsychological Test Automated Battery; IGT, Iowa Gambling Task; PST, Picture Set Test; TMT, Trail-Making Test; ToH, Tower of Hanoi; VFT, Verbal Fluency Task; WCST, Wisconsin Card Sorting Test.

On the other hand, 2 significant differences between AN subtypes have been reported. Although Robertset al. (2010) concluded that poor set shifting is a transdiagnostic feature in eating disorders (present in AN-R, AN-BP, and BN), a broader range and higher number of perseverative errors was

reported in individuals with bingeing/purging AN compared to patients with restrictive AN, using the Wisconsin Card Sorting Test. In the same line, Claes et al. (2012) studied differences between patients with restrictive AN and a general bingeing/purging eating disorder group (including AN-BP and patients with bulimia nervosa and eating disorder not otherwise specified).They reported a greater mean reaction time in the ED-BP group compared to AN-R, using the Trail-Making Test.

In one study (Roberts et al., 2010) a “composite set-shifting variable” was calculated from the outcome measures of 4 tasks. Approximately 46% of women with AN-BP displayed poor set shifting compared to 23% of women with AN-R. No statistical test was mentioned for the comparison of both proportions. The proportions of poor set-shifting performers in both AN groups were found to be significantly higher than the proportion of poor performers found in HC (9%).

Conclusions

This study reviews articles that examined central coherence and set-shifting abilities in AN and that report on the direct comparison between restrictive AN and bingeing/purging AN.

The first observation when systematically searching the literature was that very few studies on central coherence/set shifting in AN differentiate and compare AN-R and AN-BP. Most studies do not mention the distribution across AN subtypes or do not look for eventual differences while the number per subtype is given; other studies only include patients with AN-R to the common denominator of AN. Furthermore, the available studies mainly have small sample sizes (especially the patient group with AN-BP), preventing us from drawing strong conclusions about the comparative analyses.

Concerning eventual group differences on the level of central coherence, one study (Roberts et al., 2013) established that the percentage of patients with a weak central coherence was very similar for both AN-R and AN-BP (approximately 40%). When considering the 2 parts of weak central coherence separately (a superior detail processing and a lower global processing), a more complex picture seems to emerge. Two studies focusing on global processing were included in this review (Harrison et al., 2011; Van Autreve et al., 2013). Possible group differences between AN-R and AN-BP were not observed in one study, which used the Fragmented Pictures Test. The second study, however, reported a significantly worse performance in AN-R compared to AN-BP using the Object Assembly Task. This result might suggest that the commonly observed global integration difficulties in AN compared to healthy subjects are mainly due to global integration difficulties in AN-R. At present, the available evidence for this hypothesis is however limited.

Regarding detail processing (the second part of central coherence), 2 small discrepancies between patients with AN-R and AN-BP could be observed in that the expected superiority in detail processing could be solely shown in restrictive patients (Roberts et al., 2013; Toner et al., 1987). In 2 other studies, no differences could however be established. Furthermore, one study reported on a worse performance of patients with AN-R compared to patients with AN-BP using the Block Design Test. Assuming that this task requires, as often described, a detail focused style, this study could not confirm the hypothesised superiority in detail processing in AN and, furthermore, contradicts the previous reported suggestions that this superiority would only be present in AN-R. A possible explanation for this last finding can be found in the suggestion given in previous research that global approaches are also involved in performing the Block Design Test (Lopez et al., 2008).

Eight studies that focused on set-shifting abilities were included in this review. In 2 studies, bingeing/purging patients were shown to perform significantly worse compared to patients with AN-R on 2 different outcome measures (the Wisconsin Card Sorting Task and the Trail-Making Test) (Claes et al., 2012; Roberts et al., 2010). In the other 6 studies, using a broad range of set-shifting tasks, no significant differences between AN-R and AN-BP could however be observed (Galimberti et al., 2012; Galimberti et al., 2013; Sato et al., 2013; Tchanturia et al., 2004a; Tchanturia et al., 2004b; Van Autreve et al., 2013).

In 2 studies included (one on central coherence and one on set shifting), the percentage of participants with “poor central coherence/ set-shifting abilities” was calculated based on different outcome measures of different tasks. For central coherence as well as set shifting, the proportion of participants with AN with poor abilities (approximately 40% showed weak central coherence, 33% had poor set shifting) was found to be significantly higher than the proportion of HCs having weak abilities (approximately 18% had weak central coherence, 9% showed poor set shifting). The finding that poor central coherence/set-shifting abilities are not demonstrated by all patients but can indeed

be found in healthy people is often established in studies on executive functioning and might reflect the heterogeneity within (clinical) groups (Happé and Frith, 2006).

In general, the diversity found within patient groups is not adequately captured within a purely categorical system of diagnoses (Helzer et al., 2006). Within the field of eating disorders, this is particularly interesting given the well-known diagnostic cross over during lifetime from one eating disorder category to another. Research shows that approximately 40% of patients with the diagnosis of AN-R develop bingeing/purging behaviors later in life (Anderluh et al., 2009). Given this diagnostic instability, a dimensional approach could improve the diagnostic investigation and treatment choices (Castellini et al., 2011).

It is interesting to wonder whether variances in cognitive functioning, in this case central coherence/set-shifting performance, could have a certain value in formulating prognoses or in predicting the further course of the disorder. Previous research suggests that personality traits may shape the lifetime course of the eating disorder (Tozzi et al., 2005). For instance, obsessive-compulsive traits might be a maintenance factor for the restrictive phenotype (Anderluh et al., 2009; Castellini et al., 2011). In addition, a significant correlation between temperament and neuropsychological functioning has been shown in some studies (Galderisi et al., 2011; Pignatti and Bernasconi, 2013; Tchanturia et al., 2004b), although not in all (Galimberti et al., 2012). Maybe the differences within the AN-R group in cognitive style could play a role in the risk of developing a bingeing/purging eating disorder after a period of restrictive eating.

Furthermore, establishing that AN-R differs from AN-BP (on a cognitive level) could have important treatment implications in that both AN types could benefit from a differentiated treatment approach. Recently, research has begun into the usefulness of cognitive remediation strategies in which these cognitive features are the scope of treatment (Tchanturia et al., 2013). No information is as yet available on the specific indications for these approaches.

To summarize, few studies report on a direct comparison between AN-R and AN-BP on the level of central coherence and set shifting. Although a few small indications for possible differences between AN-R and AN-BP are available, this does not enable us to draw definitive conclusions about group differences. Further research is needed to understand whether differential cognitive processes underlie differences in symptomatic presentation. Studying the neural correlates of CC/SS processes in AN might give more insight into this issue. With regard to treatment, further understanding of this topic can be important in adapting appropriate treatment strategies.

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Chapter II. Do restrictive and bingeing/purging subtypes of anorexia nervosa differ on central coherence and set-shifting?[4]

Anorexia nervosa (AN) has been associated with weak central coherence (CC) and weak set shifting (SS). The main aim of this study was to examine possible differences between restrictive AN (AN-R) and bingeing/purging AN (AN-BP) on these features. A total of 31 patients with AN-R, 20 patients with AN-BP and 26 healthy controls (HC) completed five neuropsychological tests (Block Design, Object Assembly, an adapted task-switching paradigm, Wisconsin Card Sorting Test and Trail Making Test). Using Block Design and Object Assembly, indicative for CC, AN-R patients performed significantly worse than AN-BP patients and HC, without any difference between AN-BP and HC. On SS measures, no group differences were observed. The results suggest that cognitive profiles of AN-R and AN-BP patients differ significantly on CC and not on SS. Our current findings support the idea that the two subtypes of AN have a distinctive underlying nature and might need a different approach in cognitive remediation.

[4] Van Autreve, S., De Baene, W., Baeken, C., van Heeringen, C., Vervaet, M. (2013). Do restrictive and bingeing/purging subtypes of anorexia nervosa differ on central coherence and set shifting? *European Eating Disorders Review, 21 (4)*, 308-314.

Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder characterised by a refusal to maintain a healthy body weight, the intense fear of gaining weight despite being significantly underweight and a distortion in the patient's perception of their own body shape and weight. Given the high rates of concomitant psychosocial difficulties, psychiatric comorbidity, chronicity of the illness and the increased mortality risk, AN has a serious course and a poor prognosis (Ben-Tovim et al., 2001; Berkman, Lohr, & Bulik, 2007; Steinhausen, 2002). In the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV-TR), two different subtypes of AN are considered according to the behavioural approaches adopted by the patient to gain a low body weight: the restrictive type (AN-R) and the bingeing–purging type (AN-BP) (American Psychiatric Association, 2000).

In recent causal models of eating disorders (ED), the cognitive style is propounded as a core element (Herpertz-Dahlmann, Seitz, & Konrad, 2011; Schmidt & Treasure, 2006; Treasure, 2007). Eating disorder patients often deal with the tendency to over focus on detail, with problems integrating elements appropriately in context, and with cognitive rigidity, features that are frequently referred to as weak central coherence (CC) and weak set shifting (SS). Weak CC, first appointed in the domain of autism spectrum disorders, is defined as the tendency to process information in parts rather than a whole, with a relative difficulty in global or integrative thinking (Happe & Frith, 2006). In a meta-analysis including 16 studies about CC in ED, it was concluded that the weak CC hypothesis remains unresolved. There seems a consistency about lower global processing in AN and bulimia nervosa; the hypothesised superiority in local processing, however, is less clear (Lopez, Tchanturia, Stahl, & Treasure, 2008a).

Set shifting is defined as the ability to switch between tasks, operations and mental sets (Miyake et al., 2000). Impaired SS is supposed to contribute to rigid and obsessional behaviour (Bulik et al.,

2007). In a meta-analysis containing 15 studies, a consistent deficit in SS ability was found across different ED diagnoses (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007). However, using the Trail Making Test (TMT), some authors report minimal to no differences with healthy controls (Andres-Perpina et al., 2011; Fowler et al., 2006; Murphy, Nutzinger, Paul, & Leplow, 2002).

Starvation is assumed to have an impact on neuropsychological functioning. However, the relationship between body mass index (BMI) and performance could not be established in various studies (Andres-Perpina et al., 2011; Fowler et al., 2006; Roberts, Tchanturia, & Treasure, 2010; Wilsdon & Wade, 2006); this was contradicted in other studies in which cognitive impairments were related with low BMI (Andres-Perpina et al., 2011).

Furthermore, CC and SS deficits are found in healthy family members of AN patients (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Tenconi et al., 2010) and in recovered patients (Harrison, Tchanturia, & Treasure, 2011; Holliday et al., 2005; Lopez, Tchanturia, Stahl, & Treasure, 2009; Tchanturia, Morris et al., 2004), which might imply that these deficits are trait-related instead of state-dependent features of the disorder.

Possibly, the study of neuropsychological abilities can contribute to a better understanding of differences and similarities between diagnostic ED categories and improve our knowledge of the pathophysiology of ED (Galimberti, Martoni, Cavallini, Erzegovesi, & Bellodi, 2012). Concerning similarities and differences between the neuropsychological profiles of AN-R and AN-BP, little is known up to now. In the current literature on CC and SS in AN, most authors do not mention results of a comparative examination between subtypes, although they give a description of the subtypology of the included AN subjects in the method section of their work (Andres-Perpina et al., 2011; Danner et al., 2012; Fowler et al., 2006; Giel et al., 2012; Konstantakopoulos, Tchanturia, Surguladze, & David, 2011; Nakazato et al., 2009; Sarrar et al., 2011; Urgesi et al., 2012; Zastrow et al., 2009). Other studies only include AN-R patients (Abbate-Daga et al., 2011; Fassino et al., 2002), and in a third group of studies, the typology of the included AN patients is not mentioned (Hatch et al., 2010; Kim,

Kim, & Kim, 2010; Murphy et al., 2002; Ruiz, De Leon, & Diaz, 2008; Southgate, Tchanturia, & Treasure, 2008; Steinglass, Walsh, & Stern, 2006; Tchanturia et al., 2011, 2012; Tenconi et al., 2010). The few available studies about differences across AN subtypes are inconsistent. Some authors report SS problems at a higher rate in AN-BP subtypes than in AN-R (Claes, Mitchell, & Vandereycken, 2012; Roberts et al., 2010), whereas other authors could not find any significant difference (Tchanturia, Anderluh et al., 2004; Tchanturia, Morris et al., 2004). On CC measures, there is, as far as we know, only one (outdated) study, where subtypes are compared using one CC task, the Matching Familiar Figures Task. With this task, in which a detail-focused style is assumed to benefit performance, a difference in reaction times between AN-R and AN-BP patients could not been found (Toner, Garfinkel, & Garner, 1987).

In the current study, the first aim was to investigate CC and SS in the acute stage of AN, in comparison with a healthy control group, with special attention to possible differences across AN subtypes. We hypothesised that AN subtypes show a different neuropsychological profile, with AN-R patients showing a greater focus to detail, a lower global processing ability and a lower mental flexibility. Second, we examined the relationship between cognitive functioning, demographic variables (age and education) and clinical features [body mass index (BMI), depressive and anxiety symptoms, and perfectionism].

Materials and methods

Subjects

Participants (N = 77) consisted of three groups: 31 patients with the diagnosis of AN-R, 20 with AN-BP and 26 healthy controls (HC). Patients were recruited in the inpatient (94%) and outpatient (6%) units of the Centre for Eating Disorders at the University Hospital of Ghent, were diagnosed by a specialist ED clinician using DSM-IV criteria (American Psychiatric Association, 2000) and had a BMI below 17.5. HC participants were studying at the faculty of medicine (Bachelor in Medicine and Master in Nursery and Obstetrics) and were only included if past and current EDs were absent. All participants were female.

Procedure

The study was approved by the local ethical committee of the Medical Department of Ghent University. After participants gave written informed consent, they passed a clinical and cognitive assessment, with a duration of approximately 1.5 hours. The assessment was performed by a clinical psychologist.

Clinical assessment

An interview and a form were used to gather socio-demographic (age and level of education) and clinical variables (current body weight, lowest body weight from the age of 16years and height). More clinical characteristics were assessed using self-report questionnaires, including the Beck Depression Inventory II (BDI-II; Beck, Steer and Brown, 1996), the State–Trait Anxiety Inventory (STAI; Spielberger et al., 1970) and the Frost Multidimensional Perfectionism Scale (MPS-F; Frost et al.,

1990). The STAI includes both 'State anxiety' (a more temporary condition of anxiety) and 'Trait anxiety' (a more general and longstanding anxiety). The MPS-F consists of six subscales (Personal standards, Concern over mistakes, Doubts about actions, Parental expectations, Parental criticism and Organization), but in the current study, only the total score was reported.

Cognitive assessment

All participants completed a neuropsychological test battery including two visuospatial tasks assumed to be influenced by CC (Block Design and Object Assembly) and three measures of SS ability [the Wisconsin Card Sorting Test (WCST), the TMT and a task-switching paradigm (TSP)]. Block Design and Object Assembly are two subtests of the revised Wechsler Adult Intelligence Scale (Wechsler, 1981). The total score for each task is assumed to give an indication of CC (Lopez, Tchanturia, Stahl, & Treasure, 2008b). In the Block Design test, subjects are asked to produce complex geometric figures using coloured cubes to replicate a displayed figure. A detail-focused style is assumed to benefit performance. In the Object Assembly, subjects must compose a logic figure (elephant, house, body, face or butterfly) out of some given pieces. A higher score suggests a better ability to create an integrated global representation. The WCST (Bergh, 1948) computer version 4 (Psychological Corporation) consists of geometric figure cards with specific features (colour, shape and number). Subjects need to match one card at a time to one of four models using a 'matching rule' based on colour, shape or number. Subjects receive feedback on their matching by which they can learn the underlying rule. In the course of the test, the matching rule changes unannounced. A higher number of perseverative error is indicative of an impairment of SS abilities. The TMT (Reitan, 1958) consists of a first part (trail A) in which subjects are asked to connect numbered circles in the right order and a second part (trail B) in which the subjects need to link circles alternating numbers and letters (1–A–2–B–3–C–...). The pen and paper version was used. The reaction time to complete each part was

registered. Two types of ratios between part A and part B were used as measures of SS (B minus A, and B divided by A) in which a greater ratio is assumed to indicate a lower SS ability.

A TSP was adapted (for reviews on the use of this paradigm in testing cognitive flexibility, see Monsell, 2003; Kiesel et al., 2010; Vandierendonck, Liefooghe, & Verbruggen, 2010). As in a typical task-switching experiment, participants have to switch between two easy tasks. Weak SS abilities are linked with larger differences in response time and accuracy between task-switch and taskrepetition trials, so-called switch costs. In the current task-switching experiment, participants need to judge whether the presented number (the target) is odd or even or whether the number is smaller or larger than 5. Prior to the presentation of the target, a geometric figure (the cue) is presented for 500 milliseconds to indicate which task to perform. After this cue, the target is presented until the subject responds (with a maximum duration of 3500 milliseconds). The next cue is presented after a variable response-cue interval (ranging between 200 and 4050 milliseconds). All stimuli are presented at a frame rate of 60 Hz on a black background. The instruction is given to respond as fast as possible, without sacrificing accuracy.

Statistical analysis

The data were analysed with the IBM SPSS Statistics version 20 (Armonk, NY, USA). The normality of the distribution of scores was tested in each study group for each variable of interest using the Kolmogorov–Smirnov statistic and box plot diagrams. If normality was confirmed, one-way between-group analyses of variance were used to compare independent groups (AN-R, AN-BP and HC) on demographic and clinical variables (education, BMI, level of depressive symptoms, anxiety and perfectionism) and neuropsychological measures (Block Design and Object Assembly). The Tukey's multiple range test was used for post hoc comparisons. For comparison of two study groups (AN versus HC or AN-R versus AN-BP), independent samples t-tests were performed.

For some variables (age, education, STAI state anxiety, MPS-F, TMT B-A, TMT B/A, WCST and TSP), scores were not normally distributed for at least one of the study groups. A log transformation of the data did not result in a normal distribution, which obliged us to use nonparametric statistical tests (Mann–Whitney U test for the comparison of two groups and Kruskal–Wallis for the comparison of three groups). Again, pairwise comparisons were performed with correction for multiple comparisons.

To explore relationships between neuropsychological and demographic/clinical variables, Pearson correlations (r; for normal distributed variables) or Spearman correlations (rho; for not normal distributed variables) were calculated for each study group separately.

Results

Sample characteristics

Table 1 gives an overview of means (M) and standard deviations (SD) for demographic and clinical variables across the three study groups and the results of a group comparison using one-way analysis of variance or Kruskal–Wallis. All study groups differed mutually in terms of their BMI, with AN-R patients having a lower mean BMI (M=14.4, SD=2.0) than AN-BP patients (M=16.4, SD=1.1) and HC subjects (M=20.9, SD=1.8). In the same way, groups all differed pairwise on the lowest BMI from the age of 16years, with the AN-R patients having the lowest reported BMI (M=14.0, SD=2.0). On (years of) education and age, no significant differences could be shown between groups (p> .05). Concerning the clinical variables (depressive symptoms, state and trait anxiety and perfectionism), only differences between clinical groups and HC subjects were found, without any significant differences among clinical groups (AN-R versus AN-BP). With this, no covariates had to be included in further analyses of variance.

Table 1 Demographic and clinical data

	M (SD)				Post hoc tests[c]		
	AN-R (n =31)	AN-BP (n =20)	HC (n = 26)	p	I-II	I-III	II-III
Age (years)	26 (12)	20 (4)	19 (2)	.179[a]		*	*
Education (years)	13 (2.5)	12 (2)	13 (1)	.415[a]		*	*
BMI (kg/m^2)	14.4 (2)	16.4 (1.1)	20.9 (1.8)	<.001[b]		*	*
Lowest BMI (kg/m^2)	14.0 (2.4)	16.5 (1.5)	19.3 (1.5)	<.001[b]		*	*
BDI-II	30 (12)	32 (12)	7 (6)	<.001[b]		*	*
STAI state anxiety	55 (13)	56 (13)	35 (13)	<.001[a]		*	*
STAI trait anxiety	61 (13)	60 (12)	38 (12)	<.001[b]		*	*
MPS-F (total)	119 (24)	107 (25)	80 (22)	<.001[a]		*	*

AN-R, anorexia nervosa restrictive type; AN-BP, anorexia nervosa bingeing/purging type; HC, healthy control; BMI, body mass index; BDI-II, Beck Depression Inventory II; STAI State–Trait Anxiety Inventory; MPS-F, Frost Multidimensional Perfectionism Scale. [a]KruskalWallis; [b]One-way analysis of variance; [c]Pairwise comparisons with I=AN-R, II =AN-BP and III= HC *Significant p-value (p< .05) for post hoc comparison.

Group comparisons on neuropsychological data

By comparing AN patients as one group to HC (Table 2), a significant difference on Block Design could be determined (t(67) = 4.713, p<.001), with AN patients performing lower than HC (M = 39.8, SD = 14.5 versus M = 53.4, SD = 10.3). No significant group differences could be established on Object Assembly (t(71) = 1.269, p = .209) or on the three measures of SS (p>.05).

Table 2 Performance on neuropsychological measures in anorexia nervosa subjects and healthy controls

	M (SD)		
	AN (n=51)	HC (n=26)	p
Central coherence			
Block Design	39.8 (14.5)	53.4 (10.3)	<.001[a]
Object Assembly	36.7 (8.6)	39.3 (8.0)	.209[a]
Set shifting			
TMT B-A	29.8 (13.6)	28.7 (11.8)	.832[b]
TMT B/A	1.9 (0.4)	2.0 (0.5)	.422[b]
WCST perseverative responses	9.1 (8.4)	7.5 (4.7)	.923[b]
TSP Cost RT	121.5 (97.1)	141.5 (126.9)	.984[b]
TSP Cost ER	0.90 (1.6)	1.00 (4.7)	.432[b]

AN, anorexia nervosa; HC, healthy control; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; TSP, task-switching paradigm; RT, reaction time; ER, number of errors. [a]Independent samples t-test. [b]Mann–Whitney U test.

In Table 3, the performance on the neuropsychological measures across AN subtypes and HC is presented. AN-R patients were found to perform significantly lower on Block Design than AN-BP patients (M = 35.4, SD = 13.7 versus 46.8, SD = 13.0, p = .006) and HC subjects (M=53.4, SD=10.3, p=<.001), whereas a difference between AN-BP and HC could not be determined (p=.190). On Object Assembly, a difference between the three study groups was found as well (F(2) = 5.424; p = .006), with post hoc analysis showing that AN-R patients (M = 33.8, SD = 8.6) scored significantly lower than the other two groups (M = 40.8, SD = 6.8 for AN-BP and M = 39.3, SD = 8.0 for HC), without a significant difference between the last two (p = .816). On SS measures, no significant differences between groups could be found (p>.05).

Table 3 Performance on neuropsychological measures across anorexia nervosa subtypes

	M (SD)				Post hoc tests[c]		
	AN-R (n =31)	AN-BP (n =20)	HC (n = 26)	p	I-II	I-III	II-III
Central coherence							
Block Design	35.4 (13.7)	46.8 (13.0)	53.4 (10.3)	<.001[a]			
Object Assembly	33.8 (8.6)	40.8 (6.8)	39.3 (8.0)	.006[a]			
Set shifting							
TMT B-A	27.0 (12.4)	33.8 (14.5)	28.7 (11.8)	.256[b]			
TMT B/A	1.9 (0.4)	2.1 (04)	2.0 (0.5)	.212[b]			
WCST perseverative responses	9.3 (8.3)	8.7 (8.6)	7.5 (4.7)	.966[b]			
TSP Cost RT	127.1 (94.7)	112.7 (103.3)	141.5 (126.9)	.672[b]			
TSP Cost ER	0.84 (1.86)	1.00 (1.10)	1.00 (1.28)	.413[b]			

AN-R, anorexia nervosa restrictive type; AN-BP, anorexia nervosa bingeing/purging type; HC, healthy control; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; TSP, task-switching paradigm. [a]One-way between groups analysis of variance.[b]Kruskal–Wallis. [c]Pairwise comparisons with I=AN-R, II =AN-BP and III=HC. *Significant p-value (p< .05) for post hoc comparison.

Correlations between outcome measures

Correlations between cognitive outcome measures for the total AN group are presented in Table 4. A significant correlation was found between the scores on the two measures of CC, Block Design and Object Assembly (r = .52, p<.001). In addition, the two types of ratios derived from the TMT, B-A and B/A were strongly correlated (r= .74, p< .001). Between SS measures, only one significant correlation between the outcome measures of TMT and the number of perseverative responses on the WCST was found (r=.43, p=.002 for B-A and r=.38, p=.010 for B/A). The reaction time switch cost of the TSP was not significantly correlated with any other SS measure, that is, the number of perseverative responses on the WCST (r=.22, p=.184), the TMT B/A (r=.17, p=.301) and the TMT B-A (r=.13, p=.406).

Associations with background and clinical variables

Correlational analyses between demographic /clinical and neuropsychological variables were performed separately for each study group. No significant correlations were found with age, lowest

BMI from the age of 16years and current BMI (p>.05), except for the TSP scores in AN-R patients (r = .46, *p*=.030). In one group (AN-R), education (in years) was positively correlated with the Block Design (r= .40, *p*< .05). No significant correlations were found with the level of depressive symptoms and anxiety (as measured with the BDI-II and STAI), except for Object Assembly and trait anxiety in the AN-BP group (r = .55, *p*<.05). Perfectionism (as measured with the MPS-F) was correlated with TMT B-A (r = .57, *p*=.004) and TMT B/A (r = .51, *p*=.014).

Table 4 Correlations between neuropsychological measures in anorexia nervosa

		Block Design	Object Assembly	TMT B-A	TMT B/A	TSP cost RT
Object Assembly	r(ho)	.52				
	p	p < .001*				
TMT B-A	r(ho)	.04	.01			
	p	p= .782	p= .962			
TMT B/A	r(ho)	.19	.10	.74*		
	p	p= .196	p= .512	p < .001		
TSP cost RT	r(ho)	.25	.23	.13	.17	
	p	p= .112	p= .155	p= .406	p= .301	
WCST perseverative responses	r(ho)	.24	.01	.43*	.38*	.22
	p	p= .096	p= .969	p= .002	p= .010	p= .184

TMT, Trail Making Test; TSP, task-switching paradigm; RT, reaction time; WCST, Wisconsin Card Sorting Test. r =Pearson's correlation; rho = Spearman's correlation. *Significant correlation with 0.05 level of significance (in bold).

Discussion

The major aim of this study was to examine CC and SS abilities in AN, specifically across AN subtypes. Five neuropsychological tests were completed with three groups of participants (AN-R, AN-BP and HC). With regard to global processing, the total group of AN did not show a different performance when compared with HC. Interestingly, studying the two subtypes of AN separately using the Object Assembly test, we found that AN-R patients scored significantly lower than AN-BP and HC, whereas the latter did not show a different performance. The Object Assembly test has been used earlier in AN (Lopez et al., 2008a), but the current study is to our knowledge the first to compare AN subtypes using this measure. These results suggest that the widely mentioned problem in AN to integrate information in a 'bigger picture' is specifically present in the AN-R patients. The fact that a different performance between AN and HC on Object Assembly is repeatedly confirmed in earlier research and not in the current study may be due to the potential under representation of AN-BP patients in AN samples in previous studies.

Another deviant score in AN, compared with HC, was found using the Block Design test. In finding that AN patients performed lower than the HC subjects, the current study could not confirm the hypothesised superiority in detail processing in AN. Although this detail-focused style is repeatedly confirmed in autism spectrum disorders using the Block Design test (Caron, Mottron, Berthiaume, & Dawson, 2006), the current results are in line with different studies in which this superiority could not be consistently confirmed in AN (Lopez et al., 2008b).

Remarkably, a strong correlation was established between the scores from the Block Design and Object Assembly tests (r=.51). This finding suggests a shared underlying mechanism. In previous research, it has been assumed that, alongside detail-focused approaches, global approaches could also be involved in the performance of subjects who undertook the Block Design test (Lopez et al.,

2008a). Happe and colleagues even argue that tasks that sufficiently discriminate between the specific contributions of local versus global processes are not yet available (Happe & Booth, 2008). Interestingly, a similar difference between AN subtypes' performance was discovered from the Block Design and Object Assembly tests, in that AN-R patients scored significantly lower than AN-BP patients and HC without there being any difference between AN-BP and HC.

In finding no SS deficit for any AN subtype when compared with HC, the current study corresponds with the findings of some other studies in which no or highly limited SS problems were established (Andres-Perpina et al., 2011; Fowler et al., 2006; Murphy et al., 2002). The majority of the published papers concerning SS in AN report, however, a significant SS difference between AN and HC, even using the WCST in a large sample (Tchanturia et al., 2012).

Evidence from the literature in other psychiatric disorders, mainly in schizophrenia, indicates that cognitive remediation therapy (CRT), which focuses on cognitive processes and not on cognitive content, is an effective strategy for teaching new cognitive skills relevant for everyday functioning as well as having a positive impact on clinical outcomes (Wykes et al., 2007). Exploratory research with an adapted version of CRT for AN shows an improvement in the cognitive performance of AN patients (Tchanturia et al., 2008). Because sufficient cognitive abilities are most probably an important precondition for psychotherapy, a cognitive remediation strategy may be a useful introduction to more in-depth psychotherapeutic approaches (Tchanturia, Anderluh et al., 2004). Our findings support the idea that AN subtypes might, however, need a different CRT approach, in that AN-BP patients will benefit less from remediation strategies focusing on the enhancement of global processing abilities than AN-R patients.

Finding a difference between the AN subtypes with regard to cognitive functioning can also be of theoretical interest. Our results suggest that the two subtypes of AN not only differ on a behavioural level but also have a distinctive underlying nature. Taking into account the common diagnostic crossovers from AN-R to bingeing/purging ED (Castellini et al., 2011), we can speculate that AN-R

patients with a higher degree of global processing impairment are more likely to develop a chronic AN-R pathology, whereas AN-R patients with a lower degree of global processing impairment are more likely to develop a bingeing/ purging ED. Longitudinal research taking into account diagnostic crossovers can be useful to gain insight in this topic.

Our data could not confirm a possible relation between BMI and CC or SS. Although a correlation analysis, as used in this study, is not a conclusive method to test the trait-related nature of cognitive impairments, to some extent, the results provide support for the theory that cognitive deficits in AN are not purely a result of starvation. Previous research is inconsistent on the link between BMI and cognitive performance. Examining the result of weight restoration on cognitive possibilities can contribute to a better understanding of this topic.

This study has some limitations. First, the groups studied were rather small. Second, our samples had a great heterogeneity with regard to their age. Next, the patient group (N = 51) consisted of both inpatients (N = 48) and outpatients (N = 3). In addition, the IQ of the participants was not considered, although this may have influenced performance, and mean IQ can differ between study groups. Further, there are some generally acknowledged weaknesses in the interpretation of the profiles from neuropsychological tasks. The measures used all require a complex mix of different skills, and as a result, we cannot conclude precisely which underlying mechanism is responsible for a certain performance (Lopez, Tchanturia, Stahl, & Treasure, 2008c; Southgate et al., 2008; Tchanturia et al., 2012). This is illustrated by the aforementioned correlation between the Block Design and Object Assembly scores. Adding a task in which CC is assumed to be involved, but on a semantic instead of on a perceptual level, could perhaps have given more certainty about sharing underlying mechanisms. In addition, the use of functional neuroimaging could contribute to our understanding about the underlying nature of these functions.

To conclude, this study confirms visuospatial difficulties in AN, indicating a bias in CC. On a conceptual level, our results give support for the usefulness of the subtypology in AN and the idea

that both subtypes have a distinctive underlying nature. In relation to therapeutic approaches, our findings suggest that not all AN patients will gain benefit from the same (cognitive remediation) strategies.

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Chapter III. Differential neural correlates of set-shifting in the bingeing/purging and restrictive subtypes of anorexia nervosa: An fMRI study[5]

In this study, possible differences in the neural correlates of set-shifting abilities between the restrictive (AN-R) and binging/purging (AN-BP) subtypes of anorexia nervosa have been explored. Three groups of participants performed a set-shifting task during functional magnetic resonance imaging: patients with AN-R (N=16), AN-BP (N=13) and healthy control participants (N=15). As in a typical set-shifting experiment, participants had to switch between two easy tasks (i.e. “Is the presented number odd/even” or “Is the presented number smaller/larger than 5”). The trials in which the task was repeated (repeat trials) were compared with trials in which the task was switched (switch trials). With regards to the level of task performance, no significant group differences could be established. However, when comparing switch specific brain activity across study groups, a stronger activation was found in the insula and the precuneus in AN-R when compared to AN-BP and HC. These results suggest that the both subtypes of AN might have different neurobiological correlates, and thus, might benefit from different treatment approaches.

[5] Van Autreve, S., De Baene, W., Baeken, C., Vancayseele, N., van Heeringen, C., Vervaet, M. (2016). Differential neural correlates of set-shifting in the begeing/purging and restrictive subtypes of anorexia nervosa: An fMRI study. *European Eating Disorders Review* (DOI: 10.1002/erv.2437)

Introduction

Anorexia nervosa (AN) is an eating disorder characterized by a low body weight (< 85% of the expected weight for age and height), body image disturbance, fear of weight gain, and amenorrhea (American Psychiatric Association, 2000). Two subtypes are described in the Diagnostic and Statistical Manual 4th edition (DSM-IV) (American Psychiatric Association, 2000). The restricting subtype of AN (AN-R) involves energy restriction, increased energy consumption, fasting and other non-purging compensatory behaviours, in the absence of binge eating behaviours. The bingeing/purging type (AN-BP) includes the presence of binge eating and/or purging behaviours.

Using advanced technologies that measure brain structure and function, insights into the underlying neurobiological mechanisms of AN have been growing. Next to brain volume changes in grey and white matter (Titova, Hjorth, Schioth, & Brooks, 2013), alterations in the dopaminergic and serotonergic systems (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Goethals et al., 2007) have been found. Further, the current findings from functional imaging suggest disturbances in prefrontal cortical areas (i.e. the dorsolateral prefrontal, the medial prefrontal, the orbitofrontal and the anterior cingulate), parietal, temporal and insular cortices in AN (Pietrini et al., 2011; van Kuyck et al., 2009; Brooks, Rask-Andersen, Benedict, & Schioth, 2012). The majority of these functional brain imaging studies evaluate the neuronal processes of subjects at rest or the brain responsiveness to visual stimulation with body or food images. What has been less studied is the brain functioning related to the neuropsychological inefficiencies found in AN.

A neuropsychological profile for patients with AN has, however, been described, including impairments in set-shifting (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Tchanturia et al., 2012; Lopez, Tchanturia, Stahl, & Treasure, 2008). Set-shifting can be defined as the ability to switch between tasks, operations and mental sets (Miyake et al., 2000). Impairments in set-shifting are

supposed to contribute to rigid and obsessional behaviours and cognitive inflexibility and are expected to hamper the possible effects of psychotherapeutic treatments that place emphasis on the adaptation of essential cognitions and behaviours (Lock et al., 2013).

Set-shifting is often studied using the task-switching paradigm in which participants need to switch between different tasks (for reviews, see Kiesel et al., 2010; Vandierendonck, Liefooghe, & Verbruggen, 2010). In general, people seem to be slower when switching between tasks than when repeating them. This performance difference is called the 'switch-cost' (Jersild, 1927). Using set-shifting tasks in functional brain imaging, it has been shown that frontoparietal brain areas are more strongly activated during switch trials than during repetition trials. These areas include the left inferior frontal gyrus, the medial frontal cortex and the left superior parietal lobe (e.g. Sohn, Ursu, Anderson, Stenger, & Carter, 2000; Braver, Reynolds, & Donaldson, 2003; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Kimberg, Aguirre, & D'Esposito, 2000; Rushworth, Paus, & Sipila, 2001; Rushworth, Hadland, Paus, & Sipila, 2002; Smith, Taylor, Brammer, & Rubia, 2004). When comparing the switch specific brain activity in participants with and without AN, the dorsal anterior cingulate cortex, the ventral putamen, the right ventrolateral prefrontal cortex and the bilateral parahippocampal cortex have been found to be activated to a lesser extent in participants with AN (Zastrow et al., 2009; Sato et al., 2013). In those studies, the AN samples include patients with AN-R as well as patients with AN-BP. A direct comparison between both subtypes has not as yet been made.

Although many studies do not differentiate between AN-R and AN-BP (e.g. Kaye et al., 2013), there is growing evidence for AN-R being a distinct illness. It has been consistently shown that patients with an eating disorder share some common personality features such as high perfectionism, harm avoidance, low self-directedness and low cooperativeness (Cassin & von Ranson, 2005; Degortes, Zanetti, Tenconi, Santonastaso, & Favaro, 2014). However, there seem to be consistent differences between eating disorder patients who exhibit bingeing and/or purging behaviours and patients who

do not display these behaviours. Patients with AN-BP seem to show more impulsive traits or lower behavioural inhibition than AN-R patients, while the latter seem to show a higher compulsiveness (Claes, Vandereyeken, & Vertommen, 2002; Claes, Robinson, Muehlenkamp, Vandereycken, & Bijttebier, 2010; Rosval et al., 2006; Vervaet, Van Heeringen, & Audenaert, 2004).

With regards to cognitive style, possible differences between AN-R and AN-BP have not been consistently found. A previous study from our own research group was not able to establish significant differences between AN subtypes using different set-shifting measures (Van Autreve, De Baene, Baeken, Van Heeringen, & Vervaet, 2013). However, in a recent meta-analysis on set-shifting abilities in different eating disorders, set-shifting inefficiencies related to AN-R, bulimia nervosa and binge eating disorder were established, but not in relation to AN-BP (Wu et al., 2014).

Brain imaging studies may provide additional insight into possible differences between AN subtypes. As mentioned by Collier and Treasure (2004), some study results indeed suggest a differential biological bias for AN subtypes. However, most of these findings are based on the comparison of each AN subtype with a healthy control (HC) sample, without a direct comparison being made between both subtypes (except for Sato et al. (2013), see below). In a review on functional brain imaging in AN, results were organised on a diagnostic subtype basis if available and, if not, were presented for the total AN sample (Pietrini et al., 2011). It has been noted that some of the established alterations in the cerebral functioning found in AN-R (compared to HC) were not found when the clinical distinction (AN-R, AN-BP) was not made (Pietrini et al., 2011). A more recent study that clearly distinguished between AN-subtypes performing a set-shifting task showed an increased activation in response to shifting in the putamen, insula and head of the caudate head in the AN-R group compared to HC. These increased activations were not found in the AN-BP group when compared to HC (Sato et al., 2013). No significant differences could be shown by making a direct comparison between AN subtypes. This study was not, however, designed to evaluate possible

differences between AN-R and AN-BP. Consequently, the small samples make it difficult to draw any firm conclusions.

The aim of the current study was to investigate the possible differences in the neural correlates of set-shifting abilities between the two subtypes of AN (i.e. AN-R, AN-BP) and a group of HC participants. For this purpose, we used a set-shifting task during functional magnetic resonance imaging, measuring blood oxygen level dependent (BOLD) signals. The BOLD signal during switch versus repeat trials was compared across study groups.

Materials and methods

Subjects

Forty-seven right-handed women participated in this study. Three were removed due to technical problems during scanning or motion artefacts, resulting in a total of 44 participants. Participants consisted of three groups: 16 patients fulfilling the DSM-IV-criteria of AN-R, 13 fulfilling the DSM-IV criteria of AN-BP and 15 healthy control participants (HC) (American Psychiatric Association, 2000). Patients were recruited in the inpatient unit of the Centre for Eating Disorders at the Ghent University Hospital and were diagnosed by a specialist eating disorder clinician. All patients had a BMI below 17.5. The HC participants had no current or past eating problems. The minimum age for participating in the study was 16 years old.

Set-shifting task

We used a set-shifting task that was developed for our previous study (Van Autreve et al., 2013). As in a typical set-shifting experiment, participants had to switch between two easy tasks. Switch costs were calculated, subtracting the mean response time in task-repetition trials from the mean response time in task-switch trials. The switch cost is used as a measure of set-shifting abilities. In the current set-shifting experiment, participants needed to judge whether a presented number (1 to 9, except 5) was odd or even or whether the number was smaller or larger than 5. Prior to the presentation of the target, one out of four cues (circle, square, triangle or diamond) was presented for 500 ms to indicate which task the participants had to perform. Each task was associated with two cues. These cue-to-task assignments were counterbalanced across subjects and were taught during the training phase of the task (see below). In task-repeat trials, cues were never repeated.

After this cue, the target was presented with a maximum duration of 3500 ms. The next cue was presented after a variable response-cue interval (ranging between 200 and 4050 ms following a pseudo-logarithmic distribution). 70% of all trials were repeat trials; the remaining 30% were switch trials. All stimuli were presented on a black background. Instructions were given to respond as fast as possible without sacrificing accuracy.

Procedure

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The local ethical committee of the Ghent University approved the study. Participants gave their written informed consent and were then given instructions concerning the set-shifting paradigm. Two short training blocks were carried out, in which the two easy tasks were presented separately (16 trials each). The order of these tasks was counterbalanced across subjects. Next, the participants performed a third training block in which the two tasks were mixed (48 trials).

Subsequently, participants were positioned head first-supine in the magnetic bore. Images were collected with a 3 Tesla Magnetom Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany), using an eight-channel head coil. Anatomical images were acquired using a T1-weighted 3-D MPRAGE sequence that yielded images with a 1 mm resolution (TR = 2250 ms, TE = 4.18 ms, slice thickness = 1.0 mm, voxel size 1.0 x 1.0 x 1.0 mm, FOV = 256 mm, flip angle = 9°, distance factor = 50%). Whole brain functional images were collected by means of a T2-weighted EPI sequence, sensitive to BOLD contrast (TR = 2000 ms, TE = 30 ms, slice thickness = 3 mm, voxel size 3.0 x 3.0 x 3.0 mm, FOV = 192 mm, flip angle = 80°, distance factor = 0%, 33 slices). In the scanner, participants went through two separate blocks of 100 trials of the set-shifting task; the scanner was stopped in between. Each block started with an instruction screen reminding the participants of the rules that had previously been learned. Due to the self-paced procedure, a varying number of images was acquired per run.

Following the scanning procedure, participants underwent a clinical assessment by a clinical psychologist. An interview and a form were used to gather socio-demographic and clinical variables for each participant. This procedure was supplemented by self-report questionnaires.

Self-report questionnaires

Additional clinical characteristics were assessed using self-report questionnaires, including the Beck Depression Inventory II (BDI-II; Beck, Steer and Brown, 1996) and the State–Trait Anxiety Inventory (STAI; Spielberger et al., 1970). The STAI includes both 'State anxiety' (a more temporary condition of anxiety) and 'Trait anxiety' (a more general and longstanding anxiety).

Data analysis

Group comparisons on sample characteristics and task performance

To compare the independent study groups (i.e. AN-R, AN-BP and HC) on demographical variables and task performance, one-way between group analyses of variance (ANOVAs) were performed using the software package SPSS Statistics (version 20). Post hoc multiple comparisons were done, applying the Tukey multiple range test. To explore relationships between task performance and other variables (i.e. BMI and age), Pearson correlations (r) were calculated.

Pre-processing imaging data

Image processing was performed using the SPM8 software (Welcome Department of Cognitive Neurology, London, UK) in MATLAB 2013. Following slice-time correction, realignment, and functional-to-anatomic co-registration, the functional images and the structural volume were normalized to the Montreal Neurological Institute (MNI) template using the DARTEL procedure

(Ashburner, 2007) to ensure an anatomically informed normalisation. Motion parameters were estimated for each session separately. A commonly applied filter of 8 mm full-width at half maximum (FWHM) was used. The time series data at each voxel were processed using a high-pass filter with a cut-off of 128 s to remove low-frequency drifts. During task performance the head movement was evaluated. All included participants' movement was between acceptable borders (< 4 mm).

Whole brain analyses

First, the main effect of condition was tested in order to look for areas reflecting switch-specific activity (for the total sample). For this purpose, two contrasts were defined: switch > repeat and repeat > switch. Secondly, possible group differences in switch-specific brain activity were examined.

To analyse the possible differences across all 3 study groups, a Flexible Factorial Design was configured with 3 factors: subject, condition (task-repeat or task-switch) and group (AN-R, AN-BP, HC). In addition, all study groups were mutually compared on the whole brain level using t-tests. Group maps significance was defined using a threshold of $p < .005$ at voxel level and cluster level corrected for the whole brain at $p < .05$.

For the anatomic labelling of Montreal Neurological Institute (MNI) coordinates, the XjView 8 (http://www.alivelearn.net/xjview8/) and MRIcron (Rorden, 2012) were used.

Region of interest analyses

The regions that were found to be relevant through whole brain analyses were further examined in region of interest (ROI) analyses in order to execute further correlational analyses with important variables (described below) or with the purpose of graphing the mean BOLD signal across task conditions and study groups (Figure 2; Figure 4). MarsBaR 0.43 (2011) was applied. ROIs were performed across all voxels within the observed areas.

Results

Sample characteristics

Table 1 gives an overview of means (M) and standard deviations (SD) for demographic and clinical variables across the three study groups and the results of a group comparison using one-way ANOVA.

Table 1. Demographic and clinical characteristics of the sample

	M *(SD)*			*p*	Post hoc tests[a]
	AN-R (*n* = 16)	AN-BP (*n* = 13)	HC (*n* = 15)		
Age (years)	22 (6*)*	24 *(4)*	22 *(4)*	.497	
BMI (kg/m²)	14.9 *(1.7)*	16.0 *(1.5)*	22.0 *(2.1)*	<.001	AN-R<HC, AN-BP<HC*
BDI-II	30 *(11)*	42 *(22)*	2 *(2)*	<.001	AN-R>HC, AN-BP>HC*
STAI state anxiety	63 *(11)*	62 *(17)*	29 *(7)*	<.001	AN-R>HC, AN-BP>HC*
STAI trait anxiety	61 *(11)*	68 *(12)*	30 *(7)*	<.001	AN-R>HC, AN-BP>HC*

M = mean; *SD* = standard deviation; [a] pairwise comparisons with AN-R, AN-BP and HC, *significant *p*-value (*p*<.05) for post hoc comparison with Tukey correction

Participants were aged between 16 and 36 years. The mean age did not differ significantly between study groups (AN-R: 22, AN-BP: 24 and HC: 22; p=.497). The body mass index (BMI) ranged from 12 to 17.5 in the patient group and from 19 to 26 in the HC group. The mean BMI and the mean scores on all clinical variables (BDI-II, STAI) differed between study groups. Post hoc analyses could not identify a significant difference between the patient groups (AN-R versus AN-BP) in terms of their mean BMI (AN-R: 14.9 and AN-BP: 16.0, p=.289). There was, however, a difference between these groups and the HC (BMI = 22.0, both p's < .001). Concerning the clinical variables (depressive symptoms, state anxiety and trait anxiety), only differences between both clinical groups and HC subjects were found, without any significant differences being detected amongst patient groups (all p's > .06).

Task performance

The main reaction times for each group are presented in Table 2. The study groups did not show significantly different switch costs in reaction time (AN-R: 85 ms, AN-BP: 71 ms, HC: 45 ms; F < 1). Further, reaction times were not significantly correlated with BMI, age, trait anxiety or the level of depressive symptoms (all p's > .05).

Table 2. Set-shifting task performance across study groups

Outcome variable[a]	M (SD)			Group comparison *p* [b]
	AN-R (*n* = 16)	AN-BP (*n* = 13)	HC (*n* = 15)	
Repeat trials	830 (193)	846.32 (135)	793.66 (243)	.767
Switch trials	916 (209)	916.99 (128)	839.03 (297)	.565
Switch cost	85 (84)	71 (64)	45.37 (144)	.568

[a] reaction times in ms, [b]one-way ANOVA with Tukey correction, M = mean, SD = standard deviation

Brain activation

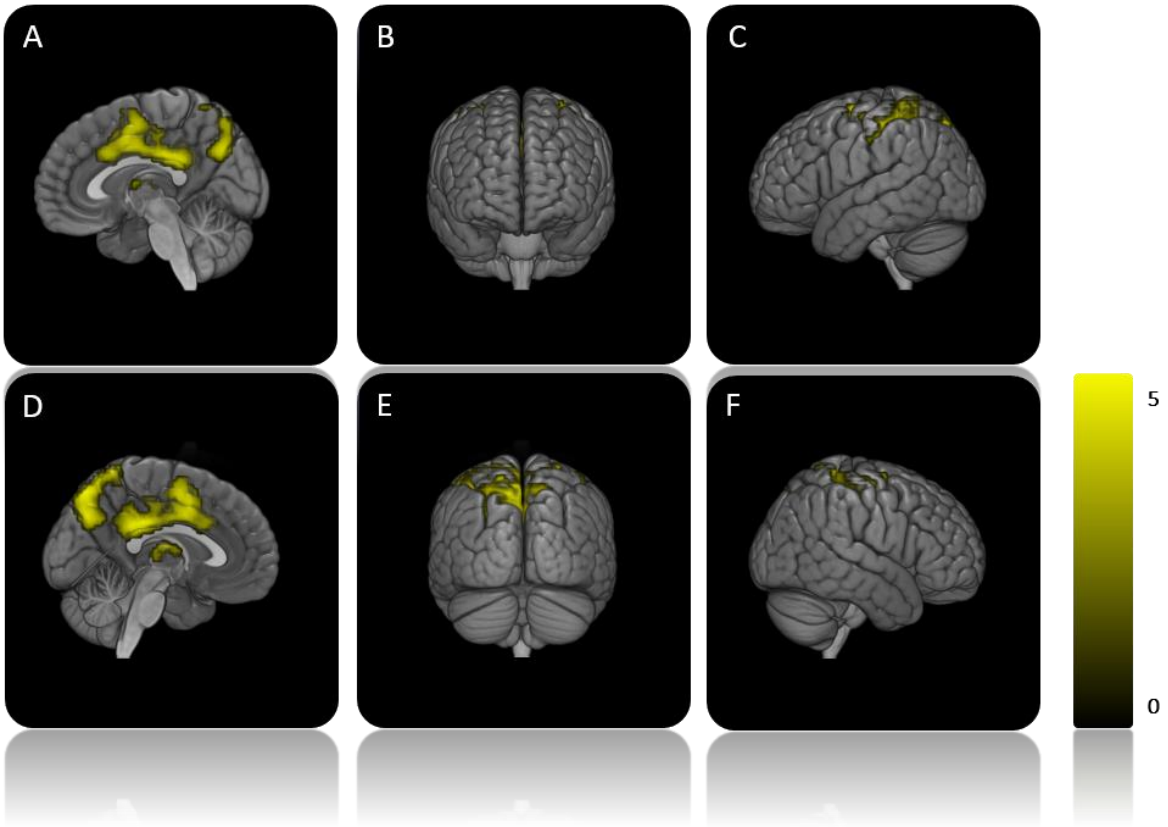
On the whole brain level, a main effect of task condition (switch versus repeat trials) was found, as presented in Figure 1 and Table 3. Across all study groups, a greater BOLD signal was established during switch trials (switch > repeat) in left superior parietal lobe, cingulate gyrus and left middle frontal gyrus.

Table 3. Main effect of task condition for the total sample

L/R	Anatomical region	Cluster size (in voxels)	*Z*-value[a]	Peak coordinate
Switch > repeat				
L	Superior parietal lobe	2063	5.59	-12 -69 54
L/R	Cingulate gyrus	729	4.96	-3 -36 27
L	Middle frontal gyrus	221	4.52	-30 -3 63

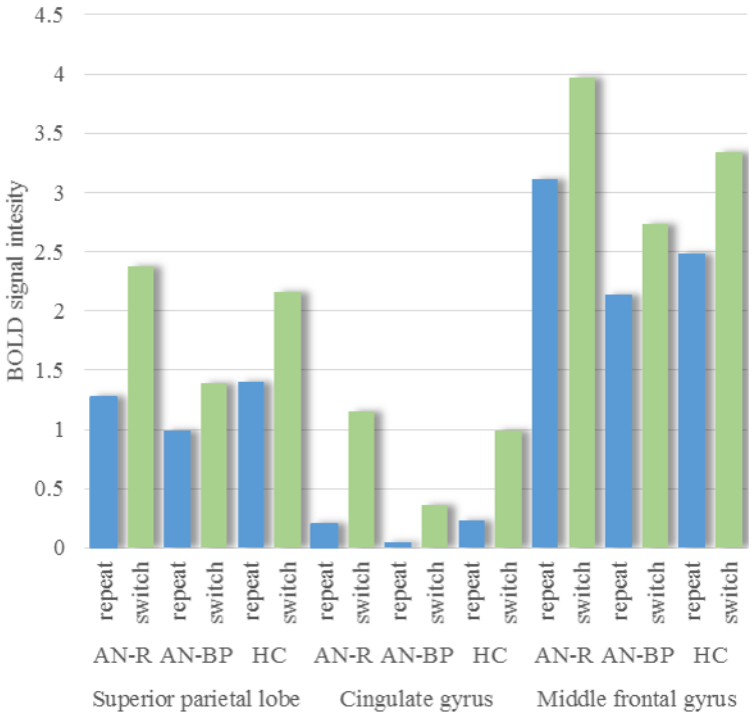
L/R = Left/Right hemisphere; [a] contrast switch versus repeat; cluster peak coordinate = MNI coordinates of the cluster peak in mm

Figure 1. The main effect for task condition (switch versus repeat trials) for the total sample.



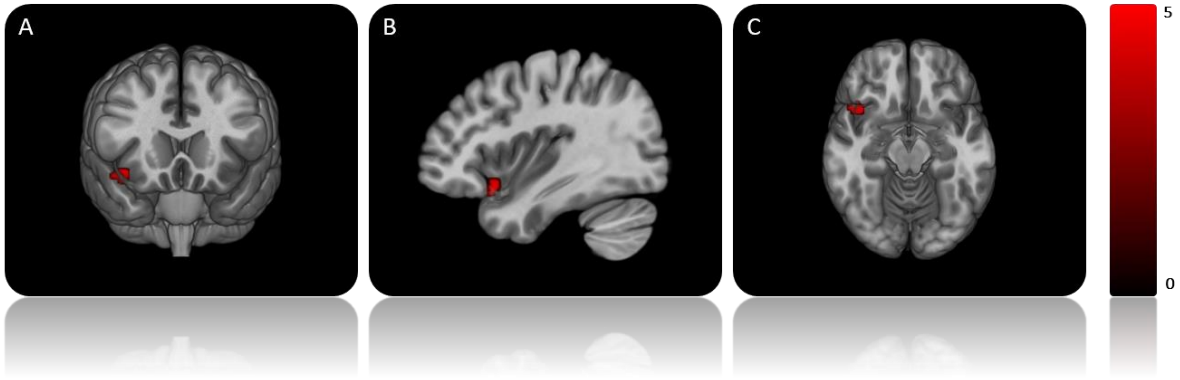
Switch specific activations (switch > repeat) are shown in yellow ($p < .005$). (A,D) midsagittal views right and left hemisphere, (B,E) anterior and posterior views, (C,F) lateral views left and right hemisphere.

Figure 2. The mean BOLD signal intensities in superior parietal lobe, cingulate gyrus and middle frontal gyrus in switch and repeat trials for all study groups.



The interaction effect of task condition and study group, comparing switch-specific activity across study groups (i.e., AN-R>AN-BP>HC), showed an increased activation in right insula: see Table 4 and Figure 3. Switch specific activity in this region was not correlated with task performance (i.e. switch cost), BMI, age, trait anxiety or the level of depressive symptoms (all p's > .05) for all groups separately. The mean BOLD signal intensity in the insula during repeat and switch trials was graphed in Figure 4.

Figure 3. The interaction effect of task condition and study group



Group differences in switch specific brain activity (switch > repeat) (AN-R > AN-BP > HC) are shown in red (p < .005). (A) Coronal slice, (B) sagittal slice right hemisphere, (C) horizontal section ventral view.

A comparison between AN-R and HC on the whole brain level (t-test), controlling for BMI, revealed six significant clusters with a higher switch-specific activity for the AN-R group (AN-R > HC) (see Table 4 and Figure 5). These clusters were situated in bilateral insula, bilateral precuneus (extending into the superior parietal lobule), left inferior parietal lobule (and supramarginal gyrus) and right dorsal premotor cortex. No significant clusters could be found for the reverse comparison (HC > AN-R).

Figure 4. The mean BOLD signal intensities in insula across switch and repeat trials for all study groups.

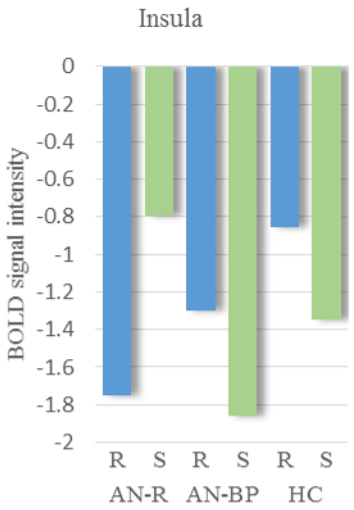
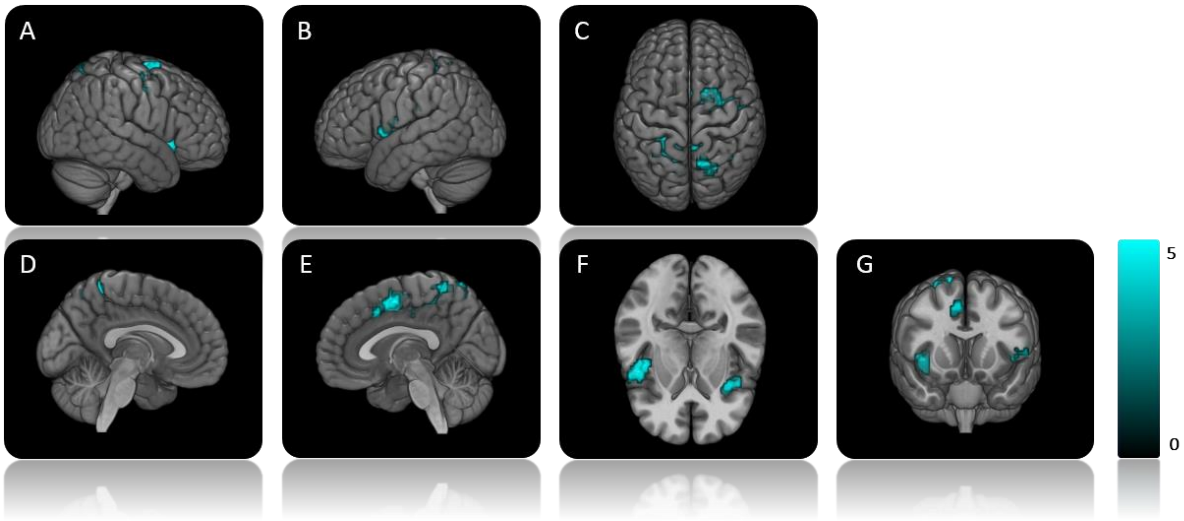


Figure 5. The switch specific brain activity in AN-R versus HC.

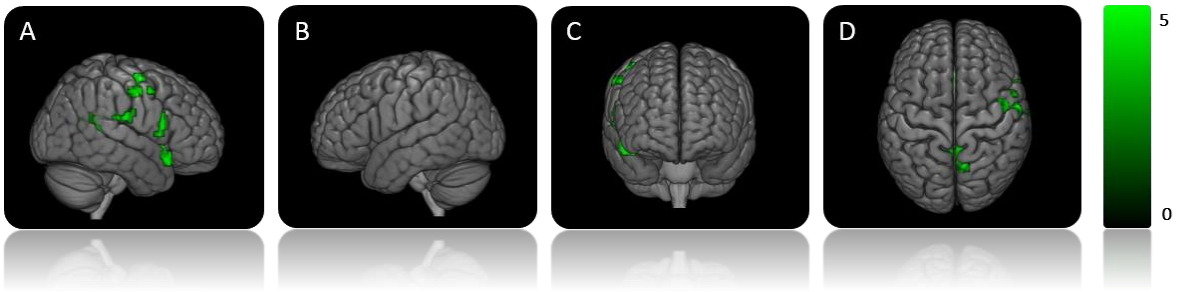


Switch specific brain activity (switch > repeat) for AN-R > HC are shown in blue ($p < .005$). (A,B) lateral views right and left hemisphere, (C) dorsal view, (D,E) midsagittal views right and left hemisphere, (F) horizontal section ventral view, (G) coronal slice.

When comparing AN-R and AN-BP on the whole brain level (t-test) two clusters were established with a stronger activation in AN-R (although not significant on a cluster level): right insula and right precuneus (extending into the left precuneus) (see Table 4 and Figure 6). No significant clusters could be found for the reverse comparison (AN-BP > AN-R).

When comparing AN (both AN-R and AN-BP) and HC on the whole brain level (t-test), with BMI as a covariate, six significant clusters were established with a stronger activation in AN (AN > HC). These clusters were situated in bilateral insula, bilateral precuneus (extending into superior parietal lobule), left inferior parietal lobule (and supramarginal gyrus) and right dorsal premotor. No significant clusters were found for the reverse comparison (HC > AN).

Figure 6. Differences in switch specific brain activity in AN-R versus AN-BP.



Switch specific brain activity (switch minus repeat) for AN-R > AN-BP are shown in green ($p < .005$). (A,B) lateral views right and left hemisphere, (C) anterior view, (D) dorsal view.

Table 4. Results Group Comparisons (whole brain level)

L/R	Anatomical region	Cluster size (in voxels)	*Z*-value	Peak x, y, z
Interaction effect group x condition (AN-R > AN-BP > HC)				
R	Insula	48	3.56	45 18 -15
Direct comparison AN-R > HC[a]				
L	Inferior parietal lobule, supramarginal gyrus	136	4.33	-51 -30 24
R	Insula	96	4.30	39 18 -6
R	Dorsal premotor cortex	491	4.11	9 0 51
R	Precuneus, superior parietal lobule	315	4.09	21 -66 63
L	Insula	156	3.70	-45 0 0
L	Precuneus, superior parietal lobule	140	3.52	-18 -45 63
Direct comparison AN-R > AN-BP				
R	Insula	77	3.56	48 18 -15
R/L	Precuneus	66	3.14	-3 -75 42
Direct comparison AN > HC				
R	Precuneus, superior parietal lobule	349	4.21	21 -66 63
L	Precuneus, superior parietal lobule	236	3.92	-21 -45 66
R	Insula	159	3.68	33 21 -6
L	Inferior parietal lobule, supramarginal gyrus	125	3.61	-48 -27 21
R	Dorsal premotor cortex	618	3.58	21 -6 63
L	Insula	212	3.46	-36 -3 15

L/R = Left/Right hemisphere; x, y, z = MNI coordinates of the cluster peak (mm); [a]with BMI as covariate

Discussion

The main aim of this study was to investigate the neural correlates of set-shifting in anorexia nervosa, compared to healthy control subjects and more specifically to explore the possible differences between anorexia nervosa subtypes. A study was set up in which three groups of participants (AN-R, AN-BP and HC) performed a set-shifting task while undergoing fMRI.

When comparing the brain activity during switch and repetition trials for the whole sample, an increased activity was found in the left lateral and medial prefrontal cortex and in the superior parietal lobe. These findings are consistent with previous studies showing the involvement of those regions in switching, using different set-shifting tasks (Muhle-Karbe, De Baene, & Brass, 2014; Buchsbaum, Greer, Chang, & Berman, 2005; Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Piguet et al., 2013; Smith et al., 2004; Braver et al., 2003; De Baene & Brass, 2011; De Baene, Kuhn, & Brass, 2012; Kimberg et al., 2000; De Baene et al., 2015). Finding a strong involvement of frontoparietal regions is consistent with the known status of set-shifting tasks as attention-demanding and complex (Lie, Specht, Marshall, & Fink, 2006).

From a comparison of the three study groups on the whole brain level during switching, one significant cluster was established, situated in the right insula. Interestingly, the same region was found when comparing patients with AN-R and controls (AN-R > HC) and between the two clinical groups mutually (AN-R > AN-BP; although not statistically significant on the cluster level). Previous research has shown that in healthy subjects the sensory perception of food-related stimuli (including seeing, smelling, and tasting) elicits increased activation in the anterior and mid-dorsal parts of the insular cortex (Frank et al., 2013). For its role in gustatory processing, the insula is also called the primary ‘taste cortex’. Although dysfunctions in the insular cortex seem crucial for the development of eating disorders, actual evidence of this is still unclear (Brooks et al., 2012). For instance, the processing of high-calorie food items (versus neutral objects) has been found to induce a hypo-

activation in the anterior insula, pre- and post-meal, in comparisons between participants with AN and HC (Holsen et al., 2012; Oberndorfer et al., 2013; Lawson et al., 2013). On the other hand, a stronger activation in the right anterior insula could be shown during pain anticipation in subjects with AN (and subjects who have recovered from AN) in comparison to a HC group (Strigo et al., 2013). While classically considered a limbic region, the anterior insular cortex has also been described as a part of the 'cognitive control network' (Craig, 2009). In this hypothesis, it forms (together with the anterior cingulate cortex) the "salience network" that functions to segregate the most relevant among internal and external stimuli to guide behavior (Menon & Uddin, 2010). Interestingly, in the current study, the insula was not found to be more strongly engaged during switching for the total sample: this was especially the case for patients with AN-R.

Furthermore, our study has shown that the precuneus (bilateraly) is more strongly activated in AN-R during switching than in AN-BP. The precuneus is considered to be a part of the "default mode network", a brain network that is active when the brain is at rest (i.e. not engaged with an external task) (Crowther et al., 2015). It is considered an essential neural substrate of (self-) consciousness, self-processing and interoceptiveness in healthy subjects (Cavanna & Trimble, 2006; Northoff et al., 2006; Terasawa et al., 2013; McAdams & Krawczyk, 2014). Importantly, the precuneus has been shown to be relevant in the pathology of AN. A lower activation was established in this region when comparing (recovered) AN with HC in an identity-appraisal task (McAdams & Krawczyk, 2014). A reduced default mode network activity in the precuneus has also been repeatedly found in women with AN (or with a history of AN) compared to controls (McFadden, Tregellas, Shott, & Frank, 2014; Cowdrey, Filippini, Park, Smith, & McCabe, 2014; Lee et al., 2014). Previously, the precuneus was shown to be more strongly involved during switching in a mixed AN sample (of both, AN-R and AN-BP participants) compared to controls (Lao-Kaim et al., 2015).

In the current study, the insula and the precuneus were not found to be involved in switching for the total sample, but these regions were explicitly found to be more implicated in patients with AN-R

compared to patients with AN-BP and HC. One might speculate that an increased activation in those regions during switching in AN-R might reflect a stronger self-consciousness or internal orientation (in contrast to external or task-oriented) in these attention-demanding situations.

How can the results of the current study be related to our knowledge of the behavioural performance of patients with AN using set-shifting tasks? As mentioned before, set-shifting inefficiencies have been, on the basis of a meta-analysis, found in different eating disorder diagnostic groups (AN, bulimia nervosa, binge eating disorder), except in AN-BP (Wu et al., 2014). This might be in line with the results of the current study in that we did not find any differences between AN-BP and HC on the brain level. It has been mentioned that set-shifting inefficiencies are a common underlying feature for all eating disorders, but the aforementioned findings relating to AN-BP suggest a more complex picture.

It is challenging to try and understand the results of the current study in the light of the well-known cross-overs from one eating disorder diagnostic category to another over the life-cycle (Eddy et al., 2008; Lavender et al., 2011). Due to this phenomenon, one might argue that the distinction between AN-subtypes is somehow artificial (Pietrini et al., 2011). Finding a difference in biological correlates of both subtypes suggests, however, that a distinction on a subtype basis might indeed be meaningful.

Another important question is whether the alterations in set-shifting and the associated alterations in brain mechanisms in AN are trait- or state-related features. Previous research has shown that the changed activations found in the precuneus in response to 'self' stimuli (i.e. "I am") in participants with AN could also be established in participants that have recovered from the acute state of AN (Oberndorfer et al., 2013; Strigo et al., 2013; McAdams & Krawczyk, 2014). In the current study no significant correlation could be found between the switch-specific brain activations and some state-related characteristics of the participants, i.e. body mass index and age. However, the use of cross-sectional study designs prevents us from drawing firm conclusions about possible pre-existing vulnerabilities.

In the last decennia, the discovery of functional differences in cortical regions in people with psychiatric disorders has resulted in the search for interventions directly targeting brain functioning (e.g. neuromodulation techniques, real-time neurofeedback, …). The use of these treatment approaches for people with AN requires further exploration. The results from our study suggest that not all patients with AN will benefit from the same treatment approaches.

Our results require replication because of some limitations of the study. Firstly, the study had an explorational design using analyses on the whole brain level. Furthermore, we were only able to work with small sample sizes, especially for the comparison between AN-subtypes.

To summarize, this functional brain imaging study has demonstrated functional alterations in AN compared to healthy control subjects during set-shifting. Interestingly, taking the two diagnostic AN sub-types into account, the increased activation established in the bilateral insula and bilateral precuneus was only found to be present in AN-R.

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Chapter IV. Enhanced attention to local detail in the restrictive and bingeing/ purging subtypes of anorexia nervosa: An fMRI using the Embedded Figures Task[6]

Previous research shows that subjects with anorexia nervosa (AN) have a superiority in detail-focused processing. To assess this enhanced attention to detail, the Embedded Figures Task (EFT) has been used. This was the first study to directly compare the brain activations in the restrictive and bingeing/purging subtypes of anorexia nervosa (AN-R; AN-BP) during the performance of the EFT using functional magnetic resonance imaging. The task comprised two task conditions: an EFT condition (where participants are asked to find an embedded shape in a complex figure) and a MATCH condition (in which participants are asked to find a copy of a simple shape). No significant group differences could be established between the two task conditions (EFT > MATCH) on the whole brain level. However, comparing the groups on the complex task only (EFT > implicit baseline), stronger activations were found in precuneus and inferior frontal gyrus in AN-R (as compared to AN-BP and healthy controls (HC)). These regions are involved in goal-directed cognition and behavioral inhibition. We speculate that this differential brain activation is somehow related to the inhibited versus more impulsive behavioural styles we identify in clinical practice in patients with AN-R and AN-BP, respectively.

[6] Van Autreve, S., Vanderhasselt, M., Baeken, C., van Heeringen, C., Vervaet, M. (under review). Enhanced attention to local detail in the restrictive and bingeing/ purging subtypes of anorexia nervosa: An fMRI using the Embedded Figures Task. *Neuroscience Letters*

Introduction

Anorexia nervosa (AN) is characterised by a significantly low body weight, an intensive fear of gaining weight and a disturbance in the way in which one's body weight or shape is experienced (American Psychiatric Association, 2013).

Overall in AN, obsessive-compulsive features are often prominent (Sauro et al., 2013). In the 'cognitive interpersonal model' that is developed to explain the onset and maintenance of AN, alterations in *cognitive processing styles* such as weak central coherence are thought to underpin these obsessive-compulsive traits (Treasure & Schmidt, 2013). The concept of "central coherence" was created to refer to the tendency in typical development to process incoming information for meaning and gestalt (global) form, often in disadvantage of attention to details (Happé & Frith, 2006). 'Weak central coherence' was first introduced in the literature about autism and refers to the combination of strengths in detail/local processing and weaknesses in global integration (Happé and Booth, 2008). Similar as in autism, a recent meta-analysis in AN reported a tendency to focus on local detail at the expense of global processing (Lang et al., 2014). In the current paper, we will focus on the detail-focused processing part of weak central coherence.

A neuropsychological paradigm that is used in the field of research of central coherence is the Embedded Figures Task (EFT) (Witkin, Oltman, Raskin & Kars, 1971), which requires the location of a simple shape within a much more detailed and complex shape. The time taken to find the embedded shape is used as a measure of detail-focused processing. In a modified version of the EFT (e.g. Fonville et al., 2013; Garett et al., 2014) participants are asked to indicate in which of two complex shapes the embedded figure appears; in another EFT version (e.g. Damarla et al., 2010; Manjaly et al., 2007; Spencer et al., 2012), participants have to indicate whether or not the simple shape is embedded in the complex figure. The task has also been applied in fMRI studies examining the

neurobiological correlates of detail-focused processing. Apart from the different versions of the EFT paradigm itself, the procedure in these neuroimaging studies varies in the use of a control condition.

On a behavioural level, patients with AN - as compared to controls - exhibit faster reaction times and greater accuracy on the EFT, similar to what is reported for people with autism spectrum disorder (Treasure & Schmidt, 2013). In these subjects with autism spectrum disorder (relative to healthy samples), functional brain imaging during the EFT demonstrated greater activations in occipital and parietal regions and reduced activations in frontal regions (Lee et al., 2007; Ring et al., 1999, Damarla et al., 2010, Manjaly et al., 2007, Spencer et al., 2012a, 2012b). In AN, on the other hand, thus far, only two studies are available investigating alterations in brain activity related to EFT performance (Garrett, Lock, Datta, Beenhaker, Kesler & Reiss, 2014; Fonville et al., 2013). In the study of Fonville and colleagues (2013) a lower activation in precuneus and stronger in fusiform gyrus were found in AN (when compared to HC). A control condition was missing in their paradigm, preventing us from drawing strong conclusions. Because a healthy comparison group was not included in the study of Garrett et al. (2014), only the main effect of the task was reported, comparing the whole brain activation during EFT conditions with those in a control condition. For this contrast, significant activations were found in the bilateral posterior occipital lobe, superior parietal lobe, and left superior frontal gyrus. It therefore seems that further research to the neural correlates of central coherence in AN is necessary to pinpoint the characteristics of AN.

Two subtypes of AN are described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). First, individuals with the *restrictive type* of AN (AN-R) present with which weight that is accomplished primarily through dieting, fasting and/or excessive exercise. Second, individuals with the *binge-eating/purging type* of AN (AN-BP) show an additional engagement in recurrent episodes of binge eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas) during the last three months (American Psychiatric Association, 2013).

Although many studies do not differentiate between AN-R and AN-BP (e.g. Kaye et al., 2013), there is growing evidence for the usefulness of this subtypology. Next to common personality features such as high perfectionism, harm avoidance, low self-directedness and low cooperativeness (Cassin & von Ranson, 2005; Degortes, Zanetti, Tenconi, Santonastaso, & Favaro, 2014), consistent differences have been found between eating disorder patients who exhibit bingeing and/or purging behaviours and patients who do not binge/purge: AN-BP seems more related with impulsive traits or lower behavioural inhibition while AN-R seems to be associated with a higher compulsiveness (Claes, Vandereyeken, & Vertommen, 2002; Claes, Robinson, Muehlenkamp, Vandereycken, & Bijttebier, 2010; Rosval et al., 2006; Vervaet, Van Heeringen, & Audenaert, 2004). We might assume that, next to temperamental discrepancies, variations in detail-focused processing might underlie the different behavioral presentations in the subtypes of AN.

In the present exploratory fMRI study, we examined EFT performance-related changes in brain activity in adult females with AN. We used a modified version of the EFT (Lee et al., 2007). To the best of our knowledge, this is the first study in which a direct comparison is made between the restrictive and bingeing/purging subtypes of AN, using this paradigm. Moreover, a healthy control group will be included.

Materials and methods

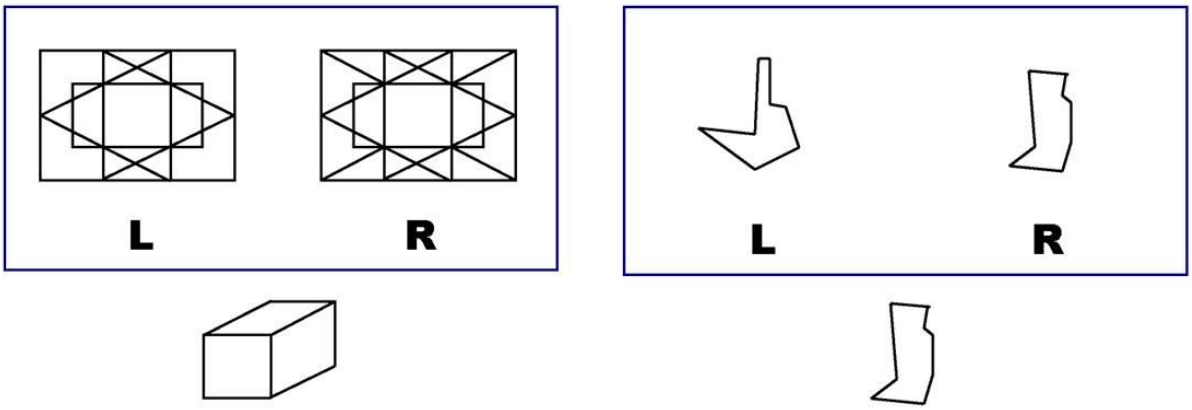
Subjects

Forty-seven right-handed women participated in this study. Five were removed due to technical problems during scanning or motion artefacts, resulting in a total of 42 participants. Participants consisted of three groups: 16 patients fulfilling the DSM-IV-criteria of AN-R, 12 fulfilling the DSM-IV criteria of AN-BP (American Psychiatric Association, 2000) and 14 healthy control participants (HC). Patients were recruited in the inpatient unit of the Centre for Eating Disorders at the Ghent University Hospital and were diagnosed by a clinician specialised in eating disorder. All patients had a BMI below 17.5. The HC participants were recruited through advertisement. HC participants had no current or past eating problems. The minimum age for participating in the study was 16 years old.

Embedded Figures Task

We used an experimental EFT design that was developed by Lee and colleagues (2007) for an fMRI study in patients with autism spectrum disorder. The task comprises two conditions, the EFT condition and the MATCH condition. In each condition one stimulus display consists of 3 figures: a single simple target shape (below, in the middle) and two probe figures presented above it. In the *EFT condition*, the target shape was a part of one of the (complex) probe figures; participants were instructed to decide of which one (left or right). In the *MATCH condition*, the simple target shape was identical to one of the (simple) probe figures. Participants had to decide to which probe (left or right) the target was identical. The letters “L” and “R” were presented below the probe figures; participants had to respond with their corresponding hand (left or right). See Figure 1 for an illustration of a stimulus display.

Figure 1. Illustration stimulus material



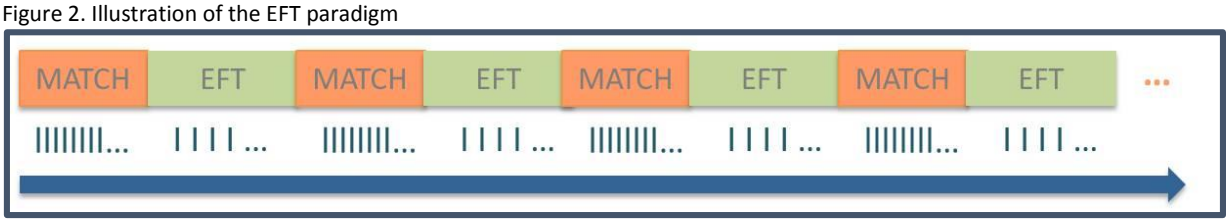
Example of a stimulus presentation in the EFT condition (left) and the MATCH condition (right); stimuli were adopted from Lee at al., 2007.

For the EFT trials, stimuli comprised 40 pairs of complex figures that served as probe figures and 40 target shapes that were embedded within one of the probe figures. For the MATCH trials, stimuli comprised 50 pairs of simple figures that served as probe and target figures. Trials of each type were presented in a blocked design; each block lasting for at least 30 seconds, depending on the pace of the participant (see below). As a result of the self-paced design, participants were likely to complete a higher number of trials in the easier MATCH condition than the more complex EFT condition. Therefore, more MATCH than EFT stimuli were required to ensure sufficient stimuli for all trials.

Stimuli were presented in ePrime (Psychological Software Tools, Inc., Pittsburgh, PA). Responses were recorded via two fiber optic button boxes, one held in each hand. Head movement was minimized by small foam cushions placed on the sides of the subject's head.

Each subject performed one run, lasting for 5 min. Trials were self-paced in alternating EFT and MATCH blocks. Within each block, stimulus displays were selected randomly without repetition during the task; however, some target shapes occurred in both EFT and MATCH conditions. The response initiated the subsequent trial. Full counterbalancing of left and right button responses was not possible, given that the stimuli were drawn at random by ePrime from the full set that had equal left and right responses for the EFT and MATCH.

Figure 2. Illustration of the EFT paradigm



In this paradigm, EFT-blocks (*grey*) alternate with MATCH-blocks (*orange*). Each trial is presented with a "I". Participants can answer on their own pace. As a result, participants were likely to complete a higher number of trials in the easier MATCH condition than in the more complex EFT condition. The total duration of the task was 5 minutes. Each block lasted for 30 seconds.

Subjects proceeded through the trials in each block at their own pace, and thus, the length and total number of trials within each block differed across subjects. However, the two types of blocks alternated such that each block lasted for at least 30 s[7]. The task terminated at 5 min, regardless of the number of trials or blocks completed. While it was plausible that a single trial/block would last the entire 5 min if no response was given, this did not occur for any subject. All subjects completed at least three blocks each of the EFT and the MATCH. While such an experimental design is unusual, Lee et al. (2007) reasoned that it was optimal for ensuring that visualized processes reflected EFT engagement and resolution without processing time limitations.

All stimuli were presented on a black background. Instructions were given to respond as fast as possible without sacrificing accuracy.

Neuroimaging data collection

Images were collected with a 3 Tesla Magnetom Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany), using an eight-channel head coil. Anatomical images were acquired using a T1-

[7] In the event that a subject had not yet responded to the trial that began prior to and extended past 30 s from the beginning of the block, the current trial continued until a response was given, allowing for blocks longer than 30 s. For instance, if a subject began a trial 29 s from the beginning of a block and responded 5 s later, that trial would have continued and the block would have lasted 34 s before switching to the first trial of the next block.

weighted 3-D MPRAGE sequence that yielded images with a 1 mm resolution (TR = 2250 ms, TE = 4.18 ms, slice thickness = 1.0 mm, voxel size 1.0 x 1.0 x 1.0 mm, FOV = 256 mm, flip angle = 9°, distance factor = 50%). Whole brain functional images were collected by means of a T2-weighted EPI sequence, sensitive to BOLD contrast (TR = 2000 ms, TE = 30 ms, slice thickness = 3 mm, voxel size 3.0 x 3.0 x 3.0 mm, FOV = 192 mm, flip angle = 80°, distance factor = 0%, 33 slices).

Procedure

The study was carried out in accordance with the latest version of the Declaration of Helsinki (2013). The local ethical committee of the Ghent University approved the study. Participants gave their written informed consent and were then given instructions concerning the experimental design.

Subsequently, participants were positioned head first-supine in the magnetic bore and performed the EFT while neuroimaging data was collected.

Following the scanning procedure, participants underwent a clinical assessment by a clinical psychologist. An interview and a self-report form were used to gather socio-demographic and clinical variables for each participant. This procedure was supplemented by self-report questionnaires.

Data analysis

Group comparisons on sample characteristics and task performance

To compare the three study groups (i.e. AN-R, AN-BP and HC) on demographical variables, one-way between-group analyses of variance (ANOVAs) were performed using the software package SPSS Statistics (version 20). Post hoc multiple comparisons were done, applying the Tukey multiple range test.

To analyse EFT task performance, a repeated measures ANCOVA was performed for each outcome variable, with the EFT outcome measure as the within-subject factor and study group as the between-subject factor. Analyse were performed for the three EFT outcome measures separately, namely number of trials completed, reaction time, percentage of errors. BMI was added as a covariate. The significance level was set at $p<.05$ (two-tailed) for all analyses.

Pre-processing imaging data

Image processing was performed using the SPM8 software (Welcome Department of Cognitive Neurology, London, UK) in MATLAB 2013. Following slice-time correction, realignment, and functional-to-anatomic co-registration, the functional images and the structural volume were normalized to the Montreal Neurological Institute (MNI) template using the DARTEL procedure (Ashburner, 2007) to ensure an anatomically informed normalisation. Motion parameters were estimated for each session separately. A commonly applied filter of 8 mm full-width at half maximum (FWHM) was used. The time series data at each voxel were processed using a high-pass filter with a cut-off of 128 s to remove low-frequency drifts. During task performance the head movement was evaluated. All included participants' movement was between acceptable borders (< 4 mm).

Whole brain analyses

First, the main effect of task condition (EFT > MATCH) was tested for the total sample. Secondly, possible group differences were examined on the whole brain level for EFT > MATCH and for EFT > (implicit) baseline.

To analyse the possible differences across all three study groups, a Flexible Factorial Design was configured with 3 factors: subject, task condition (EFT or MATCH) and group (AN-R, AN-BP, HC). In addition, all study groups were mutually compared (AN-R versus HC; AN-R versus AN-BP; AN-BP versus HC) on the whole brain level using t-tests. Group maps significance was defined using a

threshold of $p<.005$ at voxel level and cluster level corrected for the whole brain at $p<.05$. For all analyses, BMI was added as a covariate.

Results

Sample characteristics

Table 1 gives an overview of means (*M*) and standard deviations (*SD*) for demographic and clinical variables across the three study groups and the results of a group comparison using one-way ANOVA. Participants were aged between 16 and 36 years and age did not differ significantly between study groups (F(2,39)=1.275; *p*=.291). The body mass index (BMI) ranged from 12 to 17.5 in the patient group and from 19 to 26 in the HC group. A main effect of group was found for BMI and the scores on all clinical variables (BDI-II, STAI).

Table 1. Demographic and clinical characteristics of the sample (*n* = 42)

	M (SD)			P	Post hoc tests[a]
	AN-R (*n* = 16)	AN-BP (*n* = 12)	HC (*n* = 14)		
Age (years)	22 (6)	24 *(4)*	21 (4)	.291	
BMI (kg/m²)	14.9 (1.7)	15.9 (1.6)	21.6 (2.2)	<.001	AN-R<HC, AN-BP<HC*
BDI-II	30 (11)	43 (23)	3 (2)	<.001	AN-R<HC, AN-BP<HC[#]
STAI state anxiety	63 (11)	63 (17)	28 (*7)*	<.001	AN-R<HC, AN-BP<HC*
STAI trait anxiety	61 (11)	68 (13)	31 (8)	<.001	AN-R<HC, AN-BP<HC*

M = mean; *SD* = standard deviation; [a] pairwise comparisons with AN-R, AN-BP and HC, *significant *p*-value (*p*<.05) for post hoc comparison with Tukey correction, [#]a more conservative alpha level was used (p<.025) since the assumption of equality of variances was violated

Post hoc analyses could not identify a significant difference between the patient groups (AN-R versus AN-BP) mutually (*p*=.383) in terms of their BMI, but could show a difference between these groups and the HC (both *p's* < .001). Concerning the clinical variables (depressive symptoms, state anxiety

and trait anxiety), differences between each clinical group and the HC group were found (all $p < .001$), without any significant differences being detected amongst patient groups (all $p > .02$[8]).

Task performance

In Table 2, the means and standard deviations for three EFT outcome measures are presented for each study group separately. The mean number of completed trials was lower in the EFT condition (M=15, SD=6) than the MATCH condition (M=76, SD=17) (F(1,36)=4.133 ; $p<.05$). The main effect of study group was not significant (F(2,38)=.317; $p=.730$).

Table 2. Embedded Figures Task performance across study groups

Outcome variable	M (SD)			Group comparison
	AN-R (*n* = 16)	AN-BP (*n* = 12)	HC (*n* = 14)	p
Number of trials completed				.730
EFT	14 (6)	15 (6)	16 (6)	
MATCH	75 (17)	75 (19)	79 (16)	
Reaction time (sec)				.996
EFT	13 (11)	13 (10)	10 (5)	
MATCH	1.7 (0.5)	1.7 (0.4)	1.6 (0.4)	
Percentage of errors				.145
EFT	24 (16)	16 (16)	19 (13)	
MATCH	4 (2)	4 (1)	4 (2)	

[a] reaction times in ms, M = mean, SD = standard deviation

The mean reaction time per trials was higher in the EFT (M=12.2 ms, SD=9.0 ms) than in the MATCH condition (M=1.7 ms, SD=0.4 ms) ($p<.0001$), but after BMI correction this difference did not remain significant (F(1,36)=1.969; $p=.169$). The main effect of group (F(2,36)=.004; $p=.996$) was not significant either.

[8] For the BDI-II scores, the Levene statistic showed that the homogeneity of variances was violated (F(2,38)=.007; $p<.05$). For that reason, Alpha was set at .01 instead of .05. From a comparison of AN-R and AN-BP of the mean BDI-II, no significant differences could be established ($p=.048$).

For the last EFT oucome variable, the difference in percentage of errors in the EFT (M=20, SD=15) and the MATCH conditions (M=4, SD=2) was significant (p<.0001), but not after BMI correction (F(1,36)=3.411; p=.073). Study groups did not differ significantly for this outcome measure when controlling for BMI (F(2,36)=1.206; p=.311).

The interaction between each EFT outcome variable and BMI were not significant (p>.05).

Brain activation

On the whole brain level, a main effect of task condition (EFT versus MATCH) was found, as presented in Table 3. A greater BOLD signal was established during EFT trials (EFT > MATCH) in two clusters. The first cluster included left cingulate gyrus, cingulum and medial frontal gyrus. The second cluster was found in bilateral precuneus.

Table 3. Main effect of task condition for the total sample[a]

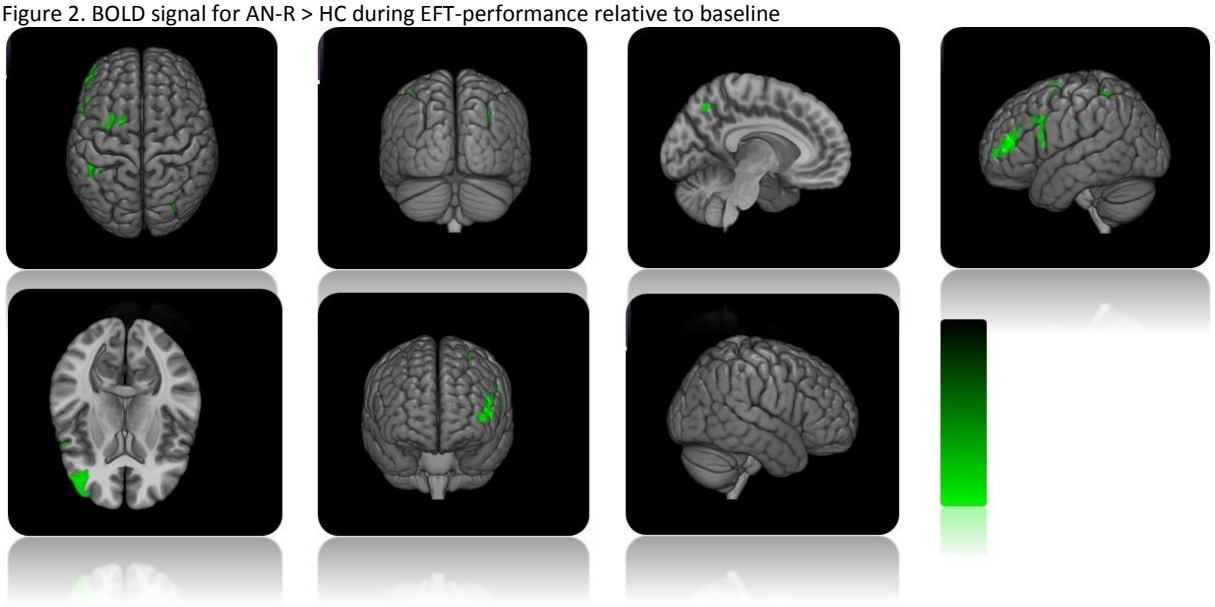
L/R	Anatomical region	Cluster size (in voxels)	*Z*-value[a]	Peak coordinate
L	Cingulate gyrus, cingulum Medial frontal gyrus	670	4.34	-3 -9 69
R/L	Precuneus	308	4.01	3 -69 33

[a] significant clusters for the contrast EFT > MATCH; L/R = Left/Right hemisphere; peak coordinate = MNI coordinates of the cluster peak in mm

No interaction effect of task condition and study group could be established, comparing EFT > MATCH activity across study groups (i.e., AN-R > AN-BP > HC and HC > AN-BP > AN-R), with correction for BMI.

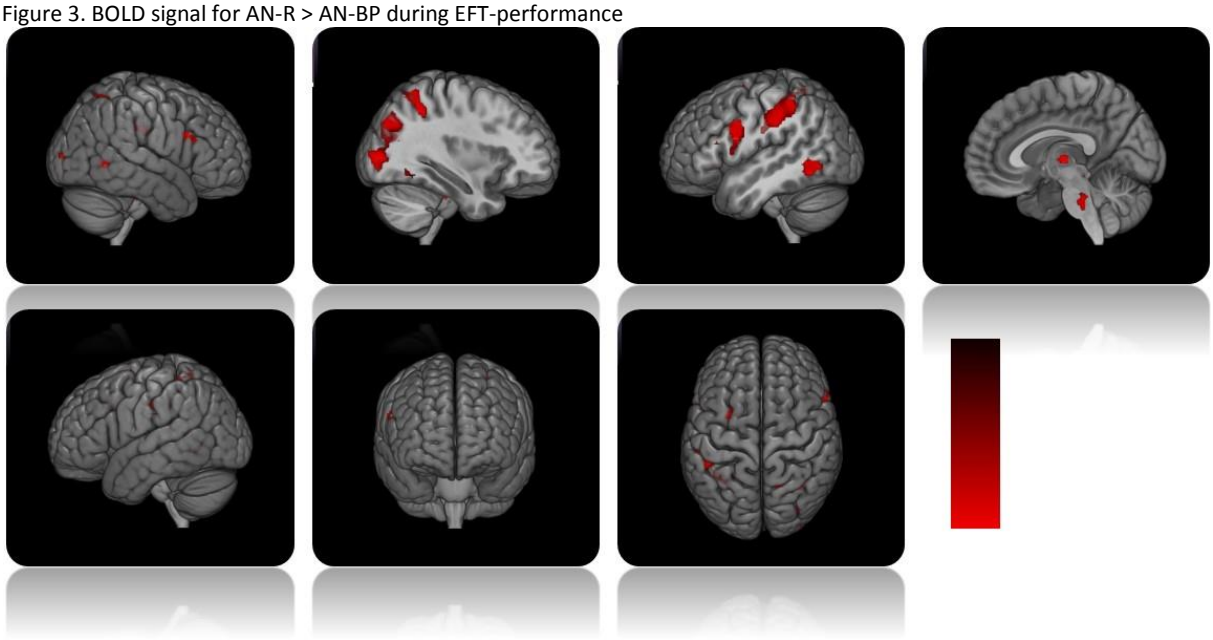
The interaction between task and group was further explored comparing the EFT condition with the implicit baseline (without MATCH condition). A comparison between AN-R and HC on the whole brain level (t-test), controlling for BMI, revealed two significant clusters with a higher activity for the AN-R group (AN-R > HC), see Table 4 and Figure 3. These clusters were situated in left inferior frontal gyrus and bilateral precuneus (extending into the inferior parietal lobule).

Figure 2. BOLD signal for AN-R > HC during EFT-performance relative to baseline



When comparing AN-R and AN-BP on the whole brain level (t-test), with BMI correction, three clusters were established with a stronger activation in AN-R: bilateral precuneus (extending into the inferior parietal lobule) and left inferior frontal gyrus (and thalamus), see Table 4 and Figure 4.

Figure 3. BOLD signal for AN-R > AN-BP during EFT-performance



When comparing AN-BP and HC on the whole brain level (EFT > baseline), no significant differences could be found.

Table 4. Results Group Comparisons EFT blocks (whole brain level)

L/R	Anatomical region	Cluster size (in voxels)	*Z*-value	Peak x, y, z
Direct comparison AN-R > HC[a]				
L	Inferior frontal gyrus	505	3.77	-51 24 36
L	Precuneus, inferior parietal lobule	451	3.49	-51 -39 45
Direct comparison AN-R > AN-BP[a]				
R	Precuneus, inferior parietal lobule	587	3.71	36 -60 6
L	Inferior frontal gyrus, thalamus	1483	3.57	-3 -15 3
L	Precuneus, inferior parietal lobule	931	3.32	-30 -48 5

L/R = Left/Right hemisphere; x, y, z = MNI coordinates of the cluster peak (mm); [a]with BMI as covariate

Discussion

This functional neuroimaging study aimed at investigating the neural activity in individuals with anorexia nervosa while performing an Embedded Figures Task. The bingeing/purging and restrictive subtypes of anorexia nervosa were mutually compared, as well as with a healthy control sample.

The present behavioral results did not reveal any significant differences between groups in accuracy, number of trials completed or reaction times. Although this finding is inconsistent with previous behavioral studies using the EFT in AN (Lopez, 2008; Robert 2012), it is in line with brain imaging studies employing this paradigm using smaller sample sizes (Lee, et al., 2007; Damarla et al., 2010). Furthermore, it is noteworthy that the performance in our clinical groups seems more variable than in the HC sample, which is in line with previous research (Renwick, Musiat, Lose, et al., 2015). Possibly, within a purely categorical system of diagnoses, the diversity found within patient groups is not adequately captured (Helzer et al., 2006).

When comparing the brain activity during the complex and simple task condition (EFT > MATCH) for the whole sample, an increased activity was found in bilateral precuneus and in a left hemispheric cluster containing parts of medial frontal gyrus, cingulate gyrus and cingulum. This is in line with the main effect of task condition that was reported in a previous study using the exact same procedure (Lee et al., 2007). Medial frontal involvement during local processing had been posited to reflect the suppression of the bias toward global perceptual processing, based upon that region's role in conflict resolution in other studies (Lux et al., 2004).

A comparison of the three study groups on the whole brain level during detail focus, using the EFT > MATCH contrast, revealed no significant clusters. This result is in line with the behavioural data. However, in a comparison of the brain activity across study groups during the EFT-condition

compared to the implicit baseline, some interesting inconsistencies emerged. When comparing AN-R and HC for this complex condition, the left precuneus (extending into inferior parietal lobule) and left inferior frontal gyrus were stronger involved in patients with AN-R. Interestingly, an increased activation in the same neural regions was found when mutually comparing the two clinical groups (AN-R > AN-BP). In this last comparison, also parts of the right hemispheric precuneus/inferior parietal lobule were stronger involved in AN-R.

Interestingly, an increased activation during EFT performance in a cluster containing parts of the precuneus and inferior parietal lobule was also found in a study comparing patients with autism spectrum disorder and a healthy control sample (i.e. compared to baseline, without control condition) (Damarla et al., 2010). This might again point at possible similarities between patients with autism spectrum disorder and patients with AN. For patients with AN, the precuneus and inferior parietal lobule are suggested to be involved in *body image distortion*, although the results seem confusing: both a hypo- (Gaudio et al., 2012) versus a hyper-functionality (Castellini et al., 2013) in the precuneus/inferior parietal lobe were reported in studies comparing AN and HC while showing body images. In particular, functional alterations in the precuneus, the PCC and the inferior parietal lobule have been shown to account for the *perceptive* component of body image distortion in patients with anorexia nervosa (Mohr, Zimmerman & Roder, 2010 Gaudio & Quattrocchi, 2012; Vocks, Busch, Gronemeyer, et al., 2010). Both, the precuneus and inferior parietal lobe are considered a part of the *"frontoparietal control" network* which plays a role in goal-directed cognition by coupling with either the "default" network (subserving internally directed cognition) or the "dorsal attention" network (for externally directed cognition) (Vincent et al., 2008; Spreng et al., 2012). Further, the precuneus is considered an essential neural substrate of *(self-) consciousness, self-processing and interoceptiveness* in healthy subjects (Cavanna & Trimble, 2006; Northoff et al., 2006; Terasawa et al., 2013; McAdams & Krawczyk, 2014). Interestingly, we found the precuneus to be specifically more involved in AN-R, as compared to AN-BP. This parallels the results from our previous study concerning neurobiological correlates of set-shifting abilities in AN-subtypes where we also found the

precuneus to be activated more during switching in AN-R compared to AN-BP and controls (Van Autreve et al., 2016). These results might suggest that, when exposed to demanding tasks, a stronger involvement of cognitive control regions is provoked in patients with the restrictive type of AN.

Finding the inferior frontal gyrus (IFG) to be stronger activated in AN-R than HC seems to contrast with previous studies in autism spectrum disorders, in which frontal activity was lower in patients than in controls (Damarla et al., 2010; Lee et al., 2007). This region is known as a key area for executive functions, encompassing multiple high level processes to control and organize other cognitive operations. In a meta-analysis concerning neural correlates of response suppression, the authors concluded that the right IFG seems to play an important role in response inhibition (Buchsbaum et al., 2005). This was repeatedly shown using go/no-go tasks during functional MRI, tasks that are assumed to assess inhibitory control or response suppression abilities. One might wonder whether this differential activation in the IFG is somehow related to the inhibited versus more impulsive behavioural styles we recognize in clinical practice in patients with AN-R and AN-BP respectively. In the review of Pietrini and colleagues (2011), the IFG (or Brodmann area 46) was also mentioned to be more activated in AN-R than in HC, while this could not be shown comparing AN-BP with HC.

Finding a higher involvement of left hemispheric regions in AN-R might suggest that AN-R patients have a stronger focus on local elements than AN-BP: previous findings show that the perception of local elements of a visual form seems more related to left cortical areas (Lux et al., 2004; Lee et al., 2007).

Our results require replication because of some limitations of the study. Firstly, the study had an exploratory design using analyses on the whole brain level. Furthermore, we were only able to work with small sample sizes, especially for the comparison between AN-subtypes. An important limitation of the study is that no significant group differences could be established using the contrast between the two conditions of the task (EFT minus MATCH). Possibly, this “negative” result actually stresses

the existence of a continuum from normalcy to pathology, without a clear different pattern between AN and HC, as also reported by Castellini and colleagues (2013). The complex condition (EFT > baseline) we used further in analysis, is a less direct measure of detail-focused processing, because the additional domains that are measured (e.g. visual and motor processing, task characteristics) are not controlled for.

In sum, this was the first study to directly compare the brain activations in the restrictive and bingeing/purging subtypes of anorexia nervosa during the performance of an Embedded Figures Task using functional magnetic resonance imaging. From the comparison of study groups of the two task conditions (EFT > MATCH) on the whole brain level, no significant group differences could be established. However, when comparing the groups on the complex task only (EFT > implicit baseline), stronger activations were found in precuneus and inferior frontal gyrus in AN-R (as compared to AN-BP and HC). We speculate that this differential brain activation is somehow related to the inhibited versus more impulsive behavioural styles we recognize in clinical practice in patients with AN-R and AN-BP, respectively.

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General discussion

The main aim of this PhD was to further investigate set-shifting and central coherence in anorexia nervosa, with specific attention for possible differences between the restrictive and binging/purging subtypes of anorexia nervosa, on the behavioural level as well as on the level of neurobiological correlates. First, a systematic review of the literature was conducted, aiming to give a state-of-the-art overview of the available literature concerning possible differences between these diagnostic categories on the behavioural level, i.e. concerning task performance (chapter I). Secondly, a neuropsychological study was set up to further examine possible behavioural differences between anorexia nervosa subtypes (chapter II). Thereafter, this topic was additionally explored in a functional brain imaging study (fMRI), using an experimental paradigm to assess set-shifting (chapter III) and an experimental paradigm to assess the detail processing component of central coherence, the Embedded Figures Test (chapter IV).

From the systematic review of the literature, we could conclude that the evidence to date is too scarce to draw definitive conclusions about possible differences between the two subtypes of anorexia nervosa on central coherence/set-shifting task performance. Importantly, very few authors describe the results of a direct comparison of the performance of patients with AN-R and AN-BP. In what follows, we discuss what the results from the included neuropsychological and functional brain imaging studies add to this conclusion.

Findings on neuropsychological task performance

Set-shifting task performance

Set-shifting abilities in the three groups of participants (AN-R, AN-BP, healthy control subjects) were assessed in both, the neuropsychological (chapter II) and fMRI study (chapters III) using the same computerized paradigm. Additionally, in the first study, the Wisconsin Card Sorting Task and the Trail Making Test were conducted as measures of set-shifting.

Using different measures, no significant group differences could be found, comparing AN-R, AN-BP and health control subjects in their task performance. In finding no confirmation for a set-shifting deficit for any subtype of anorexia nervosa when compared to healthy controls, the current study corresponds with the findings of some other studies in which no or limited set-shifting problems were established (Murphy, Nutzinger, Paul, & Leplow, 2002; Fowler et al., 2006; Andres-Perpina et al., 2011).

Interestingly, using a meta-analytic approach, set-shifting inefficiencies could be demonstrated in different eating disorder diagnostic groups (anorexia nervosa, bulimia nervosa, binge eating disorder), except in AN-BP (Wu et al., 2014). Results from a direct comparison between AN-R and AN-BP were however not specified.

To summarize, in line with the conclusion from our systematic review (chapter I), no alterations could be found in set-shifting performance in the restrictive type of anorexia nervosa, as compared to the bingeing/purging subtype (chapter II and III). Until now, the available evidence cannot support the hypothesis that differences in the symptomatic presentation in both subtypes might be associated with differences in set-shifting abilities.

Central coherence task performance

Both components of central coherence, global and detail-focused processing, were further examined. To assess the *global processing component* of central coherence, the Object Assembly was applied (chapter II). Interestingly, patients with AN-R showed a significantly worse performance using this task as compared to AN-BP and healthy controls. We could not find evidence for a global processing deficit in AN-BP. These results suggest that the widely mentioned problem in anorexia nervosa to integrate information in a 'bigger picture' is specifically present in patients with AN-R. In this way, the fact that a different performance between anorexia nervosa (AN-R + AN-BP) and healthy subjects on Object Assembly is repeatedly confirmed in earlier research and not in the current study, might be due to the potential under representation of patients with bingeing/purging anorexia nervosa in samples in previous studies.

To assess the *detail-focused processing part* of central coherence, the Block Design Task (chapter II) and, during fMRI, the Embedded Figures Task (chapter IV) were conducted. In finding that patients with anorexia nervosa (without subdivision based on subtype) performed lower than the healthy control subjects on Block Design, our study could not confirm the assumed superiority in detail processing in anorexia nervosa. However, these results are in line with different studies in which this superiority could not consistently be confirmed in anorexia nervosa (Lopez, Tchanturia, Stahl, & Treasure, 2008). Using the Embedded Figures Task during fMRI (chapter IV), no significant group differences could be established, not even from the comparison of anorexia with control subjects. This is consistent with the behavioural results in other brain imaging studies with this paradigm using smaller sample sizes (Lee et al., 2007; Damarla et al., 2010).

Interestingly, a similar difference between anorexia nervosa subtypes' performance was discovered from the Block Design and Object Assembly tests, in that patients with AN-R scored significantly lower than patients with AN-BP and healthy control subjects without there being any difference

between the latter. A strong correlation was established between the scores from the Block Design and Object Assembly tests. This finding might suggest a shared underlying mechanism for both tasks. In previous research, it has been assumed that, alongside detail-focused approaches, global approaches could also be involved in the performance of subjects who undertook the Block Design test (Lopez et al., 2008).

It is also noteworthy that the performance in our clinical groups seems more variable than in the healthy control sample, which is in line with previous research (Renwick et al., 2015). Possibly, within a *purely categorical system* of diagnoses, the diversity found within patient groups is not adequately captured (Helzer, Kraemer, & Krueger, 2006) (see below).

To summarize, using the Embedded Figures Task, no significant differences between study groups could be shown. Since we even did not find any differences between healthy control participants and the total sample of patients with anorexia nervosa, which has been repeatedly confirmed in previous studies, the current results might be due to small sample sizes. Using the Block Design and Object Assembly, we could find evidence for differences in central coherence in AN-R, as compared to healthy controls (and not in AN-BP). Due to problems in the concept of central coherence, and its testing (see below), it is unclear, however, whether we should understand these differences as a deficit in global processing, an altered detail processing, or both.

The concept of "central coherence"

The concept of 'weak central coherence' is two-dimensional, defining both, a reduced tendency to global integration and a bias towards superior local processing. In the literature it can be noticed that the local processing dimension has gained more attention from researchers than the global

processing deficit, although it is unclear whether one facet of central coherence is of most relevance (Happe & Booth, 2008; Darcy et al., 2015). However, there is growing consensus that local and global processing should be considered as *independent constructs* with different trajectories in typical development (Lopez, Tchanturia, Stahl, & Treasure, 2009; Happe & Booth, 2008). As mentioned before, in the original 'weak central coherence theory' it was claimed that children with autism have problems integrating incoming information, and *consequently* tend to rely on piecemeal processing (Frith, 1989; Hill & Frith, 2003). In a revised version the theory was modified in such a way that the reduced global processing was appointed to as, possibly, a *secondary effect* of superior local processing (Happe & Booth, 2008). Up to now, it remains unclear whether both are dependent or independent processes. In finding evidence for a problem in global processing in the restrictive type of anorexia nervosa in our study, we might wonder whether this might include a greater necessity to fall back on detail-focussed approaches. Further research is needed to clarify this issue.

Findings on the neural level

Neurobiological findings associated with set-shifting

During our exploratory fMRI study (chapter III), the same computerized set-shifting paradigm was used as in the neuropsychological study (chapter II).

To check the used procedure, the *main effect of task condition* was examined on the whole brain level for the whole sample: from a contrast of brain activity during switch versus repetition trials, an increased activity was found in the left lateral and medial prefrontal cortex and in the superior parietal lobe. Finding a strong involvement of frontoparietal regions is consistent with previous

studies and with the known status of set-shifting tasks as attention-demanding and complex (Muhle-Karbe, De Baene, & Brass, 2014; Lie, Specht, Marshall, & Fink, 2006; De, Duyck, Brass, & Carreiras, 2015).

Comparing the three study groups on the whole brain level during switching, two significant clusters were established, situated in the *precuneus (bilateral)* and the *right anterior insula*. Interestingly, the same regions were found in different comparisons: comparing the three groups in one model, and further when comparing patients with AN (total group) and controls (AN > HC), AN-R and controls (AN-R > HC) and the two clinical groups mutually (AN-R > AN-BP; although not statistically significant on the cluster level).

In a previous study, the *precuneus* was shown to be more strongly involved during switching in a mixed anorexia nervosa sample (of both, AN-R and AN-BP participants) compared to controls (Lao-Kaim et al., 2015). According to our results, when considering the restrictive and bingeing/purging subtypes of anorexia nervosa separately, this stronger involvement of the precuneus is only present in patients with restrictive anorexia nervosa.

The precuneus is suggested to be involved in visuospatial attention, and more specifically, in the *perceptive* component of body image distortion (Mohr et al., 2010; Gaudio & Quattrocchi, 2012; Vocks et al., 2010). Next, the precuneus is considered to be a part of the *frontoparietal control network* that plays a role in goal-directed cognition by coupling with either the “default” network (subserving internally directed cognition) or the “dorsal attention” network (for externally directed cognition) (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). Further, the precuneus is considered an essential neural substrate of *(self-) consciousness, self-processing and interoceptiveness* in healthy subjects (McAdams & Krawczyk, 2014; Cavanna & Trimble, 2006; Northoff et al., 2006; Terasawa, Fukushima, & Umeda, 2013).

Finding an increased activation in a part of the frontoparietal control network during switching in anorexia nervosa is in line with the hypothesis, proposed by several research groups, that the brain

functioning in anorexia nervosa is characterised by an *imbalance* between brain systems subserving *top-down* and *bottom-up* processing (Kaye, 2013; Kaye, Fudge, & Paulus, 2009; Brooks, Rask-Andersen, Benedict, & Schioth, 2012; Ehrlich et al., 2015). In this model, individuals with anorexia nervosa are thought to have an *increased* activation in top-down modulatory regions, combined with *decreased* activations in bottom-up mesolimbic regions, which is assumed to result in an excessive self-control dominating primary drives. The excessive cognitive control is assumed to be, to a considerable degree, responsible for the highly restrained behaviour, mental flexibility, excessive regulation and self-control in anorexia nervosa (Kaye, 2013).

In this PhD, we found corroborating evidence for this hyperactive cognitive control system in anorexia nervosa. Additionally, when taking the subcategories in the diagnosis of anorexia nervosa into account, this stronger activation in cognitive control regions, was shown to be present only in the restrictive type of anorexia nervosa. This differential activation seems related to the inhibited versus more impulsive behavioural styles we recognize in clinical practice in patients with AN-R and AN-BP respectively.

Next to the increased activation in the precuneus, we have found the right *anterior insular cortex* to be stronger involved in AN-R, compared to AN-BP and controls, during set-shifting. While classically considered a limbic region, the insula has also, together with the anterior cingulate cortex, been described as a part of the “salience network”. This network responds to behaviourally salient events and is thought to be important for the initiation of cognitive control and the segregation of the most relevant among internal and external stimuli to guide behaviour (Menon & Uddin, 2010).

Interestingly, the mentioned imbalance between cognitive control and mesolimbic regions in anorexia nervosa, was previously described to have an impact on the insular functioning. Brooks et al. (2012) suggested that these imbalanced activations might lead to a ‘rate-limiting’ defect in the insula and other somatosensory regions, normally providing a solid sense of ‘emotional self’.

Whereas the dysregulated neural activation in the insular cortex was previously described as a commonality in all eating disorder categories in response to food stimuli (Pietrini et al., 2011; Craig, 2009), in this study it has been shown to be solely dysregulated in the restrictive type of anorexia nervosa, during set-shifting. It is interesting to observe the same neural pattern using neutral material instead of symptom-provocative stimuli.

Neurobiological findings associated with attention to local detail

To explore neural correlates of detail-focused processing, the Embedded Figures Task was used during fMRI (chapter IV).

Again, the *main effect of task condition* was explored on the brain level, to check for the quality of the used procedure. When comparing the brain activity during the complex and simple task condition for the whole sample, an increased activity was found in the precuneus (bilateral) and in a left hemispheric cluster containing parts of the medial frontal gyrus, cingulate gyrus and cingulum. This is in line with the main effect of task condition that was reported in a previous study using the same procedure (Lee et al., 2007). Interestingly, in other studies medial frontal involvement during local processing has been posited to reflect the suppression of the bias toward global perceptual processing, based upon that region's role in conflict resolution in other studies (Lux et al., 2004).

A comparison of the three study groups on the whole brain level during detail focus (using the contrast complex condition minus control condition) revealed no significant clusters. However, in a comparison of the brain activity across study groups during the complex task condition compared to the implicit baseline, some interesting inconsistencies emerged. When comparing AN-R and healthy control subject for this complex condition, the *left precuneus* (extending into *inferior parietal lobule*)

and the *left inferior frontal gyrus* were stronger involved in patients with AN-R. An increased activation in the same neural regions was found when mutually comparing the two clinical groups (AN-R > AN-BP). In this last comparison, also parts of the right hemispheric precuneus/inferior parietal lobule were stronger involved in AN-R.

Finding the *precuneus* and *inferior parietal lobule* to be specifically more involved in AN-R, as compared to AN-BP, parallels the results concerning neurobiological correlates of set-shifting abilities in anorexia nervosa subtypes, as described above. Here, we also found the precuneus to be more activated during switching in AN-R compared to AN-BP and controls (Van Autreve et al., 2016).

Next, the *inferior frontal gyrus* was found to be stronger activated in AN-R than in AN-BP and control subjects, which is in line with the review of Pietrini and colleagues (2011), where the inferior frontal gyrus was also mentioned to be more activated in AN-R than in healthy controls, while this could not be shown comparing AN-BP with healthy controls. The inferior frontal gyrus is known as a key area for executive functions, encompassing multiple high level processes to control and organize other cognitive operations. It also seems to play an important role in response inhibition (Buchsbaum, Greer, Chang, & Berman, 2005).

Again, these results might suggest that, when exposed to demanding tasks, a stronger involvement of cognitive control regions is provoked in patients with restrictive anorexia nervosa. As mentioned above, this differential activation in the two diagnostic categories of anorexia nervosa seems related to the inhibited versus more impulsive behavioural styles we recognize in clinical practice in patients with AN-R and AN-BP respectively.

Implications for the diagnostic process in anorexia nervosa

The psychiatric nosology of DSM-IV and DSM-5 proposes for anorexia nervosa a subdivision between patients who do and do not engage in binge eating and/or purging. This subdivision has also been included in the other widely established system for classifying mental disorders: the International Classification of Diseases, 10th version (ICD-10) (World Health Organization, 2010). The nosology in these manuals is based on observational *behavioural features* and current psychopathology alone (Fairburn & Cooper, 2007). During the DSM-5 construction process, the original intention was to develop a progressive and *dimensionally* oriented manual reflecting more recent research in psychopathology/psychiatry where there has been a move towards examining more stable features such as temperamental and neurobiological traits (Ciccollo et al., 2002). Despite this intention, the DSM-5 became mainly an updated version of DSM-IV (Krueger, Hopwood, Wright, & Markon, 2014).

Concerning the diagnosis of anorexia nervosa, one could question whether the subdivision between the restrictive and bingeing/purging subtype is relevant. Regarding this topic, the well-known phenomenon of the *diagnostic cross-overs* from one eating disorder diagnostic category to another over the life-cycle should be considered (Eddy et al., 2008; Lavender et al., 2011; Uher & Rutter, 2012). These diagnostic cross-overs seem more common in the initial years of the illness and seem to follow a predictable sequence (Uher & Rutter, 2012). The majority of women with anorexia nervosa seem to experience diagnostic cross-over during follow up (Eddy et al., 2008). Many cases evolve into bulimia nervosa (Bulik, Marcus, Zerwas, Levine, & La, 2012) but there seems to be a difference between the subtypes: 10% of restrictive anorexia nervosa and 54% of bingeing/purging anorexia nervosa evolve to bulimia nervosa (Eddy et al., 2008). According to Catellini and colleagues (2011) one third of individuals with an initial diagnosis of anorexia nervosa develop bulimia nervosa, while only 10-15% of those with an initial diagnosis of bulimia nervosa develop anorexia nervosa. Between the two subtypes of anorexia nervosa, there are high rates of cross-overs in both directions (Eddy et

al., 2008). Cross-over from anorexia nervosa to bulimia nervosa is often preceded by a period of binge eating/purging-type anorexia nervosa (Eddy et al., 2008).

One might argue that the sequential diagnoses during a lifetime might represent stages of the same disorder rather than separate disorders and thus, that the distinction between diagnostic subcategories is somehow artificial (Pietrini et al., 2011; Uher & Rutter, 2012). Specifically for the two subtypes of anorexia nervosa, it has been argued that the subtypes often represent developmental stages of the same illness (Eddy et al., 2008).

However, finding in our studies considerable differences in neurobiological correlates between the two diagnostic categories of anorexia nervosa, gives evidence for the relevance of this *categorical* conceptualization. In line with studies showing differences on the level of temperamental characteristics (e.g. in reward sensitivity, compulsiveness, behavioural inhibition), these results show that variations between these groups of patients are not solely present on the symptomatic level (Claes, Robinson, Muelenkamp, Verdereycken, & Bijttebier, 2010; Vervaet, van Heeringen, & Audenaert, 2004; Matton, Goossens, Vervaet, & Braet, 2015).

On the other hand, considering the great variance in set-shifting and central coherence performance we observed within our clinical samples (chapter II and IV), we can assume that, when reflecting on the heterogeneity in anorexia nervosa, a *dimensional* approach can have an important additional value on top of the categorical model. A combined categorical and dimensional approach for the conceptualization of eating disorders was earlier suggested by Brooks and colleagues (2012) in their description of the *"impulse control model"*. In this model the different eating disorder diagnostic categories from DSM-IV are placed on a single continuum from restrained to impulsive: with the restrictive type of anorexia nervosa on the left hand side of the continuum, the binge eating disorder on the extreme right hand side, and bulimia nervosa in between. In this model, varying degrees of cognitive control (from high to low across the spectrum) are presumed to contribute to the differential pathologies in anorexia nervosa, bulimia nervosa and binge eating disorder.

In our studies, additional evidence is provided for this impulse control spectrum model, finding a heightened cognitive control in AN-R and not in AN-BP. Since previous studies show a decreased activation in cognitive control regions in bulimia nervosa (Brook et al., 2011), one might assume that AN-BP lies somewhere in between AN-R and bulimia nervosa. The same positioning has been suggested in temperament studies (Vervaet, Van Heeringen, & Audenaert, 2004; Claes, Robinson, Muehlenkamp, Vandereycken, & Bijttebier, 2010).

Given the high rates of diagnostic cross-overs that occur mainly from restrictive to bingeing/purging eating disorders and secondly, given the heterogeneity that was observed in our clinical samples, we might assume that a part of the restrictive sample has a higher risk to develop a bingeing/purging eating disorder. Presumably, taking the underlying (neurobiological) features into account could contribute to the prediction of future diagnostic cross-overs.

Brooks at al. (2012) suggest that, in the "impulse control spectrum" model, the true place on the spectrum is dictated by the *temperamental dominance* and not by the (instantaneous) behavioural presentation. Our results confirm that, in the positioning on the continuum, the degree of cognitive control should also be taken into account.

Implications for the treatment of anorexia nervosa

According to the current guidelines for the treatment of anorexia nervosa from the National Institute for Clinical Excellence (NICE), for adult patients with anorexia nervosa no 'gold standard' treatment is available. For anorexia nervosa in adolescents, the leading treatment is family based therapy (NICE, 2004). Cognitive behaviour therapy (CBT) is considered the treatment of choice for adults and adolescents with bulimia nervosa and binge eating disorder (NICE, 2004). More recently, CBT has

been adapted to make it suitable for any form of eating disorder, thereby making it “transdiagnostic” in its scope (Fairburn, 2008).

Basically, the results from our studies suggest that *not all patients* with anorexia nervosa might benefit from the same treatment approaches. At least, in the total group of patients with anorexia nervosa a variability on the level of cognitive control should be taken into account.

Firstly, within the *categorical* framework of DSM-IV and DSM-5, the results from our studies suggest that treatment approaches towards an ineffectively high top-down control are particularly indicated for patients with the restrictive subtype of anorexia nervosa.

Additionally, based on the impulse control spectrum model and our study results, we suggest that the place of a specific patient on the *continuum* should be deduced from the level of cognitive control and not solely from the behavioural features. Subsequently, one should think about treatment approaches specifically indicated for patients having maladjusted inflexibility.

Different authors suggest that the described decreased mental flexibility is a limiting factor for psychotherapeutic treatments that place emphasis on the adaptation of essential cognitions and behaviours (Lock et al., 2013; Tchanturia, Lloyd, & Lang, 2013).

Cognitive remediation therapy (CRT) is a possible approach towards enhancing mental flexibility in anorexia nervosa. CRT aims at addressing cognitive *processes* rather than cognitive content, using simple cognitive exercises[9]. The growing insights into the increased attention to detail and cognitive inflexibility in anorexia nervosa led to the development of CRT specified for anorexia nervosa

[9] CRT was originally developed to use in brain injuries and was further adapted for schizophrenia (Cicerone et al., 2011; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011).

(Tchanturia et al., 2013)[10]. Based on a meta-analysis of effectiveness studies, CRT for anorexia nervosa seems indeed associated with cognitive and clinical improvements (Tchanturia et al., 2014).

In this line, when applying CBT (Dalle Grave R., Calugi, Doll, & Fairburn, 2013)[11] patients should also be encouraged to be aware of their own thinking styles. Different from CRT which is applying neutral material to address cognitive processes, CBT could target cognitive processing in anxiety-provoking situations as well.

Of course, when thinking about directly targeting the hyperactive top-down control in anorexia nervosa, *neuromodulation procedures* (e.g. transcranial magnetic stimulation, TMS) are also worth considering. However, to date, the evidence for the effectiveness for these approaches in anorexia nervosa is scarce (McClelland et al., 2014). Subsequently to the included research in this PhD, a next study in our eating disorder research group will deal with the effects of low frequency TMS in targeting excessive cognitive control in patients with anorexia nervosa (cfr. research protocol Vanderhasselt & Vervaet, 2016).

Strengths and limitations of the included studies

The rather small sample sizes in the included studies are a first limitation. Especially for the comparison between anorexia nervosa subtypes, a greater number of participants, could possibly have led to clearer results on the level of task performance.

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[10] CRT for anorexia nervosa is a brief, manualised intervention, which consists of various cognitive flexibility and gestalt processing exercises. Individual CRT is delivered in 10 sessions, twice weekly, for 45 minutes each session. During CRT-sessions patients complete simple cognitive tasks and the therapist gradually encourages to reflect on their thinking styles and strategies and to think about how these strategies can be linked to examples from everyday life (Tchanturia, Lounes, & Holttum, 2014).

[11] Focus on the cognitive processing, rather than cognitive content, is in line with the 'third wave' CBT (Churchill et al., 2014).

Further, considering the choice of the applied neuropsychological measures some remarks can be made. It is an acknowledged problem that neuropsychological tasks require a complex mix of different skills or functions, and as a result, it can be difficult to conclude precisely which underlying mechanism is responsible for the performance. Since this also seemed a difficulty in our neuropsychological study (using Object Assembly; Block Design; Trail Making Test), we chose to apply purely experimental designs in our functional brain imaging studies (a developed set-shifting task; Embedded Figures Task).

The fact that in the fMRI study using the Embedded Figures Task no significant group differences could be established using the contrast between the two conditions of the task (EFT minus MATCH) on the whole brain level, can be interpreted as a limitation of this study. The complex condition (EFT > baseline) we used further in analysis, is a less direct measure of detail-focused processing, because the additional domains that are measured (e.g. visual and motor processing, task characteristics) are not controlled for. However, this “negative” result might actually stress the existence of a continuum from normalcy to pathology, without a clear different pattern between patients and controls, as also reported by Castellini and colleagues (2013).

The included studies contribute to the field since, to date, very few studies concerning possible variations in information processing features between the restrictive and bingeing/purging subtypes of anorexia nervosa are available. Even fewer studies are constructed specifically to test possible differences between the two subtypes. Furthermore, in the published functional brain imaging studies in eating disorders, mainly symptom-provocing material (e.g. pictures of food and bodies) has been applied. Using more neutral material as we did in all the included studies makes our findings all the more relevant. Further, by controlling for body mass index in our functional brain imaging studies, we were more likely to identify brain alterations relevant to the disorder, as opposed to results that could be partly related to the effects of starvation.

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Summary

The main goal of the included studies was to compare the restrictive and bingeing/purging subtypes of anorexia nervosa on the level of set-shifting and central coherence task performance as well as on the associated neurobiological functioning. We assumed that these studies could provide additional insight into similarities and differences in the behavioural presentations in these two patient groups and that this knowledge could contribute to our understanding about what specific treatment is indicated for whom.

Firstly, from systematically reviewing the literature (chapter I), we concluded that the available indications for possible group differences (AN-R versus AN-BP) on the level of behavioural set-shifting and central coherence task performance are not strong enough to draw definitive conclusions.

From our neuropsychological study (chapter II) clear indications were presented for a significantly worse task performance in patients with AN-R and not AN-BP when compared to healthy controls, in two tasks assumed to assess central coherence (Block Design; Object Assembly). No differences could be shown between these study groups using different set-shifting tasks (Wisconsin Card Sorting Test; Trail Making Test; an experimental set-shifting paradigm).

Further, the functional brain imaging during set-shifting task performance (chapter III) demonstrated increased activation in the precuneus and insula in patients with anorexia nervosa compared to healthy control subjects, which is in line with the previous reported excessive cognitive control in anorexia nervosa. Interestingly, taking the two diagnostic anorexia nervosa subtypes into account, this increased activation in cognitive control regions was only present in AN-R.

Using functional magnetic resonance imaging during the performance of an Embedded Figures Task (chapter IV), an increased activation could be established in the precuneus/inferior parietal cortex

and inferior frontal gyrus, comparing patients with AN-R with patients with AN-BP and healthy control subjects. Again, these results suggest that the excessive top-down cognitive control that is often assumed to play a role in anorexia nervosa, is mainly present in AN-R.

Basically, the results from our studies suggest that within the diagnostic process as well as in the assignment of indicated treatment approaches, a variability should be taken into account in the total group of patients with anorexia nervosa on the level of cognitive control.

Finding in our studies considerable differences between the two diagnostic categories of anorexia nervosa as proposed by DSM-IV, gives evidence for the relevance of this *categorical* conceptualization. Within this categorical framework, treatment approaches towards an ineffectively high top-down control should be offered for patients having restrictive anorexia nervosa.

On the other hand, considering the great variance in task performance we observed *within* our clinical samples, we assume that, when reflecting on the heterogeneity in anorexia nervosa, a *dimensional* approach has an important additional value on top of the categorical model. Based on the impulse control spectrum model and our study results, we suggest that the place of a specific patient on the *continuum* should be deduced from the level of cognitive control and not solely from the behaviour features. Subsequently, one should think about treatment approaches that are specifically indicated for patients having maladjusted inflexibility.

Neuromodulation techniques and cognitive remediation are possible approaches in targeting the ineffective increased cognitive control. Also, when applying cognitive behavioural therapy for anorexia nervosa, next to specific cognitive content, cognitive processing features should be a major focus.

Samenvatting (Nederlandstalig)

Het belangrijkste doel van de ingesloten studies was de vergelijking tussen de restrictieve en eetbuien/purgerende subtypes van anorexia nervosa (AN-R; AN-BP) op het niveau van set-shifting en centrale coherentie, zowel op gedragsmatig (neuropsychologisch) vlak, als in het geassocieerde hersenfunctioneren. We veronderstellen dat deze studies kunnen bijdragen aan een beter begrip van de gelijkenissen en verschillen in de gedragsmatige presentaties in deze twee patiëntengroepen en dat deze kennis een toegevoegde waarde kan betekenen in de toewijzing van geïndiceerde behandelingen voor elke individuele patiënt.

Vanuit een systematisch literatuuronderzoek (hoofdstuk I) konden we besluiten dat de aanwezige aanwijzingen voor mogelijke groepsverschillen (AN-R versus AN-BP) in taakperformatie op vlak van set-shifting en centrale niet sterk genoeg zijn om definitieve conclusies te trekken.

In onze neuropsychologische studie (hoofdstuk II) konden we duidelijke aanwijzingen vinden voor een significant verminderde taakperformantie bij patiënten met AN-R, en niet bij patiënten met AN-BP, wanneer ze werden vergeleken met gezonde controles op twee central coherentie taken (Blokpatronen; Figuur leggen). Er konden geen groepsverschillen vastgesteld worden in de prestatie op drie set-shifting taken (Wisconsin Card Sorting Test; Trail Making Test; een experimenteel set-shifting paradigma).

Vervolgens toonde het functioneel beeldvormend onderzoek van de hersenen tijdens de uitvoering van een set-shifting taak (hoofdstuk III) een verhoogde activatie in de precuneus en de insula bij patiënten met anorexia nervosa vergeleken met gezonde controles, hetgeen in lijn is met eerder onderzoek dat een “excessieve cognitieve controle” in anorexia nervosa toont. Het is bijzonder

interessant dat, wanneer we de twee subtypes van anorexia nervosa in rekening brengen in onze studie, we deze verhoogde activatie in cognitieve controle regio's enkel kunnen vaststellen in AN-R.

Bij de uitvoering van de Embedded Figures Task tijdens functionele beeldvorming (hoofdstuk IV), kon een verhoogde activatie worden vastgesteld in de precuneus/inferieure pariëtale cortex en de inferieure frontale gyrus wanneer patiënten met AN-R vergeleken werden met patiënten met AN-BP en gezonde controlepersonen. Opnieuw suggereren deze resultaten dat de excessieve top-down cognitieve controle, waarvan wordt vermoed dat ze een rol speelt in anorexia nervosa, enkel aanwezig is in AN-R.

Globaal gezien suggereren de resultaten van onze studies dat in zowel het diagnostisch proces als in de toewijzing van geïndiceerde behandelingen voor patiënten met anorexia nervosa, rekening gehouden moet worden met een *variabiliteit* in de totale patiëntengroep op het vlak van cognitieve controle.

Het feit dat we duidelijke verschillen vaststellen tussen de twee diagnostische groepen in anorexia nervosa zoals voorgesteld in DSM-IV (en DSM-5), geeft bevestiging voor de relevantie van deze *categoriale* conceptualisatie. Binnen dit categoriale denkkader zouden behandelvormen die specifiek gericht zijn op de ineffectief verhoogde top-down controle enkel moeten worden aangeboden aan patiënten met anorexia nervosa van het restrictieve subtype.

Als we de grote variantie in rekening brengen die we konden observeren in de taakperformatie binnen onze klinische steekproeven, kunnen we echter vermoeden dat, als we reflecteren over de heterogeniteit in anorexia nervosa, een *dimensionele* benadering een belangrijke toegevoegde waarde heeft boven een categoriaal model. Gebaseerd op het 'impuls controle model' en onze studieresultaten stellen we voor dat de specifieke positie van een patiënt op het continuüm moet worden afgeleid van het niveau van cognitieve controle en niet alleen van de gedragsmatige kenmerken bij de patiënt. Daarenboven moet worden nagedacht over behandelvormen die specifiek geïndiceerd zijn voor patiënten met onaangepaste inflexibiliteit.

Neuromodulatietechnieken en cognitieve remediatie zijn mogelijke benaderingen in het aanpakken van de ineffectief verhoogde cognitieve controle. Daarenboven moet, bij het toepassen van cognitieve gedragstherapie bij anorexia nervosa, naast de aandacht voor cognitieve inhouden, de focus gelegd worden op cognitieve *processen*.