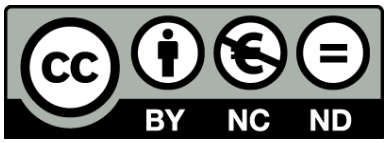
UNIVERSITAT DE BARCELONA

Alterations in social reward and body perception brain circuits in anorexia nervosa: a functional and structural neuroimaging investigation

Esther Via Virgili



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PhD Thesis-2015

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Clinical and Experimental Neuroscience
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DOCTORATE IN MEDICINE

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ALTERATIONS IN SOCIAL REWARD AND BODY PERCEPTION BRAIN CIRCUITS IN ANOREXIA NERVOSA: A FUNCTIONAL AND STRUCTURAL NEUROIMAGING INVESTIGATION.

DOCTORAL THESIS

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-SEPTEMBER 2015-

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Doctors Narcís Cardoner Álvarez and Carles Soriano-Mas certify that they have guided and supervised this doctoral thesis, entitled “ALTERATIONS IN BRAIN CIRCUITS FOR SOCIAL REWARD AND BODY PERCEPTION IN ANOREXIA NERVOSA: A FUNCTIONAL AND STRUCTURAL NEUROIMAGING INVESTIGATION”, which is presented in order to obtain the title of doctor by the candidate Esther Via. They thereby assert that this thesis fulfills all the required criteria.

L'homme sociale

"Je ne mange pas de pain. Le blé pour moi est inutile. Les champs de blé ne me rappellent rien. Et ça, c'est triste! Mais tu as des cheveux couleur d'or. Alors ce sera merveilleux quand tu m'auras apprivoisé! Le blé, qui est doré, me fera souvenir de toi. Et j'aimerai le bruit du vent dans le blé...
Le renard se tut et regarda longtemps le petit prince:
- S'il te plaît... apprivoise-moi! dit-il."

(Antoine de Saint-Exupéry, Le Petit Prince)

Man and identity

El *yo* individual es aquello que se diferencia de lo general,[…] lo que no puede ser adivinado y calculado de antemano, lo que en el otro es necesario descubrir, desvelar, conquistar.

(Milan Kundera, La insoportable levedad del ser)

Be yourself; everyone else is already taken.

(Oscar Wilde)

The importance of this work lies in the person that one day will sit in front of you…

…the patient.

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Foreword

The work presented in this Doctoral Thesis was undertaken in the Neuroimaging group, at the Psychiatry department - Bellvitge University Hospital and Bellvitge Biomedical Research Institute (IDIBELL, Catalan acronym), Barcelona, Spain. It was conducted in collaboration with the Melbourne Neuropsychiatry Center, Melbourne, Australia, and within the framework of the Ciències Clíniques group, University of Barcelona, Medical school, Barcelona, Spain.

Enclosed are two peer-reviewed published journal articles and a third one in review. It has been written in accordance with the procedures indicated by the University of Barcelona and it is presented in order to obtain the International Doctorate title, which is granted by this Institution. The supervisors of this Thesis are Dr. Narcis Cardoner and Dr. Carles Soriano-Mas, and Dr. JM Menchón Magriñá, the tutor.

Personal funding for this work includes: IDIBELL Scholarship (2010-2013), personal contract linked to a research project (2013-2014) and Endeavour Research Scholarship, Australian education department (2014-2015). Project funding is dependent on the Institute Carlos III (Ministry of Economy and Competitiveness, Spain), grants: PI 081549, PI 11210.

The present work includes, in the following order: a general introduction, aims and hypotheses, the three original articles, a summary of results, a general discussion with a presentation of a new theoretical model based on the findings, conclusions, a summary in Catalan and list of references.

These years of research have produced several scientific articles. Among those, the ones included in this work:

1. Disruption of brain white matter microstructure in women with anorexia nervosa.

Via E, Zalesky A, Sánchez I, Forcano L, Harrison BJ, Pujol J, Fernández-Aranda F, Menchón JM, Soriano-Mas C, Cardoner N, Fornito A. J Psychiatry Neurosci. 2014 Nov;39(6):367-75.

2. Abnormal Social Reward Responses in Anorexia Nervosa: An fMRI Study.

Via E, Soriano-Mas C, Sánchez I, Forcano L, Harrison BJ, Davey CG, Pujol J, Martínez-Zalacaín I, Menchón JM, Fernández-Aranda F, Cardoner N. PLoS One. 2015 Jul 21;10(7):e0133539

3. Default Mode Network alterations during self-other body perception and resting-state in anorexia nervosa.

Esther Via, Ximena Goldberg, Isabel Sánchez, Laura Forcano, Ben J Harrison, Christopher G. Davey, Jesús Pujol, Ignacio Martínez-Zalacaín, Fernando Fernández-Aranda, Carles Soriano-Mas, Narcís Cardoner, José M. Menchón. In review, Social Cognitive and Affective Neuroscience Journal.

In addition, these results have been presented in several international congresses as poster and abstract publications: Society of Biological Psychiatry, May 2014, New York; European Congress of Psychopharmacology, Barcelona, 2013; European Congress of Psychopharmacology, Vienna, 2012; International Conference on Eating Disorders, Austin, Texas, USA, 2012. Moreover, portions of them were presented as an oral presentation (Dr. Fernando Fernández-Aranda) in the SIPB Società Italiana di Psichiatria Biologica, Naples, Italy, September 2013.

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Voldria agrair a tota la gent sense la qual aquest treball no hagués estat posible, i que espero contribueixi a la recerca actual en anorexia nerviosa.

En primer lloc, a les pacients amb anorèxia nerviosa, sobretot a aquelles que van participar en aquest estudi. Espero, sincerament, que el camí us hagi conduït a un lloc millor. Gràcies també a tots els controls sans que van atrevir-se a col.laborar amb nosaltres.

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Per les coses que es guanyen i les que es queden pel camí, que en fan créixer d'altres.

List of abbreviations

ACC	anterior cingulate cortex
AI	anterior insula
Amy	amygdala
AN	anorexia nervosa
BMI	body mass index
Cau	caudate
CCQ	cross-cultural questionaire
DLFPC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EBA	extrastriate body area
EDI-2	eating disorder inventory
FA	fractional anisotropy
FBA	fusiform body area
FEye	frontal eye fields
FFA	fusiform face area
fMRI	functional magnetic resonance
HTH	hypothalamus
ICA	independent component analysis
IFG	inferior frontal gyrus
IPC	inferior parietal cortex
LSAS	liebowitz Social Anxiety Scale
MD	mean diffusivity
MFG	middle frontal gyrus
MNS	mirror neuron system
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
OFC	orbitofrontal cortex
OT	occipito-temporal cortex
Pc	precuneus
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PPC	posterior parietal cortex
PPI	psychophysiological interaction
PMC	premotor cortex
Put	putamen
RHI	rubber hand illusion
SMFG	superior medial frontal gyrus
sMRI	structural magnetic resonance
SPC	superior parietal cortex
SPM	statistical parametric mapping
SPSRQ	sensitivity to punishment and sensitivity to reward questionnaire
SSens	somato-sensorial cortex

STS	superior temporal sulcus
TCI-R	temperament and character inventory
ToM	theory of mind
TPJ	temporo-parietal junction
V1	primary visual cortex-area V1
VBM	voxel-based morphometry
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex
vPMC	ventral premotor cortex
VS	ventral striatum
MR	magnetic resonance
MRI	magnetic resosonance imaging
DMN	default mode network

Chapter 1

INTRODUCTION

Chapter 1- Introduction

1. Anorexia nervosa

After many years of research and the consequent advances in the understanding of anorexia nervosa, its conceptualization as either a somatic disease (e.g. *apepsia hysterica* (Gull, 1997)) or as a cultural- and family-dysfunction-related benign psychological disorder (Harper, 1983; Sullivan, 2003) has largely been overcome. Although much still remains to be understood, AN is no longer considered to be a disorder of food intake and weight at its core, but rather is better explained by much more complex models. Nowadays, AN is considered an **ethiopathologically multifactorial disorder** with clear **genetic and neurobiological alterations** either predisposing to - or driven by- the pathology (Kaye et al., 2009; Kaye et al., 2011).

Anorexia nervosa (AN) is a **severe and debilitating** disorder, with limited evidence for both psychological and psychopharmacological treatments ((UK), 2004). Affected patients present preoccupations about **body self-image, weight and dieting** and engage in intense food **restrictions** (American Psychiatric Association and Association, 2000). In some cases, they might also engage in **binging and purging** episodes, which led to the DSM-IV (and in following DSM manuals) classification of AN into the **restricting vs. binge eating/purging subtype** (American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000).

DSM-IV TR criteria	DSM 5 criteria
A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to a maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to **body weight less than 85% of that expected**).	A. **Restriction of energy intake** relative to requirements, leading to a significant low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than minimally expected.
B. Intense **fear** of gaining weight or becoming fat, even though underweight.	B. Intense **fear** of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. **Disturbance** in the way in which **one's body** weight or shape is **experienced**, undue influence of body weight or shape on **self-evaluation**, or denial of the seriousness of the current low body weight.	C. **Disturbance** in the way in which one's **own body** weight or shape is **experienced**, undue influence of body weight or shape on **self-evaluation**, or persistent lack of recognition of the seriousness of the current body weight.
D. In postmenarcheal females, **amenorrhea**, i.e. the absence of at least three consecutive menstrual cycles (a woman is considered to have amenorrhea if her periods occur only following hormone, e.g. estrogen administration).	Omitted
Specify type	*Specify type*
Restricting type. During the current episode of anorexia nervosa, the person has **not regularly engaged in binge-eating/purging behavior** (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas).	*Restricting type.* During the **last 3 months**, the individual has **not engaged in recurrent episodes of binge eating or purging** behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which **weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise**.
Binge-eating/purging type. During the current episode of anorexia nervosa, the person **has regularly engaged in binge-eating/purging behavior** (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas).	*Binge-eating/purging type.* During the **last 3 months**, the individual has engaged in recurrent episodes of **binge eating or purging behavior** (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Table 1. Comparison between DSM-IV TR (American Psychiatric Association and Association, 2000) and DSM 5 (American Psychiatric Association, 2013) diagnostic criteria for AN.

2. Epidemiology

Anorexia nervosa is **relatively rare** disorder, with a lifetime prevalence ranging between **0.4 and 1.7%** (with a high prevalence in adolescent populations, (Bulik et al., 2006; Preti et al., 2009; Smink et al., 2014)**.** Nevertheless, it presents the **highest mortality rate** among psychiatric disorders, estimated to be **5.6% per decade of illness** (Sullivan, 1995) (or between **0.71% and 12.8%** of increased mortality compared to the general population (Arcelus et al., 2011)) with **1 in every 5 committing suicide** (Arcelus et al., 2011)- a 57-fold increase in suicide risk compared to age-matched peers (Keel et al., 2003). The yearly **incidence of AN,** around 5 per 100000 persons/year, **has remained stable** since 1970s, when a **rise in the incidence** was observed, attributable to a specific age group (15-24 years (Hoek, 2006)). However, the actual raise in this incidence is under considerable debate, considering some methodological differences between studies as putative confounding factors (Hoek, 2006) (Fig1).

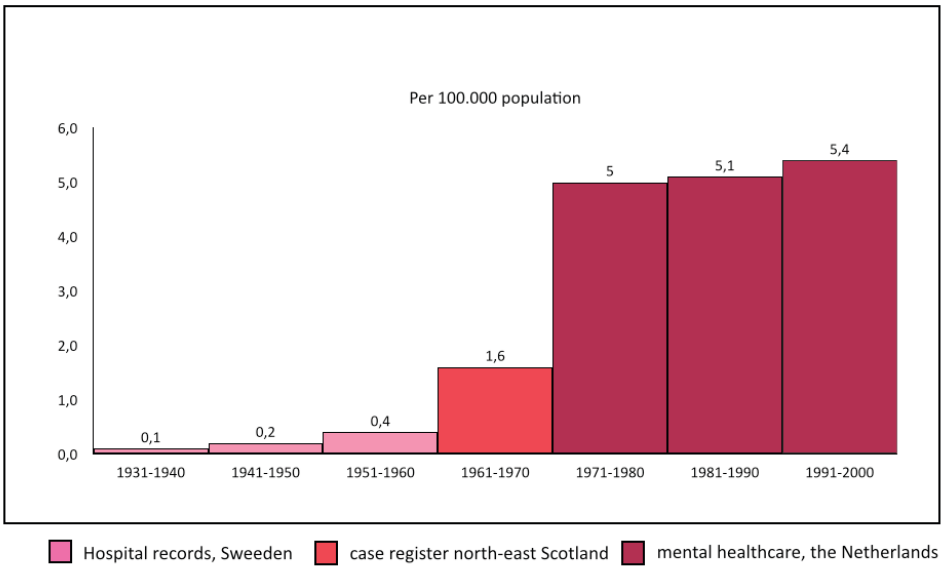

Fig. 1. Incidence of AN from 1931 to 2000 in Europe, according to the different cohort studies. Extracted and adapted from Hoek 2006 (Hoek, 2006)

The age of disorder onset is normally in **adolescence and early adulthood**, with an estimated average age between 12.3 and 17.3 years (Favaro et al., 2009; Swanson et al., 2011). Incidence trends in the last years have shown, however, a **decrease of the age at onset in younger generations** (Favaro et al., 2009), as well as an **increase in older groups** (Mangweth-Matzek et al., 2014). Moreover, although AN mainly affects females, with a **male: female ratio of 1:8** (Steinhausen and Jensen, 2015), an **increase in male incidence** has also been recently reported (Núñez-Navarro et al., 2012).

Over the course of the disorder **at least 20%** of affected patients will present a **poor prognosis**, remaining chronically ill, while about 30% will present a partial or residual recovery and 46% will be fully recovered (Steinhausen, 2002). Moreover, some of them will **transition from anorexia to bulimia** nervosa or vice versa (around 54% during 15 years of follow-up, (Bulik et al., 1997)).

3. Vulnerability factors in AN etiology

In the widely accepted multifactorial model of AN, both genetic/heritable and social/cultural factors, in conjunction with certain personality traits, are considered vulnerability factors. There is a complex interplay between psychological, environmental and neurodevelopmental factors which may trigger and maintain the disorder.

3.1. Genetics and heritability

There is a **substantial genetic component** in the etiology of AN, suggested by strong familiar aggregation, the cross-cultural presence of the disorder and the estimated **heritability** percentages from twin studies, ranging between **50 to 80%** (Brandys et al., 2015; Bulik et al., 2006). Additionally, there is an aggregation with other psychiatric disorders; for example, there is an increased risk of affective disorders within family members of patients with AN (Steinhausen et al., 2015).

As it is the case for other mental disorders, there is no evidence for large effect stemming from single-gene mutations, and, instead, it has been suggested that development of AN may be due to the additive presence of **small effects involving multiple genes, in conjunction with environmental factors affecting** their expression. In this context, a few alterations in single-nucleotide polymorphisms (SNPs) have been reported, for example related to body-weight regulation hormones, oxytocin and/or serotoninergic and dopaminergic transmission, among others (Castro-Fornieles, 2015; Trace et al., 2013), although there is a long way to explore (Brandys et al., 2015). Most likely, an **inheritable phenotype of continuous behavioural traits** might be present in AN (Connan et al., 2003).

3.2. Personality

Some personality traits have been found to be characteristic of AN, and some studies have suggested that they **occur prior to the development of the disorder and persist after symptom recovery** (Casper, 1990; Kaye et al., 2013; Srinivasagam et al., 1995; Wagner et al., 2006b). Most of these traits are linked to **anxiety and neurotic or obsessive personality traits**, such as **harm avoidance, perfectionism, rigidity or obsessionality** (Anderluh et al., 2003; Friederich and Herzog, 2011; Kaye et al., 2013; Lilenfeld et al., 2006). Other suggested predisposing factors are **poor interoceptive awareness and alexithymia, high drive for thinness and ineffectiveness** (Beadle et al., 2013; Espina, 2003; Kaye et al., 2013; Lilenfeld et al., 2006). It is also relevant to highlight the **high comorbidity with anxiety disorders** (Kaye et al., 2004) and the high **prevalence of anxiety symptoms or diagnoses, mostly for social anxiety disorder, even before disorder onset** (Godart et al., 2000; Kaye et al., 2004). Finally, obsessive-compulsive traits have been associated with a **worse outcome** (Crane et al., 2007).

In relation to diagnostic subtypes, the few studies that evaluated personality trait differences found that the **restrictive subtype** presented higher **anticipatory worry and persistence but low attachment** (a subdimension of reward dependence) and self-directness (Fassino et al., 2002). By contrast, **binge-purging subtype AN** patients are considered to represent the **most impulsive group** of patients in the spectrum of AN (Brooks et al., 2011; DaCosta and Halmi, 1992). Nevertheless, at least one study did not find any difference between diagnostic subgroups (Anderluh et al., 2003).

3.3. Social and cultural factors

AN has been described in all cultures, and **previous debates about it being a culture-bound syndrome have been refuted** (Keel and Klump, 2003). However, **cultural influences on AN are well recognized**. For example, two studies about the incidence of AN in the Netherlands Antilles (Curaçao) (Hoek et al., 2005) and among Netherlands Antilles natives living in the Netherlands (van Hoeken et al., 2010) showed that, while the incidence of AN in the black population of Curaçao was nil, within the minority of mixed and white population it was similar to those described in the Netherlands. Moreover, among those migrated to the Netherlands, the incidence was similar as compared to native Dutch. Authors pointed to the influence of the **Western idealization of thinness**, as well as possible migration-related stress effects (van Hoeken et al., 2010) as causative factors. However, some diagnostic criteria should probably be reconsidered to better adjust to different expressions of the disorder across cultures, for example, in black populations (Taylor et al., 2013).

3.4. Neurodevelopmental framework

The neurodevelopmental framework suggests that some **predisposing factors**, in addition to **environmental effects,** create a **continuum of vulnerability** features, with the disorder establishing itself after **surpassing a specific threshold** [**multifactorial threshold model,** (Connan et al., 2003; Kaye et al., 2009)]. In this context, certain developmental periods are more prone to the emergence of AN, such as **adolescence**, when the brain undergoes major **changes in development (important synaptogenesis, pruning and myelination)**. Within these changes, those in **frontal and limbic circuits** are of particular relevance, which are underpinning the integration of cognition and emotion processing (Connan et al., 2003; Pfeifer and Peake, 2012). For example, **emotion recognition** and **cognitive control** improve with **frontal efficiency and associated functional and structural connectivity changes** (Liston et al., 2006; McGivern et al., 2002), while improvement in other functions, such as **attentional set shifting** has been associated, for example, with volume increase in the **anterior cingulate cortex** (Casey et al., 1997). Importantly, functional and structural alterations in all these regions have been suggested to be relevantly involved in AN (Kaye et al., 2009). However, there is a lack of understanding to what extent these factors might be evidenced in adolescence while conforming part of a **susceptibility *package***, or, alternatively, they might be the **consequence of severe starvation during** a sensitive period of brain development (Connan et al., 2003).

Moreover, **adolescence** is a period during which major **changes in psychological –including important changes in one's own identity construction** (Kłym and Cieciuch, 2015; Sollberger, 2014)**- and sociocultural aspects,** as well as **purely biological factors** develop within the individual. These changes are important, among other aspects, to the learning about social relationships; indeed, developmental changes in different brain areas are dedicated to improvement in **social information processing**. Nelson et al. (Nelson et al., 2005) described three main circuits important to social processes which develop during this period, namely: a '**detecting node**' (fusiform area, superior temporal sulcus and anterior temporal lobe, already mature by adolescence), an '**affective node**', (amygdala, the hypothalamus, ventral striatum, septum, orbitofrontal cortex and bed nucleus of the stria terminalis), and a **'cognitive-regulatory node'** (dorsomedial prefrontal cortex and ventral prefrontal cortex). In addition, developmental changes associated with **fear learning** and **habituation to changes and novelty** might also be relevant to the consolidation of these circuits in adolescence and associated to some **personality traits linked to AN** (high harm avoidance, low novelty seeking and low reward dependence) (Strober,

2004). Finally, **environmental changes, stressful life events**, or intentional/unintentional **weight changes** during adolescence are additional factors triggering the development of the disorder (Kaye et al., 2009). **Poor eating habits during childhood** have also been identified as a risk factor for AN, among other eating disorders (Fernández-Aranda et al., 2007).

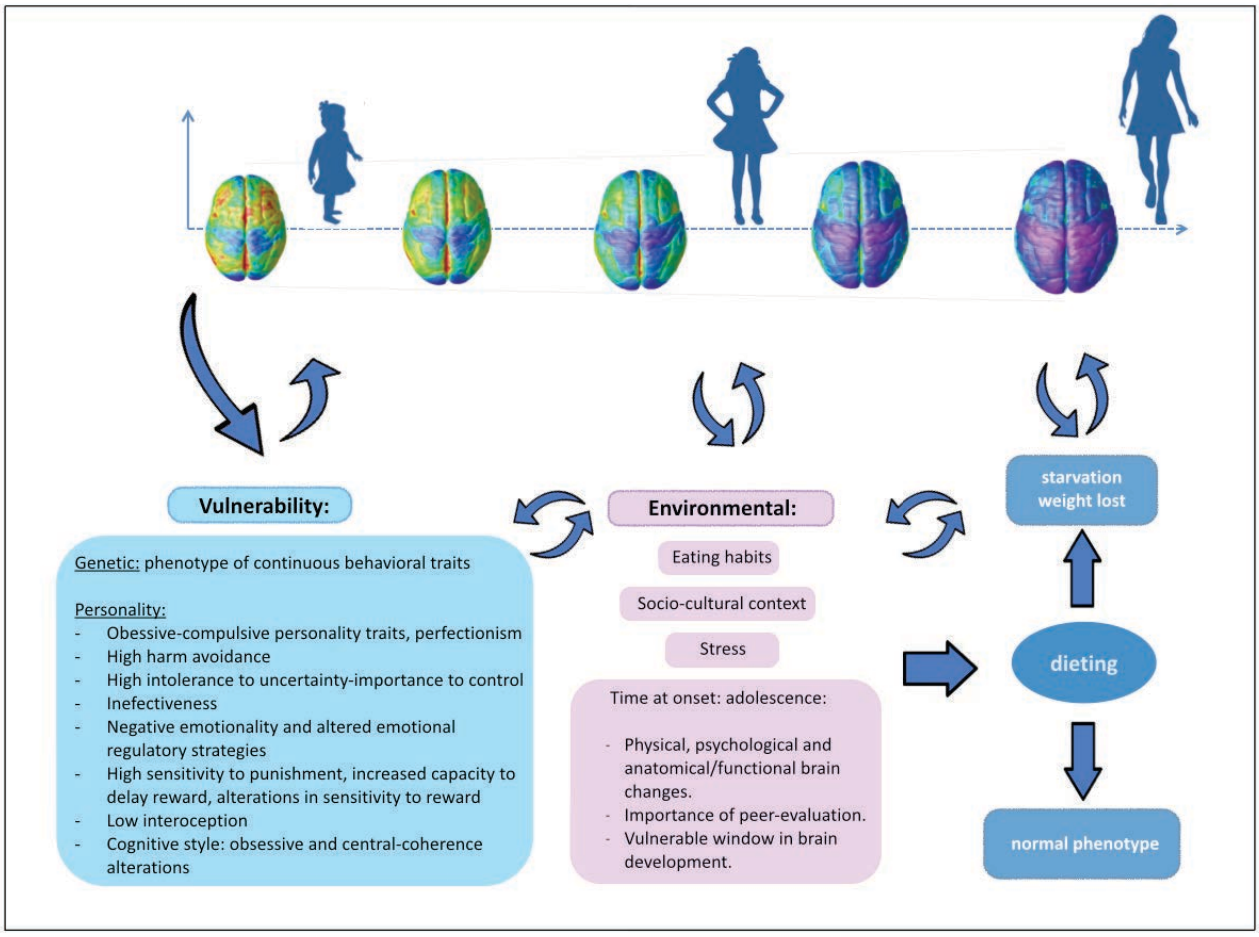

Figure1. Representation of a multifactorial model for AN. Adapted and expanded from (Kaye et al., 2009; Lilenfeld et al., 2006).

4. Brain networks involved in the pathophysiology of AN

The US **National Institute of Mental Health** stressed, back in **2008**, the need for a better understanding of the pathophysiology of anorexia nervosa and the **potential of neuroimaging** (and genetics) in improving the knowledge of altered brain systems (Chavez and Insel, 2007). Although there is still much to be learned, **great advances** have been made. There are strong lines of research worldwide focusing on quite different brain systems. For example, the group leaded by Prof. **Walter Kaye** (Eating Disorders Center for Treatment and Research, University of California, San Diego, California, USA) has conducted extensive work in elucidating putative brain systems involved in AN, currently highlighting the importance of an **anxiety-related pathway**, **reward system** alterations and the **link between the two** (Kaye et al., 2010; Wierenga et al., 2014). Another group in the United States of America, led by Ass/Prof. **Guido KW Frank** (Department of Psychiatry, University of Colorado) is further interested in alterations of the **reward system in eating disorders** (Frank, 2013). On the other hand, the work conducted at the

Maudsley Hospital and Institute of Psychiatry –IOP- in London, UK (Prof. **Janet Treasure** and Dr. **Kate Tchanturia)**, is centred on alterations in **cognitive and socio-emotional domains** in AN (Oldershaw et al., 2011; Tchanturia et al., 2014).

In recent years, the arrival of new available therapies in psychiatry, such as **deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS)** recently applied to patients with AN [see (McClelland et al., 2013)], has stressed the **need of better network-based models of the underlying pathophysiology of AN**. Indeed, an intense debate has emerged about the opportunity and ethical implications of applying these techniques without conclusively defined neurobiological models of the disorder (Coman et al., 2014; Oudijn et al., 2013). At present, data from neurocognitive and imaging studies suggest that patients with AN have impairments in neural systems implicated in **executive functions**, **visuo-spatial processing**, **self-image perception**, **fear and anxiety, (socio-) emotional regulation** and **reward processing** (Kaye et al., 2009). In the following lines, and with the purpose of introducing the three studies presented in this work, alterations in visuo-spatial processes and self-image perception within the framework of **body perception**, as well as alterations in **reward and socio-emotional processing** and the brain networks subserving these functions will be reviewed.

4.1. Alterations in brain circuits putatively underlying alterations in body distortion

4.1.1. Definition and conceptualization of body distortion

Body distortion is a **core feature** of- and a required diagnostic criterion for- AN (American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000). Relevantly, the specific evaluation of this symptom is not only key for the diagnosis of AN but is also a putative **marker of eating disorders** (Gardner and Bokenkamp, 1996) and its **development** (Jacobi et al., 2004), as well as a **predictor** of relapse (Keel et al., 2005). It describes the **overestimation of body representation**, specifically defined as a "Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight" (American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000), or a "dread of fatness that persists as an intrusive, overvalued idea" (World Health Organization (WHO), 1992). It becomes noticeable in the literature, however, that this conceptualization is rather vague and **the nature of body image distortion has long been controversial**. Partially, this problem arises from **its complexity** and the **lack of a well-defined concept of body representation** in non-clinical populations (de Vignemont, 2010).

Evidence from neurological damage to the brain and neurocognitive evaluations have distinguished two main components of body perception: one for postural and sensory–motor capacities, involving action (body schema) and another including a broad system of perceptions, attitudes and beliefs pertaining to one's own body and involved in the sense of body ownership and self-consciousness (body image) (Berlucchi and Aglioti, 1997; Berlucchi and Aglioti, 2010; Gallagher, 2005). Most definitions in AN have mainly focused on alterations of **body image**, conceptualized in two main subcomponents: **low-level perceptual** processing (e.g. involving body size and weight estimation) and a **higher-order attitudinal** component, which involves **attitudes and feelings towards the body** (Cash and Deagle, 1997; Fernández et al., 1994; Fisher and Cleveland, 1958; Skrzypek et al., 2001). In other words, '**sensory and non-sensory**

components'[1] (Gardner and Bokenkamp, 1996). Recently, a further subdivision of the second component into **affective and cognitive processes** (Cash and Deagle, 1997) has been highlighted in the **multidimensional neural model** proposed by Gaudio & Quattrocchi (Gaudio and Quattrocchi, 2012) (see Table 2). This subdivision is particularly relevant in the context of **different brain areas associated with these two subcomponents**. Importantly, **emotional and cognitive** components have been considered to be **more relevant for body distortion** (Cash and Deagle, 1997; Gardner and Brown, 2014; Skrzypek et al., 2001), although, the contribution of the **cognitive component has been disregarded particularly**. In the next lines, a summary of the findings from evaluations of each one of these aspects is presented.

Body distortion/body disturbance

(according to Gaudio and Quattrocchi's neural model and within the frame of prior conceptualizations)

1. **PERCEPTIVE COMPONENT:** Judgment of one's body size, shape and body weight relative to actual proportions (inferior parietal cortex, precuneus and occipito-temporal cortex)	PERCEPTUAL
2. **AFFECTIVE COMPONENT:** Affective response to one's own body: feelings and satisfaction/dissatisfaction of one's own body. (prefrontal cortex-insula-amygdala -and ACC and ventral striatum)	ATTITUDINAL
3. **COGNITIVE COMPONENT:** Beliefs concerning body image and appearance, as well as the mental representation of one's own body. (lack of studies. amygdala, the medial prefrontal cortex and the posterior (inferior) parietal cortex)	ATTITUDINAL

Table 2. The three main components of body distortion according to Gaudio and Quattrocchi, 2012 (Gaudio and Quattrocchi, 2012) and their relation to the perceptual and attitudinal constructs.

4.1.2. Description of the neuroanatomical pathway of body perception

The **representation of one's own body image** is a complex process in which **body sensory information** from different modalities (such as visual, tactile, proprioceptive and vestibular) is **integrated**. Unisensory information is computed in selective regions, for example in the occipito-temporal cortex for visual information (**EBA**: extrastriate body area (Downing et al., 2001), **FBA**: fusiform body area, FBA -partially overlapping but anatomically/functionally distinct from the face processing region- (Peelen and Downing, 2007)); or the **temporo-parietal junction** and the **parietal cortex** (primary somatosensory cortex) for either vestibular signals, among others (Serino et al., 2013). Subsequently, this information is **integrated, most likely in posterior parietal and prefrontal areas** (Hodzic et al., 2009b; Serino et al., 2013; Tsakiris et al., 2010). **Different regions of the parietal and prefrontal cortices** might be participating in this process, depending on the type of stimuli: static, in movement, one's own image, self-image, etc. (See Fig 2). For example, within the **posterior parietal cortex**, some regions seem responsible for **action guidance**, while others might be involved in high-level **visuo-spatial** and **semantic internal representations of the body** (Berlucchi and Aglioti, 2010). Other systems might be capturing specific information from the body, such as emotion (i.e. **amygdala, anterior cingulate cortex**) or **interceptive signals important for self-awareness,** in the **insula** (Craig, 2009; Serino et al., 2013; Tsakiris, 2010). It is additionally informative to mention the link between out-of-body experiences and the participation of these same regions, namely, frontal and parietal (inferior and superior) regions and their connections (Blanke et al., 2005; Hodzic et al., 2009b), as well as the insula (Berlucchi and Aglioti, 2010).

[1] This terminology is perhaps more accurate than the use of "perceptual" vs "attitudinal" or "emotional" and "cognitive", since all components are involved in the perceptual experience. However, the most frequently reported terms will be used in this work.

[2] In the rubber hand ilusión, participants view a rubber hand placed in front of them, slightly to one side but in a similar position to their own hand, hidden from view. Both the rubber hand and the participant's own hand are then stroked, either synchronously or asynchronously. When

Own body identification has been related to a specific **fronto-parietal circuit** including the **middle frontal gyrus, regions of the superior and inferior parietal lobes and at the FBA** (Hodzic et al., 2009a). Importantly, when **self-conscious perception of the body** was further subdivided and differently evaluated in body **agency** and **body-ownership** (Tsakiris et al., 2010)- it was found that **body ownership** was associated with the activation of **midline cortical structures** (the precuneus, the posterior cingulate cortex and the superior medial frontal gyrus), and, given the **overlap** of this network with the main **components of the default mode network** (DMN, see section 6.2.3.1), it was suggested that **ownership over the body comprises part of the network for self-referential activity**. It has to be acknowledged, however, that complex integrative functions for body processing are still rather unknown, partly given to the low incidence of lesions affecting some of these areas (i.e. lesions in medial parietal regions are rare (Cavanna and Trimble, 2006)) and the fact that isolated unisensory alterations do not produce alterations in bodily experience (Serino et al., 2013).

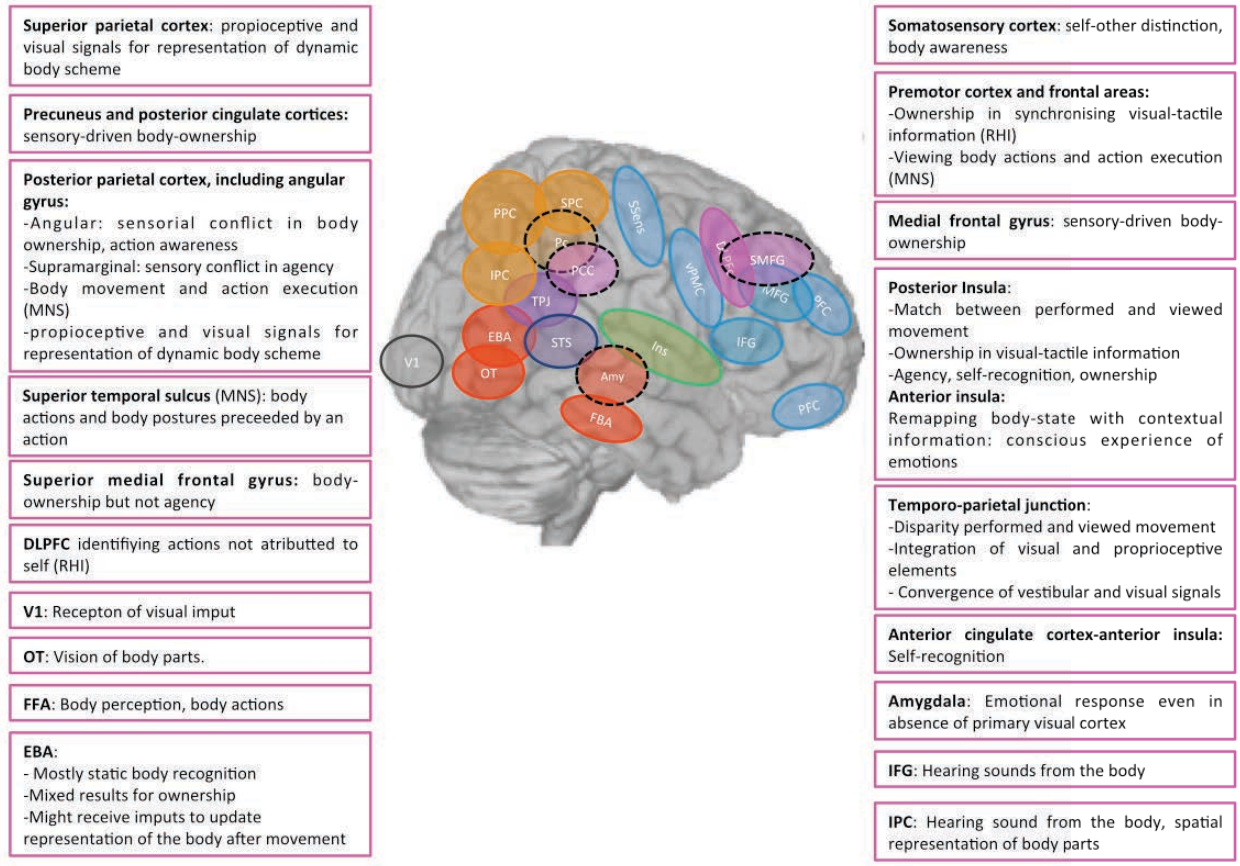

Figure2. Representation of different areas involved in body perception.
V1: primary visual cortex-area V1. FBA: fusiform body area. EBA: extrastriate body area. Amy: Amygdala. STS: Superior temporal sulcus. TPJ: temporo-parietal junction. PCC: posterior cingulate cortex. Pc: precuneus. PPC: posterior parietal cortex. SPC: superior parietal cortex. SSens: somato-sensorial cortex. vPMC: ventral premotor cortex. SMFG: superior medial frontal gyrus. PFC: prefrontal cortex. MFG: middle frontal gyrus. MNS: mirror neuron system. RHI: rubber hand illusion. Dashed circles are depicted for medial structures. OT: occipito-temporal cortex. IFG: inferior frontal gyrus. IPC: inferior parietal cortex. DLPFC: dorso-lateral prefrontal cortex. Information extracted from (Serino et al., 2013; Tsakiris et al., 2010; Tsakiris, 2010).

4.1.3. Neurocognitive alterations related to abnormal body perception in AN

There has been a long debate on whether a **primary alteration in perceptive processing deficits** may exist in patients with AN, and results are **still mixed and inconclusive** (Cash and Deagle, 1997; Fernández-Aranda et al., 1999; Gardner and Brown, 2014; Hennighausen et al., 1999; Legenbauer et al.,

2014; Skrzypek et al., 2001; Smeets et al., 1999). Indeed, one important critique of the models used to evaluate alterations in body size perception in these experiments is the lack of a direct comparison with a picture of the body size of the affected person, but rather rely on the body size storage that she/he has in her/his memory (Stein and Corte, 2003). However, most of the authors would agree in that body distortion **is not a perceptual disturbance *per se*** (Skrzypek et al., 2001).

Alterations of body image processing in AN have mostly been **evaluated through the presentation of own size-distorted body image.** However, this response seems to be highly variable, with over- but also underestimation of body sizes (Hennighausen et al., 1999; Probst et al., 1995), or no differences (Gardner and Brown, 2014). This variability of results is suggested to be related to either different **methodological** approaches (Gardner and Bokenkamp, 1996), to the putative presence of **altered perception in a more severe group of patients** (Skrzypek et al., 2001), to the **influence of interceptive awareness** on body size estimation (Kaye et al., 2009; Waldman et al., 2013), or to a **lack of differentiation between the perceptive and the affective/cognitive components** (Madsen et al., 2013). In this context, however, there is at least one clear **cognitive bias, which allows for the accurate estimation of another's body shape** estimation as opposed to an **inaccurate estimation of one's own** body shape (Benninghoven et al., 2007; Vartanian and Germeroth, 2011).

To evaluate perceptive functions irrespective of the interference of different functions associated with body processing, some other studies evaluated **visuo-spatial cognitive functions irrespective of body size**, mostly using the corresponding subscores of the Wechsler Adult **Intelligence Scale** (Wechsler, 2008) and the Rey–Osterreith Complex Figure (**RCFT**, (Meyers and Meyers, 1995)), which suggested **sub-optimal performance** in **AN and at risk-populations** (Madsen et al., 2013), although the interpretation of these findings in the context of body (visual) perception is unclear. For example, RCFT is often used to evaluate alterations in **central coherence**, a specific perceptual **cognitive style** which describes enhanced attention to local details at the expense of global processing (Lopez et al., 2009), which has been observed in both **active and recovered AN** participants and their unaffected sisters, and in **adults and adolescents** (Roberts et al., 2013; Tenconi et al., 2010). Interestingly, a few studies have suggested instead greater difficulties in the **integration of multimodal information** [i.e. visual-tactile and visuo-propioceptive (Case et al., 2012; Keizer et al., 2011)]; for example, AN patients underestimated whether an aperture was wide enough to pass through in Guardia et al. and Keizer et al. (Guardia et al., 2010; Keizer et al., 2013), or presented increased sensitivity to the and rubber hand illusion[2] in Eshkevari et al. (Eshkevari et al., 2012). However, further research in this area will be needed.

In summary, there is no conclusive evidence of purely perceptive (or bottom-up) alterations in body perception in AN, and some of the **positive results derived from neurocognitive tasks are likely to be influenced by attitudinal components of body distortion** (Epstein et al., 2001; Keizer et al., 2011).

4.1.4. Functional MRI findings related to abnormal body perception in AN

fMRI studies on AN have **rarely conceptualized body image perception as a multidimensional** construct, and, instead, have evaluated responses to body stimuli as unitary. In their review, Gaudio and Quattrocchi (Gaudio and Quattrocchi, 2012) summarized the results of fMRI studies using body image

[2] In the rubber hand ilusión, participants view a rubber hand placed in front of them, slightly to one side but in a similar position to their own hand, hidden from view. Both the rubber hand and the participant's own hand are then stroked, either synchronously or asynchronously. When the fake hand is stroked in synchrony with one's own hand, one feels the touch on the fake hand as if the fake hand belonged to oneself. However, this illusion is reduced if the stroking of the fake and real hand is asynchronic.

stimuli and divided them into one of the three dimensions explained above: a) perceptive component: studies using viewing own and other real body images or body drawings; b) affective component: studies presenting distorted own body images or viewing/listening to unpleasant words regarding one's own body; c) cognitive component: studies eliciting beliefs concerning body shape and appearance such as with the viewing of words concerning body image. With this approach, they defined a **posterior parietal network** including the inferior parietal cortex, the precuneus and the occipito-temporal cortex (including EBA) subserving the **perceptual component,** and a **prefrontal cortex-insula-amygdala network** (extending to ACC and ventral striatum) for the **affective component**. The **specific bases of the cognitive component were questioned,** and the authors highlighted the **difficulty of disentangling the affective vs. cognitive responses** in the reviewed **fMRI studies**. Indeed, the structures discussed for this *cognitive* dimension included the amygdala, the medial prefrontal cortex and the posterior (inferior) parietal cortex, in a clear **overlap** with other components (Table 2). As a general conclusion, however, they stated that while the **involvement of parietal areas (the inferior parietal cortex, the precuneus), the prefrontal cortex and the insula** in altered body image perception in AN appeared more reliably, alterations in either the **amygdala or EBA region were more inconsistent**. Despite the interesting results of this review, the interpretation was probably **limited by the different methodologies** used, and the ***a posteriori* definition** of which particular **component of body perception** was evaluated in each study (Gaudio and Quattrocchi, 2012).

A summary of fMRI studies assessing body perception in AN can be found in Table 4. Relevantly, the experimental designs used (i.e. comparing distorted versions of the participants' bodies with their real bodies or with non-bodies) might have favored the emergence of other areas involved in emotion (e.g., the fear network) and visuo-attentional processes (Castellini et al., 2013; Miyake et al., 2010; Mohr et al., 2010; Seeger et al., 2002; Wagner et al., 2003). Instead, comparing **one's own body image with the body image of another** has been suggested to be **less emotionally driving** (Sachdev et al., 2008), and to provide more specific information about self-related body processing (Berlucchi and Aglioti, 2010). Two studies used this approach, although they used headless bodies and indicated, prior to the images, the belongingness (or not) of the body to the participant (Sachdev et al., 2008; Vocks et al., 2010). Common areas of difference included a **fronto-parietal circuit**, with Vocks et al. (Vocks et al., 2010), comparing the self condition to a cross-fixation baseline, with no direct comparison between self and other conditions.

4.1.5. Body image, identity, relation to the world and social communication

Body perception involves elements of internal and external interoception, and the link between bodily-awareness (and interoception) with self-awareness is well established, with **body processing** being an important contributor to the **self-concept** (Stowers and Durm, 1996; Webster and Tiggemann, 2003) and to a more general **sense of the self** (Ainley et al., 2014; Seth, 2013). Noteworthy, the body is our **interface with others** (Adolphs, 2009), and, therefore, is relevant for social communication. Own-body awareness is likely to be involved in the perception and acknowledgement of another's movements and another's body communication (Berlucchi and Aglioti, 2010). In a more general sense, **awareness of the self is integral to many aspects of social cognition**, which suggests a strong **link between body perception and the understanding of another's mind** (Bosbach et al., 2005; Cavanna and Trimble, 2006; Tsakiris et al., 2010).

4.2. Reward and motivation

4.2.1. Reward system in the brain- responses to different stimuli

The reward system is probably the best-known network of the brain. It is mostly formed by the **dopaminergic** flow between the **ventral tegmental area (VTA**) in the **midbrain** and the **striatum (mostly ventral striatum, VS, containing the nucleus accumbens),** projecting to **frontal and limbic areas** such as the **amygdala, the ventromedial prefrontal (vmPFC) and orbitofrontal cortices (OFC) and the insular cortices** (i.e. mesolimbic and mesocortical dopaminergic pathways) (Berridge and Kringelbach, 2015; Knutson and Cooper, 2005; O'Doherty, 2004). Within this network, the **OFC, amygdala and ventral striatum code for different aspects of the rewarding stimuli**, while the **vmPFC, and insular cortices might be more involved in monitoring or predicting** reward values rather than in the pure generation of pleasure (Berridge and Kringelbach, 2015). **Dorsal parts of the striatum** (dorsal caudate and putamen) might be additionally involved in some reward responses, but they seem to respond to the **reinforcement** of an action and the feedback received, rather than in reward *per se* (Delgado, 2007). In this context, some authors suggested the existence of a **ventromedial to dorsolateral gradient in the flow of information** within the striatum during affective learnig (Voorn et al., 2004) (see Figure 3).
The firing of dopamine neurons has been linked to the facilitation of motor, cognitive and motivational processes, such as signalling for novelty, and learning (Daniel and Pollmann, 2014). Dopaminergic neurons mostly respond to the **anticipation of reward, i.e.,** response to non-predicted rewards or cues for a rewarding outcome, but do not generate a response when the reward is fully predicted (Mirenowicz and Schultz, 1994; Ungless, 2004). The difference between the responses to actual and expected reward provides an index for learning, the **prediction error signal**.

Dopamine (and the reward system in general) responds to a wide variety of stimuli, including the ones satisfying primary (e.g. food, sex) or secondary needs (e.g. money) (Kandel et al., 2012). Several studies have additionally evidenced **responses in this system to more complex forms of reward** such as **social stimuli**, including gaze direction, images of romantic partners and even to the experience of being liked, or having a good reputation, among others (Daniel and Pollmann, 2014; Davey et al., 2010; Fareri and Delgado, 2014; Izuma et al., 2008; Lin et al., 2012). The **overlapping response** between **social** and another sorts of rewarding stimulus (i.e. **money**) has been proven in at least two studies (Izuma et al., 2008; Lin et al., 2012), which showed common activation at the **level of the striatum** and **ventromedial prefrontal cortex** (vmPFC). While the **ventral striatum** (and probably some cortical areas) seem to encode for **reward irrespective of the type of stimuli**, other areas might have **specific responses** to specific stimuli, as is the case of the **dorsomedial prefrontal cortex** (dmPFC), which has been suggested to participate uniquely in **social rewards** (Izuma et al., 2008). In social contexts, however, and given the **complex nature of social relationships** [involving functions such as social cognition, emotion processing and regulation (Kennedy and Adolphs, 2012; Ochsner, 2008)], the reward system is activated in conjunction with other networks such as the ones involved in **theory of mind and self-related regions** (Davey et al., 2010). A **similar specific response** might be found in the **hippocampus** (in its connections with the VS), which could be particularly relevant in the processing **food and drug reward** (Floresco et al., 2001; Gourley et al., 2010; Kelley and Mittleman, 1999; Mittleman et al., 1998; Schmelzeis and Mittleman, 1996).

Finally, it is worth mentioning the two components in which reward can be further subdivided, **'liking'** and '**wanting**', which activate **partially overlapping but rather different neuroanatomical pathways**.

Specifically, on the one hand, '**liking**', or the **hedonic experience** of reward, is modulated by **opioid, cannabinoid** and **GABA**-related activity and involves responses in **emotion-regulation brain areas**, such as the orbitofrontal cortex and the anterior cingulate, the insular cortex, the amygdala, a specific region in the shell of the nucleus accumbens, the ventral pallidum and deep brainstem sites. On the other hand, '**wanting**', or the **motivational** value (incentive salience) of reward, mainly involves a dopaminergic response (and also other molecules such as opioids) in the core and shell of the nucleus accumbens and the aforementioned **mesolimbic and mesocortical pathways** (Berridge, 2009).

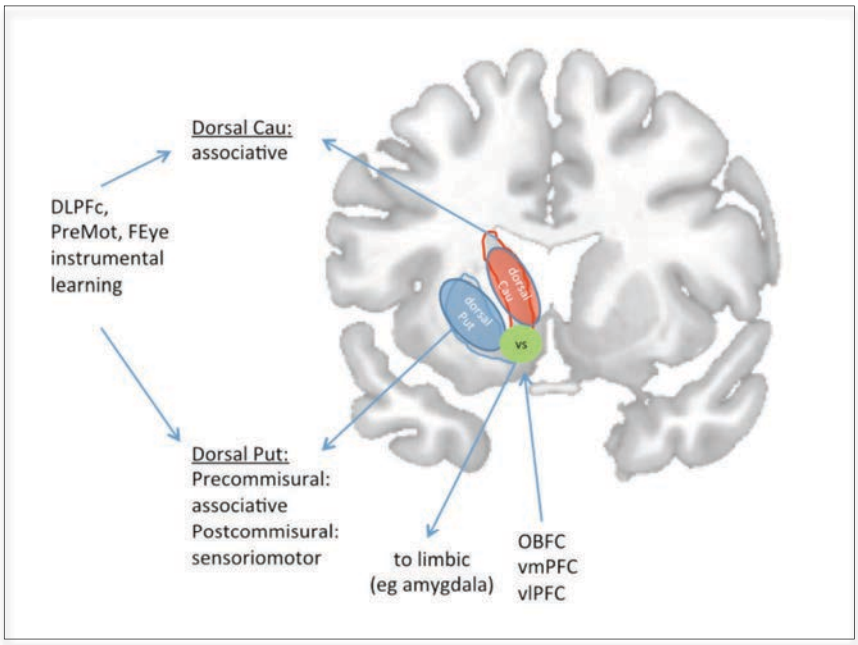

Figure 3. Representation of the ventral striatum (VS), and dorsal striatum (Cau: caudate, Put: putamen) and its connections. OFC: orbitofrontal cortex, vmPFC: ventromedial prefrontal cortex, vlPFC: ventrolateral prefrontal cortex, DLFPC: dorsolateral prefrontal cortex, PMC: premotor cortex, FEye: frontal eye fields.

4.2.2. Reward and punishment

In general, most studies **have not directly addressed responses to punishment,** but they have been explored **in conjunction with reward responses in reward-based learning** paradigms (Keating, 2010). This is probably due to the fact that reward and punishment, although being on opposite ends of a dimension, **mostly rely on the same brain regions** (Rogers, 2011). For example, the **ventral striatum despite being more sensitive to reward,** responds **to both types of stimuli** although **in opposite directions**: VS activation is **sustained after a reward but decreased after receiving a punishment** (Delgado et al., 2000). A similar pattern is suggested at the molecular level, with differences in a **tonic vs. phasic** response for **dopamine and serotonin**: while in reward, a tonic-serotonin signal might code for sustained reward and dopamine for the phasic one of reward prediction error, in punishment, the opposite might be true (phasic serotonin for punishment prediction error and tonic dopamine for sustained punishment) (Daw et al., 2002; Rogers, 2011). In this context, punishment is suggested to be **greatly modulated by the serotoninergic** flow (Cools et al., 2008), and, indeed, some studies have suggested that activation of the ventral striatum during punishment is non-dopaminergic (Ungless et al., 2004).

According to the notions above, it is logical to expect a **greater involvement of limbic or emotionally-regulatory regions** in punishment as compared to reward, such as the **dorsal anterior cingulate, the insula, thalamus and orbitofrontal cortex, but with some degree of overlap with reward responses** (Blair et al., 2006; Wrase et al., 2007). Although not sufficiently explored, evidence for **some specificities** between rewarding and punishing motivational systems involve the **vmPFC** being more involved in **reward** while **ventro-lateral parts of the PFC in punishment** (Blair et al., 2006; O'Doherty et al., 2001). Interestingly, the responses in the **dorsal anterior cingulate** and the **anterior insular cortex** have been also associated with responses to **pain and negative social experiences** and rejection (Eisenberger, 2012; Meyer et al., 2015). The response in the **inferior frontal cortex and anterior insula** has been additionally linked to punishment (Hester et al., 2013), although the **insula** seem to code for the **probability of the outcome** (either rewarding or punishing) more than punishment *per se* (Chase et al., 2015).

4.2.3. Alterations of the reward system in AN

Patients with AN have an **ego-syntonic resistance to eating** despite the intrinsic and adaptive rewarding properties of food (Kaye et al., 2009). In addition, they are less prone to experience physical pleasure throughout their lifetime (Davis and Woodside, 2002). Increasing evidence has suggested **distortions of reward (and punishment) brain system response**, both for disease-specific and disease-nonspecific stimuli in AN. These alterations have been observed in acutely ill AN patients and in recovered subjects, and have been considered a **potential trait marker** of the disorder (Frank et al., 2012a).

While early studies already suggested a **rewarding effect of starvation itself** (hypothesized through an hypercortisolemic and hyperdopaminergic state) (Bergh and Södersten, 1996), some years later, the **animal model** of **self-starvation/activity-based anorexia (ABA**) provided evidence for the implication of the reward system in starvation and in AN (see (Kim, 2012)). Specifically, when ABA rodents are imposed with a restricted food schedule, such as 60 minutes/day of food access, weight is maintained until a running wheel is introduced at all times except for eating time. In these circumstances, the rodent will decrease food intake and might starve to death. This model shows alterations in the responses to reward and behavioral changes which mimic AN symptoms (hyperactivity) only derived from changes in the pattern of food consumption. Other biological evidences of this imbalance come from alterations in the **concentrations of dopamine and its D2 receptor** found both in AN **patients and recovered** subjects (Frank et al., 2005; Frank, 2013; Kontis and Theochari, 2012), and the **low dopamine metabolites** found in the acute state and after recovery (Kaye et al., 1984; Kaye et al., 1999). Another rather abandoned but possibly partly complementary theory would be the auto-addiction opioid model, which suggested self-starvation as a chemical dependence to endogenous opioids (Davis and Claridge, 1998; Marrazzi et al., 1997). Indeed, some studies found either increased levels of CSF opioid activity (Kaye et al., 1982) or increased plasma levels (Marrazzi et al., 1997) in AN. This system might participate in dopamine level increases by incrementing its release in the ventral striatum (Leone et al., 1991).

Other **conditioning processes** based on (or evolving to) this aberrant reward-system response have also been implicated in the pathophysiology of AN, where primary rewarding stimuli (such as food) might become aversive, and negative stimuli might become rewarding, as suggested by the ***contamination reward theory*** (Keating, 2010; Södersten et al., 2008). From a neurocognitive perspective, AN patients might be characterized by an **increased capacity to delay reward** [e.g. in a monetary task in AN, (Steinglass et al., 2012)], although **this was not replicated** in a second study [AN patients and recovered subjects (Ritschel et al., 2015)] or normalized with recovery in a third study (Decker et al., 2014). However, at least AN patients seem to **associate a greater value to long term reward –staying thin- than**

to satiating hunger in the short term (Kaye et al., 2009); indeed, cognitive–behavioral models suggested the **potent reinforcement value associated with dieting and weight loss** (Garner and Bemis, 1982).

It is unclear, however, whether these alterations represent a cause or a consequence of the disorder. They might be linked to certain personality traits which, in conjunction with other factors, provide elevated **vulnerability** for AN. Alternatively, if a normal reward-system is present in AN, when facing the physiological alterations of the disorder, it might be forced to respond in a **compensatory** manner. It could also be that all of these possibilities are true (Berridge, 2009).

4.2.4. Social interactions in AN and its relationship with reward and punishment

Being able to **adaptively process rewarding** (and non-rewarding) information is **essential** in daily life, most relevantly in our social environment (Behrens et al., 2009; Kennedy and Adolphs, 2012). Learning from trial and error (reinforcement learning) allows us to predict outcomes and to respond in a more beneficial manner, by either maximizing rewards or avoiding punishments (Daniel and Pollmann, 2014). **AN patients** tend to perceive **low (or negative) reward** in **social contexts** (Schmidt and Treasure, 2006), while being **oversensitive and attention-biased towards being rejected, but also avoidant of social rewards** (Cardi et al., 2013; Watson et al., 2010). This **negative bias** is considered to be a key element of poor social relationships and ultimately in the maintenance of the disorder (Rieger et al., 2010). Other interacting systems, such as the ones for social cognition and emotion regulation, are explained in section 5.4.

4.2.5. Summary of functional MRI findings

A summary of the fMRI studies in AN using reward paradigms is shown in Table 5. Most the studies have evaluated the response to **tasting pleasurable stimuli**, which naturally activates the reward system, and involves the use of a stimuli (i.e. a pleasurable drink) that is highly salient in the context of AN. Interestingly, two studies (in adults and adolescents) explored the response to **stimuli not related to the disorder**, using a **gambling paradigm** (Bischoff-Grethe et al., 2013; Wagner et al., 2007). Most of the studies have used **region-of-interest analysis** (ROI), mainly at the level of the **ventral striatum**. In this region, studies have found either an **exaggerated response** to the **visualization of underweight subjects** (Fladung et al., 2010) or to **monetary losses** in acutely ill AN patients (Bischoff-Grethe et al., 2013), but a **decreased** response during **sweet tasting** (Wagner et al., 2008) or a **non-discriminative** activation for **wins and losses** during a monetary reward task in recovered subjects (Wagner et al., 2007). Other reward-related structures have also been identified as dysfunctional during reward tasks in AN, including the **anterior insula** cortex and the **ventromedial prefrontal cortex** (Frank, 2013; Kaye et al., 2013; Keating et al., 2012). Additionally, the **anterior cingulate cortex** and its connections was suggested to be relevantly implicated in the generation of *contamined* conditioning responses in AN, although it has not been formally tested (Keating, 2010).

4.2.6. Integration of reward system alterations to a dysfunctional BIS-BAS system

Some authors have suggested that patients with eating disorders (including AN) present, along a continuum, an **imbalance between alterations in inhibitory and reward responses** (Wierenga et al., 2014). In this model, **alterations in rewarding responses would be associated with increased inhibitory** control in AN, associated with high levels of **anxiety and increased sensitivity to punishment**. These alterations would be mediated by a failure in the **ventral limbic circuit** (ACC, vmPFC, VS) and the **dorsal**

cognitive network (dACC, vlPFC, DLPFC, insula, parietal cortex) (Kaye et al., 2009; Wierenga et al., 2014). This model fits with the idea of a circuit for an **approach and avoidance** system (BIS-BAS) (Gray, 1981), or the corresponding **positive and negative valence** systems of ROAMER criteria (Schumann et al., 2014)).

4.3. Social cognition network

4.3.1. Social impairment in AN

Patients with AN present **difficulties in interpersonal social relationships** and these are suggested to be present **prior to the disorder**, contribute to its **maintenance** and influence **prognosis** (Zucker et al., 2007) and **recovery** (Noordenbos, 2011). AN patients and recovered subjects are more likely to be **single, unemployed, report greater work and social difficulties,** suffer from **social anhedonia** (Harrison et al., 2014; Tchanturia et al., 2012), and tend to have **small social networks** (Striegel-Moore et al., 2003) and **little social interaction** (Krug et al., 2013). Several factors might contribute to the well-accepted **socio-emotional dysfunctional pattern** of AN patients (Harrison et al., 2010a; Oldershaw et al., 2011; Schmidt and Treasure, 2006), such as alterations in **social cognition processes**, **emotion identification** and **emotion dysregulation**, alterations in **self-evaluation**, comorbid **anxiety** or high anxiety-avoidant traits, or even alterations in **social learning and reward evaluation** functions (as detailed in section 5.3.4) (Cardi et al., 2013; Fonville et al., 2013; Harrison et al., 2012; McAdams and Krawczyk, 2011; Schmidt and Treasure, 2006).

Alterations in the **identification of emotional states** have long been observed in patients with AN (Bruch, 1962). Studies have identified **high levels of alexithymia** in AN patients and their healthy siblings (Rozenstein et al., 2011). These deficits are characterized by difficulties in **differentiating emotion from body sensations** (Nowakowski et al., 2013), the **interpretation of these sensations or by suffering from low levels of interoceptive awareness** (Lilenfeld et al., 2006). Relevantly, **exerting control over food, eating, body shape, weight and the achievement of thinness** is suggested to be a **compensation of such socio-emotional dysregulatio**n (Frank, 2013; Rusell, 1995; Wildes et al., 2010; Zucker et al., 2007). Indeed, this might provide the feeling of **being in control** of the **inherent unpredictably of social relationships** and, at least in early stages, produce **social reward** through changes in appearance (Fassino et al., 2004; Walsh, 2013). In close relation, **high levels of intolerance to uncertainty**, or the inability to cope with the discomfort of having to handle a changing context without an immediate solution (Birrell et al., 2011), were also identified in AN (Abbate-Daga et al., 2015; Frank et al., 2012b; Sternheim et al., 2011). Interestingly, intolerance to uncertainty is a measure associated with **worry and closely linked to anxiety disorders** (Abbate-Daga et al., 2015; Anderson et al., 2012). Importantly, some studies have pointed to the presence of **anxiety as at least a partial mediator** of **socio-emotional difficulties** (Hambrook et al., 2012; Zucker et al., 2007), being suggested that **social stimuli could be threatening to AN patients** (Harrison et al., 2010a; Harrison et al., 2010b). Indeed, AN patients tend to present **emotion avoidance while having rigid and maladaptive emotion regulation strategies** (Abbate-Daga et al., 2015).

Most studies have mainly focused on the evaluation of emotion processing through the presentation of **emotional faces** as well as on the study of **social cognition processes**. When emotional faces where presented, a majority of the studies found **poor performance in emotion recognition**, including studies of **recovered** subjects (Castro et al., 2010; Harrison et al., 2010a; Jansch et al., 2009; Jones et al., 2008; Kucharska-Pietura et al., 2004; Oldershaw et al., 2010; Russell et al., 2009). Likewise, AN patients also performed poorly at **recognizing emotions from body motion** (Lang et al., 2015). These results, however, were not supported in at least two studies (Kessler et al., 2006; Mendlewicz et al., 2005), and some

authors have reported instead an **attentional avoidance of faces** (Cardi et al., 2015; Harrison et al., 2010b; Watson et al., 2010), with increased attention being given to another's body (Watson et al., 2010)]. Addintionally, in a second study by Harrison et al. (Harrison et al., 2010a) a **bias towards negative-valance faces** was reported, further supporting a general **negative bias during emotional processing**.

Other experiments evaluated putative deficits in **social cognition processes**, preferably through the examination of **Theory of Mind** processes (ToM, or the ability to infer mental states and emotions in others). In this context, some authors have highlighted the link between AN and autism, on the basis of an increased proportion autistic traits in samples of AN and similar behavioral traits and neuropsychological profiles, including alterations in ToM tests (Gillberg, 1992; Rhind et al., 2014). Results, however, have been **rather conflicting,** and, if present, alterations might be more **associated to emotion recognition** alterations rather than to cognitive processing (Adenzato et al., 2012; Oldershaw et al., 2010). Nevertheless, there seems to exist a particular **cognitive style shared** with autism, including **rigidity and weak central coherence** (detail-focused over global processing, commonly found in autism, see 5.2.3), which is suggested to be a vulnerability trait (Treasure, 2013) that might be relevantly involved in **disturbed social interactions** in AN (Treasure and Schmidt, 2013a). Weak central coherence might be specifically impaired in restrictive subtype patients but not in the binging-purging subtype (Van Autreve et al., 2013).

4.3.2. Definition of the social cognition system

Social cognition is a broad term used to include all those functions which, by conforming **mental representations of the relationships that exist between oneself and others**, is used to **respond** adaptively to the **social environment** (Adolphs, 2001). It involves processes such as perceiving social signs, but also connecting them with motivation and emotion, requiring memory, decision-making and attentional abilities (Adolphs, 2001). According to the classification by Gazzaniga (Gazzaniga, 2009), components and networks of the *social brain* can be divided in those relevant to self-awareness, mentalizing, self-regulation and detection of threat, although others have also been suggested (Happé and Frith, 2014).

Self	1. SELF-AWARENESS: a. selfhood: ventromedial prefrontal cortex, -vmPFC- . b. keeping track of own actions, representation of one's goals, agency: intraparietal sulcus –IPS-. c. autobiographical memory: retrosplenial cortex, parahippocampal gyrus, temporoparietal junction –TPJ-,medial frontal cortex, temporal pole, cerebellum, and the hippocampus.
Other	2. MENTALIZING (inferring another's states of mind or emotions): Medial prefrontal cortex –MPFC-, TPJ, medial parietal cortex.
Relationship with other	3. SELF-REGULATION 4. THREAT DETECTION: Prefrontal cortex-anterior cingulate cortex (ACC)-dorsal and ventral, amygdala.

Table 3. Areas included in the social cognition network and their classification according to Gazzaniga (Gazzaniga, 2004) and its relationship to a self-other-relationships model.

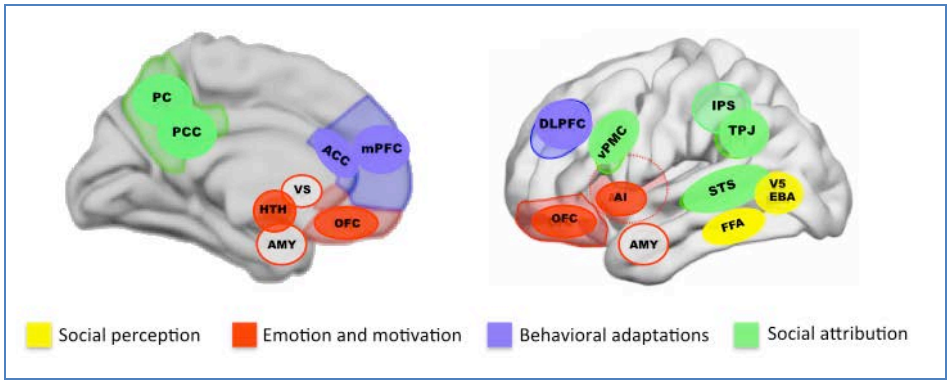

Figure 4. Social cognition network. Extracted (and partially adapted) from Billeke & Aboititz (Billeke and Aboitiz, 2013). Yellow: social perception. Red: emotion and motivation. Purple: behavioral adaptations. Green: social attribution (self and other). EBA: extra-striate body area, FFA: fusiform face area, AMY: amygdala, AI: anterior insula, ACC: subgenual and perigenual anterior cingulate cortex, OFC: orbitofrontal cortex, VS: ventral striatum, HTH: hypothalamus, dlPFC: dorsolateral prefrontal cortex, mPFC: medial prefrontal cortex, vPMC: ventral premotor cortex, STS: superior temporal sulcus, PCC: posterior cingulate cortex, PC: precuneus, IPS: inferior parietal sulcus.

4.3.3. Self-reference, the default mode network and their relationship with social cognition

There is a high overlap between the areas relevant for self-reference and mentalizing, as the **self is most probably used as a frame to understand others' thoughts and behaviors** (Adolphs, 2001; Gazzaniga, 2009). While the areas involved in the understanding of the 'other' have mainly been evaluated through ToM tasks, the neural circuit for **self-reference processes** has mainly been evaluated during resting conditions. Indeed, one of the networks with high-syncronic activity during resting periods, the **default mode network** (DMN, see 6.2.3.1.), is the main brain network considered to be involved in self-related processes such as autobiographical memory recall, prospective thinking and self-judgments (Harrison et al., 2008; Northoff et al., 2006; Preedy, 2011; Raichle et al., 2001; Zhu et al., 2012), including the **evaluation of one's own body and the sense of body-ownership** (Northoff et al., 2006; Tsakiris et al., 2010). These areas include the **posterior cingulate cortex and the precuneus, the inferior parietal cortices, bilateral lateral temporal cortex, the insula, and the dorsal and ventral areas of the medial frontal cortex** (Raichle et al., 2001) (a figure corresponding to DMN areas is included as Supplementary material in Study 3, chapter 5). Despite the overlap in networks subserving *self* and *other* (social cognition) processing, only recently a study has evaluated them together (Herold et al., 2015).

4.3.5. Summary of functional MRI findings

Only a few studies have evaluated **socio-emotional responses** in AN using fMRI, and tasks are methodologically diverse. However, a pattern of decreased activity in ToM regions such as the **temporal sulcus and middle temporal gyrus** has been observed (McAdams and Krawczyk, 2011; Schulte-Rüther et al., 2012). In addition, alterations in **midline structures** seem to be present when the task relates to identity (McAdams and Krawczyk, 2014).

Other studies have evaluated **resting-state alterations** in the **connectivity of DMN** regions, finding alterations either between the anterior cingulate and the precuneus (Lee et al., 2014; Mcfadden et al., 2014), or between the DMN and the frontal and parietal cortices (Cowdrey et al., 2014), which were

suggested to imply a dysfunctional self-referential network involved in rumination about body shape, weight and eating (Cowdrey et al., 2014). Finally, Boehm et al. (Boehm et al., 2014) found increased functional connectivity in the anterior insula, which was associated with self-reported deficits in interoceptive awareness in controls. A summary of studies using socio-emotional paradigms and during resting state can be found in Tables 6 and 7.

4.4. Network identification in structural MRI studies

Voxel-based morphometry studies have usually found a **decrease in the volume of brain gray matter** in patients with AN (Van den Eynde et al., 2012). **Consistent with all the functional findings** commented above, studies with currently ill AN patients with anorexia nervosa have shown **widespread grey matter decreases** in the **neocortex and in areas linked to emotion regulation and reward**, such as the anterior cingulate, orbitofrontal cortex, insular cortex, hippocampus/parahippocampus, the amygdala and striatum (Brooks et al., 2011; Van den Eynde et al., 2012; Fonville et al., 2014). However, other studies have reported grey matter increases in neocortical (Brooks et al., 2011; Frank et al., 2013a; Frank et al., 2013b) and limbic regions (Frank et al., 2013a; Frank et al., 2013b). Similar findings have been also observed in **white matter**. Of the few studies evaluating regional changes in white matter volume, most showed **decreases in fronto-temporo-parietal** and **sensoriomotor** regions in adult patients (Frank et al., 2013a; Kazlouski et al., 2011; Swayze et al., 2003), although three **other studies found either no differences** (Boghi et al., 2011; Roberto et al., 2010) or white matter **increases in temporal and hippocampus** regions of **adolescent** patients (Frank et al., 2013b). Complementarily, studies evaluating **microstructural alterations** with diffusion tensor imaging have commonly found alterations either in **long-range fibers** connecting **fronto-parietal** (Frank et al., 2013a; Frieling et al., 2012; Nagahara et al., 2014) or **fronto-occcipital** (Frank et al., 2013a; Hayes et al., 2015; Kazlouski et al., 2011) regions, or in **subcortical connections –most relevantly in the fimbria-fornix region** (Frank et al., 2013a; Frieling et al., 2012; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014). Although **some of these alterations may normalize** in recovered patients (Castro-Fornieles et al., 2009; Van den Eynde et al., 2012; Lazaro et al., 2013; Wagner et al., 2006a), **other studies have shown the persistence of volume alterations** in recovered patients (Frank et al., 2013a; Joos et al., 2011; Mühlau et al., 2007). A summary of these studies can be found in Table 8.

Table 4. Summary of fMRI studies using body stimuli paradigms.

Author, year	Study	n	Subtype	Technique	Age	Stimuli		Instructions	Contrast	Comparison	fMRI analysis	Correction	Results
					Years(sd)	Task	Control						
Seeger 2002	T	3	AN	fMRI	17(0.5)	Body(distorted self/distorted other)	Non-body	Look	Distorted self> distorted other + non-body images	AN>HC	WB	<.001 uncorr	Brainstem, Amyg, Fus
Wagner 2003	T	13	10 RAN, 3 BPAN	fMRI	15.3(1.4)	Body(distorted self/distorted other)	Scrambled body (self)	Look	Distorted self> scrambled body	AN>HC	WB	<.001 uncorr	PFC (BA9), IPC (BA40), IPC
Uher 2005	T	13	7 RAN, 6 BPAN	fMRI	25.4(10.2)	Body drawings (other-lowBMI/other-normal/other-highBMI)	Non-body	Look, rate and feel	All body drawings>non-body drawings	AN<HC	WB	<.01, cluster-level	SPL, Fus
Sachdev 2008	T	10	5 RAN, 5 BPAN	fMRI	22.6(2.07)	Body (self)	Body (other)	Look	Self>other	AN<HC	WB	<.001, uncorr cluster-level	Pc, LG, MFG, Ins
Redgrave 2008	T	6	1 RAN, 5 BPAN	fMRI	27(5.0)	Colored words (positively thin valenced/negatively fat valenced)	"XXXX"	Look and press	Positively valanced thin words>"XXXX"	AN>HC	WB	<.005 uncorr voxel + <.05 cluster-based	Cluster 1: PCG, PreCG, STG, I, TTG; cluster 2: PMC (BA6), SFG, dACC
									Negatively valanced fat words>"XXXX"	AN<HC			Cluster 1: IFG, MFG, PreCG; Cluster 2: SPL, Pc, IPC
Mohr 2010	T	16	AN	fMRI	24.1(3.4)	Body satisfaction (distorted thinner self/self/distorted fatter self)	Body shape rating (distorted thinner self/self/distorted fatter self)	Rate shape and satisfaction	Thinner-self during satisfaction>Thinner-self durnig shape	AN>HC	WB	<.001 uncorr	Ins, MFG
									Fat-self during shape rating>Fat-self during satisfaction rating	AN<HC			Pc
Miyake 2010a	T	22	11 RAN, 11 BPAN	fMRI	22.2(4.1)/ 28.3(4.5)	Body (distorted self: thin,fat/distorted other:thin, fat)	Body (real self/other)	Rate and press	Fatter self>real self	RAN<HC	WB	<.001 uncorr + 10voxels	MPFC, DLPF
Miyake 2010b	T	24	12 RAN, 12 BPAN	fMRI	27.0 (9.0)/ 27.2 (4.8)	Negative words (body/emotional)	Neutral words	Rate	Body words>neutral words	AN>HC	WB	<.001 uncorr + 10voxels	Amyg, IPC
Vocks 2010a	T	13	BPAN	fMRI	29.08(9.79)	Body (self/other)	Cross-fixation	Look	Self>cross-fixation	AN<HC	WB	<.001 uncorr + 8 voxels	uncus, SPL, MFG, Fus, IFG, SFG, Hip-PHip
									Other>Cross-fixation	AN>HC			PCG, Thal, ParaCG, PCC, Hip, uncus, Fusi, Ins, MFG, MdlFG, Clau, SpMG, Cau, LG, IPC, Pc

Vocks 2010b	L(3m)	5	BPAN	fMRI	26.40(6.66)	Body(self pre-treatment/self post-treatment)	Cross-fixation	Look	Self post>Self pre	ANpost>ANpre	WB	<.001 uncorr + 8voxels	MTG
									Self post<Self pre	Anpost<ANpre			Pc, IFG, PCC, IPC, Fus, PHip
Friederich 2010	T	17	10RAN, 7 BPAN	fMRI	24.9(5.6)	Body (other)	Non-body	Compare with own	Body>non-body	AN>HC	WB	<.01 voxel-based + <.0025 cluster-based	Ins, Put, PMC, PCC
										AN<HC			rACC
Castellini 2013	T	21	RAN	fMRI	24.74(7.58)	Body (distorted thinner self/self/distorted fatter self)	Non-body	Look	Thinner-self>non-body	AN>HC	WB	ANOVA <.05 corrected + post-hoc:<.005 uncorr+100voxels	MTG
									Fatter self>non-body	AN>HC			IFG
Suchan 2013	T	10		fMRI	26(9)	Body (other)	Non-body	Look	Body>non-body	AN~HC	DCM(EBA,FFA,mOC)	DCM models-corr	Different effective connectivity: HC: mOC-EBA-FFA; AN: mOC-FBA-EBA
Suda 2013	T	20	AN	fMRI	27.0(7.5)	Body action-checking (other)	Other body actions	Look and imagine	Body checking>body action	AN<HC	WB	<.01 voxel-based + <.001 cluster-based	MPFc, Fus

Table 5. Summary of fMRI studies using reward-based stimuli paradigms.

Author, year	Study	n	Subtype	Technique	Age	Stimuli		Instructions	Contrast	Comparison	fMRI analysis	Correction	Results
					Years(sd)	Task	Control						
Frank 2005	T	3	recAN: 3RAN, 7BPAN	PET (D2/D3)	24(5)			none	[11C] raclopride binding	AN>HC	ROI (antero-VS with Nacc, control areas)	<.05 corr	Biding in VS. Trend: vPut, middleCau
Wagner 2007[A]	T	13	recAN		26.6(6.8)	correct/ uncorrect number guess	NA	Guessing and press	General amplitude of response	AN>HC	ROI-extracted eigenvalues (Cau,VS)	<.05 corr	Cau
									win>loose	AN<HC	WB		VS: No differentiation wins/looses in AN
									win>loose	AN>HC			PL (larger sustained response to wins, no difference in HC)
									win<loose				Put (larger earlier response to loose in AN)
									win>loose	AN<HC			PCC (less sustained repsonse to wins)
Wagner 2008	T	16	recRAN	fMRI	26.4(6.2)	pleasant solution taste	neutral solution taste	Tasting	both tastes across time-points	AN<HC	ROI-extracted time series eigenvalues (Ins, OFC, Amyg, ACC)	<.05 corr	Ins, dCau, mCau, ACC. No association with pleasantness ratings in AN

Fladung 2010	T	14	9 RAN, 5 BPAN	fMRI	24.36(7.58)	body image (other-underweight/ overweight)	Body image (normal BMI)	Feel/Press-estimate weight	feel-underweight>feel-normal	AN>HC	ROI (VS)	<.05 FWE corr	VS
Cowdrey 2011	T	15	recAN	fMRI	23.33(3.50)	pleasant/ unpleasant solution taste+/- image	neutral solution taste +/- image	Tasting, Press-rate	taste: pleasant >neutral	AN>HC	WB	<.05 FWE corr + 30voxels	VS, Put, PCC
									sight: pleasant>neutral	AN>HC			Occ, aPFC, SgACC
									taste+sight: pleasant>neutral	AN>HC			Pal
									taste: unpleasant>neutral	AN>HC			Ins, Put
									taste+sight: unpleasant>neutral	AN>HC			ACC, P-Opc, Cau, DLPFC
Brooks 2011	T	18	11 RAN, 7 BPAN	fMRI	26(6.8)	Food images	Non- food images	Imagine eating/using the food/object	Food>object	AN<>HC	WB	<.01 FDR corr	NR
Holsen 2012	T	22	12RAN, 10recAN	fMRI	21.8(2.7)/ 23.4(2.3)	Food images (high/ low calories). Pre/ post meal	Non- food images. Pre/ post meal	Look and press	Pre meal: high calories>non-food	AN<HC	ROI(hypth, NAc, Amyg, hip,OFC, ACC, AIns)	<.01 cluster SVC-FWE corr+ <.05 voxel FWE corr	hip,OFC,ACC, hypth (trend),Amyg(trend)
									Post meal: high calories>non-food	AN<HC			Amyg, AIns
									Pre meal: high calories>non-food	recAN<HC			AIns, hypth(trend),Amyg(trend)
Frank 2012	T	21	RAN	fMRI	22.52(5.79)	Taste conditioning learning (CS-pleasant taste)	Taste conditioning learning (CS-neutral taste, CS)	Taste	CS-reward>CS-neutral	AN<HC	WB	<.05 FWE corr+ 5voxels	SupMotor
									positive-prediction error★	AN>HC			OFC, aMPFc,mCC
									negative-prediction error★	AN<HC			OFC, SupMotor, MFC, Put, aVS, aMPFc, DLPFC, mCC
Bischoff-Grethe 2013[Δ]	T	10	RAN	fMRI	16.2(1.8)	correct/ uncorrect number guess	NA	Guessing and press	win>loose	AN<HC	ROI (NAc, aPut, pPut, aCau, pCau, rACC, cdACC, mdACC)	<.05 FDR corr	aPut, pPut(no differenciation in AN), mdACC
									win<loose	AN>HC			pCau, cdAC, pPut(trend)
									wins	AN<HC	WB	<.05 cluster-corr	aIns, dPCC,MFC,IPC, DLPFC,Phip,
									looses	AN>HC			SFC,Cbll, DLPLFc, IFG,aPut,MFG, dACC,PreCG, MTG,Po-CG, angular,

													claustrum, pracentr,
								looses	AN<HC				uncus, MTG,
Oberndorfer 2013	T	14	recAN	fMRI	27.3(1.4)	sweet caloric taste	sweet non-caloric taste	Taste	sweet caloric>sweet non-caloric	AN<HC	ROI(RectG, ACC, MFG, Cau, Ins, dCG, Sn, Thal) +WB	<.05 cluster-corr	aIns, dCau
Radeloff 2014	T	15	recRAN	fMRI	25.2(4.0)	Taste (caloric/ non-caloric)	Taste (water)	Taste	ANOVA(caloric,non-caloric,water)	AN<>HC	ROI (aIns, OFC, ACC, aVS, Cau, Amyg)	<.05 FWE corr	NR
											WB	<.001 cluster-level	NR
Decker 2014	L (weight restored)	25	AN	fMRI	19.3(2.5)	Economic Gain now [small-soon/ large-later)/not-now(small-soon/ large-later)]	NA	Press-Choice	Post>pre(larger-later>smaller-sooner)	AN>HC	WB	<.01voxel+ <.01cluster+41voxels	Str,dACC,DLPFC, PL
Ehrlich 2015	T	30	23 recRAN, 7 recBPAN	fMRI	21.98(3.19)	Economic Gain (three levels)	No reward	Press	Anticipation of reward	AN>HC	ROI (VS,mOFC,DLPFC)	<.05 cluster-corr	DLPFC (global activity)
									Reward feedback	AN<HC			DLPFC (correlation decreased DLPFC- increased reward level: less steep in AN)
									Anticipation of reward	AN>HC	WB	<.05 FWE corr	DLPFC,IFG,SupMotor,1Motor,CG,IPC
									Reward feedback	AN>HC			DLPFC
Sanders 2015	T	29	15AN, 15recAN	fMRI	25.6(5)/ 24.3(5)	Food images	Non-food images	Imagine eating/using the food/object	Food>object	recAN>HC	ROI (hypth, Str, Amyg, hip, Cbll, DLPFC, mPFC, OFC, ACC, Ins, visual, SFL, IPC, PCC)		Cau, Cbll, hip, vermis, post-central
										AN>HC			Cbll, hip, vermis
										recAN<HC			MFG
										AN<HC			MFG, SFG, Pc
Wierenga 2015	T	25	recAN (16RAN, 7BPAN)	fMRI	27.7(1.6)	Delay discounting: delay to early vs late reward	NA	Choose	Early choices: Hungry>satiated	AN<HC	ROI (VS, daCau, vmPFC, dACC, PCC, SPPC, MFG (DLPFC+PMC), Ins, VLPFC	<.05 FWE corr	VS, dACC, daCau, vmPFC, PCC
									All choices: Satiated>hungry	AN<HC			Ins, VLPFC
									All choices: Satiated>hungry	AN>HC			MFG
									All choices: Hungry>satiated	AN<HC			MFG

Table 6. Summary of fMRI studies using socio-emotional stimuli

Author, year	Study	n	Subtype	Technique	Age	Stimuli		Instructions	Contrast	Comparison	fMRI analysis	Correction	Results
						Task	Control						
Uher 2003	T	17	9 recRAN, 8 RAN	fMRI	26.9 (5.3)/ 25.6(2.8)	aversive images	neutral images	look	aversive>neutral	NR	WB	<.001 cluster-level:<1cluster false positive	O
Uher 2004	T	16		fMRI	26.93 (12.14)					AN>HC	WB	<.001 cluster-level:<1cluster false positive	CbII
										AN<HC			CbII
Miyake 2009	T	30	AN	fMRI	nda	emotional decision	nda	nda	nda	AN>HC	nda	nda	Amyg. PCC/ACC varied with alexithymia
McAdams 2011	T	17	recAN	fMRI	26.2 (7.0)	shapes with social attribution movement	shapes movement	are friends?/same weight?	social>shapes	AN<HC	ROI (common activations: IFG, MTG, MPFC, Pc, Fus, ACC, Tp, Occ + TPJ)	<.05 corr	IFG, TPJ, Fus, Tp, MTG
Cowdrey 2012	T	16	recRAN	fMRI	23.06 (3.55)	fear, happy faces		press (gender)	fear>happy		WB, ROI(Amyg, Fus)	<.05FWEcorr	O
Schulte-Rüther 2012	L (T2:weight recovery)	19	13 RAN, 6BPAN	fMRI	15.7 (1.5)	shapes with social attribution movement	shapes movement	are friends/are shapes strong?	social>shapes	AN<HC	WB	<.05FWEcorr	T1:STG; T2:MTG
										AN<HC	ROI (MPFC,TPJ,STG,Tp)	SVC<.05 corr	T1: MTG,TP; T2:TP
Fonville 2013	T	31	25 RAN, 6BPAN	fMRI	23(10)	happy/mid happy faces	neutral faces	press (gender)	Happy>mildly happy>neutral	AN>HC	WB	<1 type I error per map, cluster-corrected	Fusi
									neutral>baseline	AN<HC			LG
									neutral>baseline	AN>HC			Fusi,ACC,PoCG
									mildly happy>baseline	AN<HC			PCC
									mildly happy>baseline	AN>HC			IOG, Fusi, PoC
									happy>baseline	AN>HC			Fusi, PCG
McAdams 2014	T	18	recAN	fMRI	26.1 (6.1)	written apraisal identity: self/friend/reflected		press (how much do you agree)	identity: self>friend	AN<HC	ROI (activated areas)	<.0125 corr	Pc
									identity: friend>self	AN<HC			MFG
									identity:	AN<HC			CC

				reflected>self		
		phyisical apraisal: self/friend/reflected	physical: self>friend	AN<HC		ACC

Table 7. Summary of fMRI studies using resting state.

Author, year	Study	n	Subtype	Age: Years(sd)	Technique	Defined SEED/networks	Correction	Comparison	Results
Favaro 2012	T	45	29AN,16recAN	25.8(6.9)/23.8(4.8)	fMRI-ICA	Visual(ventral, medial, lateral), SMN	<.05 FDR corr	AN<HC	Occ-Temp(vVIS)
								recAN<HC	mdlFG(vVIS)
								AN>HC	SPL(Somatosens)
Favaro 2013	T	33	AN	26.9 (7.3)	fMRI: Seed-based	DLPFC, vmPFC, vlPFC	<.05 FWE corr	AN<>HC	NR (differences betwen ANmet-met and AN val-val for COMT
Amianto 2013	T	12	RAN	16.27 (0.99)	fMRI-ICA	Cbll	<.05 FWE/<.05 FDR corr	AN>HC	med Cbll, Ins, Tp, PCC
								AN<HC	lat Cbll, PL
Cowdrey 2014	T	16	recAN	23.06(3.55)	fMRI-ICA	12 RS (medial visual, lateral visual, auditory, sensory-motor, DMN, cognitive control, and FP)	<.05 FWE corr	AN>HC	Pc, DLPFC/IFG (DMN)
Lee 2014	T	18	AN	25.2 (4.2)	fMRI-Seed-based	dACC	<.001 uncorr+30voxels	AN>HC	Pc,rSpl
								AN<HC	DLPFC, vlPFC
Kullman 2014	T	12	AN	23.3 (4.7)	fMRI-seed-based effective connectivity)	IFG	<.05 FWE corr	AN<>HC	NR
Favaro 2014	T	51	35AN(14BPAN), 16recAN (4BPAN)	26.6(7.3)/25.1(6.2)	Seed-based	dCau, drPut, NAcc	<.05 corr TFCE	AN<HC	L drPut- R drPut; R drPut- L drPut, CC, Amy, Po-CG
Boehm 2014	T	35	33 RAN, 2 BPAN	16.10(2.64)	fMRI-ICA	FP,DMN, Sal,visual,SMN	<.05 FWE corr	AN>HC	Angular to other components F-PN; aIns to other DMN components
McFadden 2014	T	44	20AN, 24 RAN	22.85 (5.74)/30.25(8.13)	fMRI-ICA	DMN, Sal, BG, SMN	<.05 FDR corr	AN<HC	dACC, Pc(Sal); Pcent, SMA(SMN)
								recAN<HC	dACC(Sal); Pcent(SMN)
Ehrlich 2015	T	34	32 RAN, 2 BPAN	16.10 (2.56)	fMRI-Graph	WB	<.05 FWE corr	AN<HC	Subnetwork: L Amy-L Thal-R Fusif-B Put- B PIns
Gaudio 2015	T	16	RAN	15.8(1.7)	fMRI-ICA	DMN,ECN, Audi, SMN, FP, visual(medial, lateral)	<.05 FWE corr	AN<HC	ACC (ECN)
Geiser 2015	T	35	33 RAN, 2 BPAN	16.10 (2.56)	fMRI-Graph	WB	<.05 FDR corr	AN<HC	global CPL; strengh: mIns,pIns,Thal
								AN>HC	CPL-mIns,pIns,Thal, LEGE- PFC

Table 8. Summary of sMRI studies.

Author, year	Study	n	Subtype	Age	Technique‡	GLOBAL VOLUMES			comparison	REGIONAL approach	ACC	FL	PL	TL	Ins	OL	Cbll	BG	GV-con	correction	comparison	Areas of findings
				Years(sd)		GM	WM	CSF	Global V													
Kornreich 1991	T	13	AN	15(1.36)	manual	na	na	na	na	Ventricle size	na	na	na	na	na	na	na	na	na	<.05	AN<>HC	Ventricle size
										number of sulcus										<.05	AN>HC	number of sulcus
										pituitary height										na	AN<HC	Pituitary height
Kingston 1996	L (T2: weight gain)	46	AN	22.1 (6.7)	manual					Ventricle size											T1:AN>HC	frontal horn, bicaudate
										pituitary and mammillary body height											T1: AN<HC	pituitary and mammillary body height
																					T2:AN>AN	reduction in ventricles, no changes in pituitary/mamillary bodies
Katzman 1996	T	13	AN	15.2(1.2)	Brain Image	Ø	Ø		AN<HC	na	na	na	na	na	na	na	na	na	na	<.05 uncorr	na	na
								Ø	AN>HC													
Swayze 1996	L (months)	10	8AN, 1BUL, 1EDNOS	24.7(7.4)	Semi and manual tracing	na	na	na	TIV: AN<>HC	na	na	na	na	na	na	na	na	na	na	<.05 corr	AN>HC	Ventricular volume
																					ANT1-T2	Decreased ventricular volume, increased TIV
Katzman 1997	T	6	recAN	17(1.4)	Brain Image	Ø	O		AN<HC	na	na	na	na	na	na	na	na	na	Ø	<.05 corr	na	na
								Ø	AN>HC													
Lambe 1997	T	25	13 AN, 12 recAN	15.2 (1.2)/ 18.9(6.9)	Brain Image	Ø	O		AN<recAN<HC	na	na	na	na	na	na	na	na	na	Ø	<.05 corr	na	na
								Ø	AN>recAN>HC													
Giordano 2001	T	20	recAN	30.0(5.1)	manual tracing	na	na	na	na	ROI (Hipp-Amyg)	na	na	na	Ø	na	na	na	Ø	O	<.05 corr		Hipp-Amyg
Swayze 2003	L (T2:weigh recovered)	17	AN	25.1(7.3)	Semi-automatic tracing	O	Ø		AN<HC	Lobes-volumes (GM, WM, CSF)	na	Ø	Ø	Ø	na	O	O	na	O	uncorr	AN<HC	WM: FL, PL, TL
								Ø	AN>HC		na	Ø	Ø	Ø	na	Ø	Ø	na	O		AN>HC	CSF: FL, PL, TL, Occ, Cbll

Wagner 2006	T	30	14 recRAN, 16 recBPAN	23.7 (5.3)/ 27.4 (7.2)	VBM	O	O	O	O	WB- GM,WM	O	O	O	O	O	O	O	O	Ø	<.05 FDR corr	O	O
Connan 2006	T	16	AN	25.4(7.5)	Manual tracing	na	na	na	TIV: AN<HC	ROI (Hipp)	na	na	na	Ø	na	na	na	na	O	<.05 corr	AN<HC	Hipp
Mühlau 2007	T	22	recAN (RAN to 8BPAN, 2BUL)	18.4-40.8	VBM	Ø	O	na	AN<HC	WB	Ø	O	O	O	O	O	O	O	Ø	<.05 FWE corr	AN<HC	ACC
Castro-Fornieles 2009	L (7 months)	12	9 RAN, 3 BPAN	14.5(1.5)	VBM	Ø	O	O	T1: AN<HC	WB -GM, WM	O	Ø	Ø	Ø	O	O	O	O	Ø	<.05 FWE corr	T1:AN<HC	STL,MTL,SpMG, Pc,Po-CG, SPL, SupMot,ParaCG,mCC,IPC
						O	O	Ø	T1: AN>HC												T2: AN<HC	SupMot,mCC,ParaCG
Joos 2010	T	12	RAN	25.0 (4.8)	VBM	Ø	O		AN<HC	WB	Ø	Ø	Ø	Ø	O	O	O	O	O	<.05 cluster-corr	AN<HC	ACC, F-Op, TP, Pc
								Ø	AN>HC													
Suchan 2011	T	15	AN	26.8 (8.4)	VBM	Ø	O	O	AN<HC	WB	O	O	O	Ø	O	Ø	O	O		<.05 FWE corr+ 12 voxels	AN<HC	Occ (EBA), STL
Joos 2011	T	17	10 AN, 5 recAN	29.6(5.1)	VBM	Ø	O	O	AN<HC	ROI (rACC ,dACC, FOp, Po-CG,Pc, Angular	Ø	Ø	Ø	O	na	na	na	na	O	<.05 corr	AN<recAN<HC	rACC, F-Opc, Po-CG, angular
						O	O	Ø	AN>HC												AN<HC	dACC
						O	O	O	recAN<>HC												AN<HC; recAN<HC	Pc
Boghi 2011	T	21	RAN	29(10)	VBM	O	Ø	O	AN<HC	WB -GM, WM	O	Ø	Ø	Ø		Ø	Ø		Ø	<.05 FDR corr	AN<HC	Op, IPC, Fus, Cau, hypth, Phipp, Cbll, PCG, SupMot, Occ, mTL, IFL, SPC
Brooks 2011	T	14	8 RAN, 6 BPAN	26(1.9)	VBM	O	O	O	O	WB	Ø	Ø	Ø	Ø	Ø	O	O	O	Ø	<.05 FDR+ <.002 cluster-corr	AN<HC	ACC, Phipp, Fus, Cbll, PCC, aIns
																					AN>HC	DLPFC
Roberto 2011	L	32	14 RAN, 18 BPAN	26.91 (6.41)	VBM	Ø	O	O	T1:AN<HC	na	na	na	na	na	na	na	na	na	na	na	na	
	(50.28 days)					Ø	O	O	T2: AN<HC													
Gaudio 2011	T	16	RAN	15.2(1.7)	VBM	Ø	na	na	AN<HC	WB	O	O	Ø	O	O	O	O	O	Ø	<.05 FWE	AN<HC	mCC-Pc, IPC-SPL-Po-CG, IPC-SPL-Angular-Po-CG
Kazlouski 2011*	T	16	10 RAN, 6 BPAN	23.9(7)	DTI-FACT	na	na	na	na	WB -WM	O	O	Ø	Ø	O	Ø	O	Ø	O	<.005+ 100voxels	AN<HC	FA: IF-O,SF-O, Fim-Fo,PCC; ADC: FP, PO
					VBM					WB -WM	O	Ø	O	Ø	O	O	O	O	O	<.005+ 100voxels	AN<HC	<.05 corr:T-paraventricular, <.01 corr: FL, SensMot

Mainz 2012	L (admission T1-dischargeT2)	19	13 RAN, 6BPAN	15.7(1.5)	VBM	Ø	O		T1: AN<HC	WB	O	Ø	Ø	O	O	Ø	O	O	O	<.05 FWE corr+ 100voxels/ T2: <.001 uncorr+ 100voxels	T1: AN<HC	cuneus, Pc, dmPFC, PCC, SMA, Prim,Mot
								Ø	T1: AN>HC												T2: AN<HC	Corr:O. Uncorr: ParaCG,SPC,IFC,IPC, Po-CG, Cuneus, SMA, Occ, SMF, Angular, Pc, SF
						O	O	O	T2													
Frieling 2012*	T	12 AN, 9 recAN	na	26.84 (6.94)/ 27.44(5.32)	DTI-SPM	na	na	na	na	WB -WM	O	O	Ø	Ø	O	Ø	Ø	Ø	O	<.05 FDR	AN, recAN<HC	FA: PThal,mdThal, PCorR, CbII,SLF
Friederich 2012	T	39	12 AN (6RAN, 6BPAN), 13 recAN (10 recRAN, 3 recBPAN)	24.3 (6.2)/ 25.0 (4.8)	VBM	Ø	O	O	AN<HC	WB, ROI (TP, SMA, ACC)	Ø	Ø	O	O	O	O	O	O	Ø	WB: <.05 cluster-corrected, ROI: <.05 cluster-uncorrected	recAN<HC	dACC, SMA, IF-Opc
											Ø	Ø	O	O	Ø	O	O	Ø			AN<HC	Amyg-Ins-Put, Hipp-Amyg-Put, dACC, SMA
Bomba 2013	T	11	9 RAN, 2 BPAN	13.63 (2.77)	FAST	Ø	Ø		AN<HC	na	na	na	na	na	na	na	na	na	na	na	na	na
								Ø	AN>HC													
Frank 2013	T	43	19 RAN, 24 recRAN	23.1(5.8)/ 30.3(8.1)	VBM	O	O	O	O	WB- GM, WM	O	Ø	Ø	Ø	Ø	O	O	Ø	Ø	<.001uncorr+ 50vox; SVC<.05 FWE corr	AN>HC	GM: OFC, avIns, amIns
																					AN<HC	WM: ITL
																					recAN>HC	GM: OFC, amIns
																					HC>recAN	GM: dCau, dPut, ITL, IPC
Frank 2013*	T	19	17 RAN, 2 BPAN	15.4(1.4)	VBM	O	O	O	O	WB- GM, WM	O	O	O	Ø	Ø	O	O	O	Ø	<.001uncorr+ 50vox; SVC<.05 FWE corr	AN>HC	GM: OFC,Fus, Hip, Phip, Ins; WM:Hip, Phip, mdTG, STG
					DTI-FACT														O	<.005 uncorr +50vox	AN<HC	FA: Fo,Cing, FoMaj, SCorR, PCorR
																					AN>HC	FA: SLF,aCorR,IFO; ADC:Fo,CC,CST, PCorR,CPT,SLF
Lazaro 2013	T	35	recAN (25 RAN, 10BPAN)	16.3 (1.3)	VBM	O	O	O	O	WB- GM, WM/ ROI(SMA,	O	O	O	O	O	O	O	O	Ø	<.05 FWE corr	O	

									ACC)													
Nagahara 2014*	T	17	10 RAN, 7 BPAN	23.8(6.68)	DTI-TBSS	na	na	na	na	WB	O	Ø	O	O	O	O	Ø	Ø	Ø	<.05 FWE corr	AN>HC	MD: Fo
																					AN<HC	FA: Cbll; MD: CC, SLF
Favaro 2014	T	51	35AN (14BPAN), 16recAN (4BPAN)	26.6(7.3)/ 25.1(6.2)	Freesurfer	na	na	na	na	ROI (Put, NAcc, Cau)	na	na	na	na	na	na	na	Ø	Ø	<.05 FDR corr	AN>HC, recAN>HC	Put
Hayes 2015*	T	8	AN (mixed, unknown)	35 (11)	DTI-MTT	na	na	na	na	ROI- Tract-based (Fo, junction PThalR-SLF, CC, ALIC, ACC, IFO, PCC, gCC)	Ø	Ø	O	O	O	Ø	O	Ø	Ø	uncorr	AN<HC	FA, AD: ALIC, Fo, IFO, ACC
																					AN>HC	RD: ALIC, Fo, IFO, ACC
Fujisawa 2015	T	20	RAN	14.15(1.81)	VBM	Ø	na	na	AN<HC	WB	O	Ø	O	O	O	O	O	O	Ø	<.05 FWE corr	AN<HC	IFG

Footnotes: Ø: With results. O: explored, negative results. na: non evaluated. NR: no results for contrasts between AN and HC. nda: no data available T: transversal/ L: longitudinal design. BUL: Bulimia nervosa. SVC: small volume correction. ROI: Regions-of-interest analysis. WB: whole-brain analysis. Corr: corrected. Uncorr: uncorrected. GM: Gray matter, WM: white matter, CSF: cerebrospinal fluid. GV-con: controlled by global volume/global gray matter volume. AN: patients with anorexia nervosa: RAN: restrictive subtype, BPAN: binging-purging subtype. recAN: recovered subjects. SPM: Statistical Parametric mapping. DTI: Diffusion Tensor Imaging. VBM: Voxel-based morphometry. FACT: fiber assignment by continuous tracking. NBS: Network-based statistics. CS: conditioned stimulus. [Δ]Wagner 2007 and Bischoff-Grethe 2013 used the same fMRI task in different samples (adults and adolescents respectively). ⋆positive-prediction error: unexpected reward received>expected reward received; negative –prediction error: unexpected no-reward> expected reward. * (Table 8) Studies using DTI evaluation. ‡(Table 8): DTI- tractography techiques were not included in the Table.

Regions' acronyms, in alphabetical order: aCau: anterior Caudate nucleus ACC: anterior cingulate cortex aCorR: anterior corona radiata AIns: anterior insula alic: anterior limb internal capsule amIns: anterior middle insula Amyg: amygdala aPFC: anterior prefrontal cortex (BA10) aPut: anterior putamen Audi: auditory network avIns: anterior ventral Insula aVS: anterior ventral striatum BG: basal ganglia Cbll: cerebellum CC: Corpus callosum cdACC: cognitive region of the anterior cingulate cortex Cing: cingulate fasciculus Clau: Claustrum CPL: characteristic path length (efficiency) CPT: corticopontine tract CST: cortico-spinal tract dCau: dorsal Caudate DLPFC: dorsolateral prefrontal cortex drPut: dorsal-rostral putamen EBA: Estriate Boby area ECN: executive control network F-Opc: frontal operculum F-PN: fronto-parietal network FBA: Fusiform Body area Fim-Fo: Fimbria-fornix Fo: fornix foMaj: forceps major Fus: fusiform gyrus gCC: genu corpus callosum Graph: graph theory hip: hippocampus hypth: hypothalamus IFG: Inferior frontal gyrus IF-O: inferior-occipital fasciculus IF-Opc: inferior frontal operculum IFO: inferior fronto-occipital fasciculus DMN: default mode network Rey Fig: the Rey-Osterrieth Complex Figure Test Ins: Insula IPC: inferior parietal cortex ITL: inferior temporal lobe IOG: inferior occipital gyrus LEGE: normalized local efficiency LG: Lingual gyrus LVIS: lateral visual network mCau: middle Caudate mCC: middle cingulated cortex mdACC: motor region of the dorsal anterior cingulate cortex MFG: middle frontal gyrus mdTG: middle temporal gyrus mdThal: mediodorsal thalamus MFG: medial frontal gyrus mOC: middle occipital cortex MPFC: medial prefrontal cortex MTG: Middle temporal gyrus NAc: nucleus Accumbens OFC: Orbitofrontal cortex Occ-Temp: occipito-temporal junction Occ: Occipital cortex PIns: posterior insula P-Opc: parietal operculum Pal: palidum ParaCG: paracentral gyrus Pc: precuneus pCau:posterior Caudate nucleus PCG: precentral gyrus PCorR: posterior corona radiata Phip: parahippocampus Po-CG(abans Pcentr): post-central gyrus pPut: posterior putamen Prece: PreCG PrimMot: primary motor area PThal: posterior thalamic radiation PThalR: posterior thalamic radiation Put: Putamen RS: resting state networks rSpl: retrosplenial cortex Sal: salience network scACC: subcallosal ACC sCC: splenium corpus callosum SCorR: superior corona radiata SF-O: superior fronto-occipital fasciculus SF: superior frontal SFG: Superior frontal gyrus SgACC: subgenual Anterior cingulated cortex SLF: superior longitudinal fasciculus SMF: superior medial frontal SMN: sensory motor network/somatonsensiry SPL: superior parietal lobule SpMG: supramarginal gyrus (BA40) SPPC: Superior Parietal Posterior cortex Srt: striatum STG: superior temporal gyrus SupMot: supplementary motor area SupMotor: supplemental motor area T-paraventricular: temporal lobe-paraventricular Tp: temporal pole TPJ: temporo-parietal junction vlPFC: ventrolateral prefrontal cortex vlPFC: ventrolateral prefrontal cortex vVIS: ventral visual network.

5. Main questionnaires used in this work

5.1. Eating Disorder Inventory (EDI-2)

(Garner, 1991)

The EDI-2 is a self-report questionnaire (91 items in a 6-option-severity graduation), which assesses a) **symptoms** of-, and b) **psychological traits** associated with- eating disorders (anorexia nervosa, bulimia nervosa, eating disorder not otherwise specified), as well as c) **composite measures**. The subscales are: a) Drive for Thinness, Bulimia, Body Dissatisfaction, b) Perfectionism, Interpersonal distrust, Interoceptive awareness, Maturity fears, Asceticism, Impulse regulation and c) Social insecurity, Ineffectiveness.

5.2. Temperament and Character Inventory (TCI-R)

(Cloninger, 1999)

The TCI-R is a self-report questionnaire (240 items in a 5-option-severity graduation) assessing **personality traits** based on the psychobiological model by Cloninger (Cloninger et al., 1993). It contains the following factors: novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence. Mean scores for a Spanish sample can be found in Gutiérrez-Zotes et al. 2004 (Gutiérrez-Zotes et al., 2004).

5.3. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)

(Torrubia et al., 2001)

The SPSRQ is a self-report questionnaire (48 items of YES/NO answers) which assesses 2 of the 3 systems of personality proposed on Gray's personality model, namely the **Behavioural Inhibition System** (BIS) and the **Behavioural Approach System** (BAS)(Gray, 1981) (the third system, the fight/flight system was less clearly defined according to Torrubia et al. (Torrubia et al., 2001)). While the BIS system was associated with **trait-anxiety (avoidance dimension)**, the BAS was suggested as an independent system responsible for **approaching behaviour in response to incentives** (reward or non-punishment). Both systems were associated with specific brain networks (Gray, 1995; Gray and McNaughton, 1996).

6. Neuroimaging methods and techniques:

The **exponential development of modern neuroimaging** techniques, such as **functional magnetic resonance** (fMRI), has provided important insights into the neurobiological basis of many psychiatric disorders, including AN (Kaye, 2008). Importantly, several discoveries established the foundation for the first fMRI studies to emerge. The first relevant finding was the establishment of a **link between blood flow and brain function**. The first suggestion of this association was in the 19th century (Angelo Mosso) which later demonstrated through several experiments conducted by Charles Roy and Charles

Sherrington in 1890 (Friedland and Iadecola, 1991; Raichle, 2009). The development of **quantitative methods to measure** brain blood flow and metabolism in humans definitively demonstrated that brain blood flow changed regionally during task performance (Seymour Kety and colleagues, University of Pennsylvania and National Institutes of Health; David Ingvar and colleagues, University of Lund, Sweeden; Neils Lassen, University of Copenhagen, Denmark, 1948-~1960).

Another cornerstone for the emergence of fMRI was the discovery of the **different magnetic properties between the oxygenated and deoxygenated haemoglobin**, the essential basis of the blood-oxygen-level dependent (BOLD) signal (see further). In 1845, Michael Faraday was the first to study this issue, and he revealed the non-magnetic properties of 'dried blood' (oxygenated), a surprising finding given the iron contained in the molecule. Later on, Linus Pauling and Charles Coryell (1936) established the differences between the **diamagnetic** properties of the oxygenated haemoglobin *versus* the **paramagnetic** state, in which the iron is exposed in the molecule when devoid of oxygen.

In addition, the emergence of positron emission tomography (**PET**) and the first cyclotron (Hammersmith Hospital, London 1955) initiated a number of studies that were important for the **understanding of brain metabolism, blood flow and the BOLD signal**. The discovery of the X-ray computed tomography (**CT**, Godfrey Hounsfield, Atkinson Morley's Hospital, London, 1971) and the **principles of MRI** [see further; Felix Bloch (Harvard University) and Edward Purcell (Stanford University) and colleagues, 1946)], and **MRI** itself (Paul Lauterbur, 1973), allowed for **high quality anatomical images** to map functional changes in metabolism or blood flow. A final important step were the experiments at Massachussetts General Hospital, which demonstrated the possibility of **measuring changes in blood volume derived from a physiological manipulation** (Belliveau et al., 1991 (Belliveau et al., 1991)). At this point, an important discovery was the refutation of prior ideas that areas of increased activity respond with increased blood flow and decreased oxygen in the returning veins. Instead, **blood flow was demonstrated to be accompanied by increased oxygen availability, which is greater than oxygen consumption** (Ray Cooper and colleagues, Burden Neurological Institute, Stapelton, Bristol, UK, 1975).

Finally, these **different discoveries were brought together** in the work of **Sieji Ogawa** and colleagues (AT&T Bell Laboratories) in 1992. Although Keith Thulborn, in 1982, had already sought to explore the difference between **oxygenated and deoxygenated haemoglobin** as a tool to **measure brain oxygen consumption with MRI**, Ogawa and colleagues' work was definitive. They realized that when exposing rodents to a room with 100% oxygen, no anatomical differentiation of brain veins was observed, whereas when rodents were exposed to normal atmospheric conditions, the detailed anatomy was clearly visible. They labelled this **indirect measure of oxygen consumption** (and increased metabolism) as the **blood oxygen level dependent contrast (BOLD)** contrast. These findings lead to the publication of the first three articles using fMRI in 1992, including one by Ogawa's group (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). The **rapid development that was taking place in cognitive neuroscience** since the 1980s played a relevant role in that moment: a new technique with great spatial and temporal resolution emerged as a perfect tool for testing many psychological hypotheses. In consequence, the **amount of articles** using this technique, as well as the **refinement and complexity of the methodology and software** used, has undergone an **exponential increase in the last 23 years**.

In parallel, the MRI development has not only benefitted the study of brain function in both non-clinical and clinical samples, but has also empowered the use and improvement of methodology to capture structural changes in regional or total volumes, tissue volume or integrity, with methodologies such as voxel-based morphometry (**VBM**) and diffusion tensor imaging (**DTI**). In **task-related functional MRI**

(fMRI), the availability of different methodologies of analysis produces a far more complex field. They might involve comparing an experimental condition to a control condition by either using an **event, block or mixed design** experiment. Other options involve testing the **functional connectivity** between two or more regions in the brain, or between one region (seed) and the rest of the brain during the performance of a task. This can be conducted via several methods, such as by psychophysiological interactions (**PPI**) analysis. Finally, over the last 13 years, some reorientation has been taking place in the field, between the study of brain function in response to external stimuli towards the study of the intrinsic functional responses of the brain, including analyses of the **resting state** of the brain and its organized **systems**, among others (Raichle, 2009).

6.1. Magnetic resonance- Structural analyses (sMRI)

6.1.1. Principles of MRI

MRI signal is based on physical principles of the protons in water when exposed to a magnetic field and a radio frequency pulse. Specifically, spinning protons in a strong magnetic field line up in parallel (or antiparallel) with the magnetic field reaching equilibrium. When radio frequency pulses (electromagnetic waves) are introduced, protons are disturbed from this equilibrium and some at a low energy state (parallel to the field) will move to the antiparallel (or high energy) position (excitation period). After a short period, they will return to the basal state (reception period) by emitting photons that correspond to the energy difference between the two states. The changing current during the reception period is captured by detector coils, which constitutes the MRI signal (Huettel et al., 2008).

6.1.2. Voxel-based morphometry (VBM); DARTEL normalization

VBM is a technique of analysis for structural data implemented in Statistical Parametric Mapping (SPM) software, among others. It involves the comparison, voxel by voxel, of local tissue concentration (gray matter/white matter/CSF) matter between two groups of subjects. Sequentially, it **segments** (separates) the different tissues in the brain, according to their different intensities, and it spatially **normalizes** the images of all the subjects within a study into a common template (same stereotactic space, by default the Montreal Neurologic Institute –MNI- space). Next, a **modulation** step returns the volume information lost during normalization. Finally, images are **smoothed** to remove high-frequency information (increases signal-to-noise ratio as it favours signal gain across contiguous voxels and helps to reduce some mismatch in the normalization process)(Ashburner and Friston, 2000). Recent methodological improvements include the **'new segmentation'** (Ashburner et al., 2011) and **DARTEL** tools (Ashburner, 2007), for segmentation and normalization processes, respectively.

6.1.3. Diffusion tensor imaging (DTI)-quantitative

Diffusion tensor imaging (DTI) methods are used to study the **organization, coherence and direction of white matter tracts.** This is conducted by measuring water diffusion through the brain (maximum in white matter), and based on the intrinsic **random movement of water** molecules, Brownian motion. Water tends to diffuse freely when unrestricted (isotropic diffusion), but water molecules contained in **white matter are constricted by the limits of the axonal membranes and myelin**, and thus they diffuse along the length of the axon (**anisotropic diffusion**). DTI is obtained by measuring the dephasing of spins of protons (as in other MRI sequences) in the presence of a magnetic field, which varies in space or '**gradient**'. Importantly, this provides a measure of the phase change resulting from the incoherent displacement of the protons along the axis of the gradient (Jones et al., 2012). The strong magnetic

gradients are applied in a minimum of 6 (usually more than 15) **noncollinear directions**. The measurement might be quantified in each voxel (voxel-based), obtaining the relative diffusivity of water into directional components for each particular voxel. A reference non-diffusion gradient is also obtained, which contains the information about the diffusion time, gradient duration and gradient strength (b value, usually =1000 in adults). Although it measures structural properties, data is retrieved from the echo-planar imaging (EPI) sequence (used for functional studies), given that temporal information is required for reconstruction.

It allows for obtaining either i) **quantitative scalar values** (ADC, FA, MD, AD, RD), ii) a reproduction of tracts: **tractography** by deterministic or probabilistic methods, or iii) **models of whole brain connectivity** (connectome approach, which is based on tractography). In quantitative methods, the commonly retrieved scalar measures are **fractional anisotropy (FA) and mean diffusivity (MD**, or the closely related apparent diffusion coefficient (ADC)). **FA** is bound between 0 and 1 and expresses the preference of **water to diffuse in an anisotropic** (1) or isotropic (0) manner. **MD** (also between 0 and 1) indexes the **overall degree of water diffusion**, regardless of direction; it is an average measure of diffusion, while ADC describes the actual water diffusion (how far water can diffuse without interruption, although not necessarily linked to anisotropy). FA and MD are **typically negatively correlated** and are considered to be **broad measures**, indicators of white matter integrity (axonal ordering, density, degree of myelination; FA is typically decreased in pathological white matter). More specific measures, derived from FA and MD, provide complementary information: **axial (AD; λll)** and **radial diffusivity (RD; λl)**, which represent either the average diffusion parallel (AD) and perpendicular (RD) to axonal fibres. **AD** is sensitive to **changes in axon integrity**, while **RD is to myelination**. The **combined quantification of all these measures is recommended** to the interpretation of white matter changes (Huettel et al., 2008; Jones et al., 2012).

6.2. Functional magnetic resonance (fMRI)

After the preprocessing of the images (realignment, normalization, smoothing), BOLD signal detection explained earlier (see introduction to 6.) is used as an indirect measure of increased brain activity within particular brain regions.

6.2.1. Task-based BOLD signal differences between conditions

Basic fMRI paradigms use the **subtraction of brain activations between two different conditions** which only differ in the psychological process of interest, to isolate its response. Different designs might be used depending on the question being tested: block designs, event designs and mixed designs (Huettel et al., 2008).

6.2.2. Task-based connectivity analyses: analysis of Psychophysiological interaction analysis (PPI)

PPI is one of the available modalities to study brain responses to a specific task in the context of functional **brain systems**, or **functionally connected regions**, instead of the isolated responses of each region. PPI gives information of the **functional coupling between one selected region and other regions** [either previously selected (region-of-interest, ROI) or not (whole brain)], built not only by its structural connections or common activation during the task, but which are **specifically influenced by the performance of the task** (Friston et al., 1997).

6.2.3. Task-independent: functional resting state connectivity analyses

During a resting state paradigm, participants are only asked to lay down (eyes open or closed) in a state of relaxation, **without performing any tasks**. There are no conditions to be subtracted; instead, the signal obtained during resting state is used to investigate **synchronous activations between different regions in the absence of a stimulus**, with most of the research focusing on spontaneous low frequency fluctuations (0.01-0.1 Hz) in the BOLD signal (Biswal et al., 1995; Huettel et al., 2008). **Several systems have been found to present synchronic fluctuations** during rest, which is believed to represent intrinsic operations and a definition of basic brain networks. Among these networks, one of the **best known is the default mode network (DMN)** (Huettel et al., 2008).

Different techniques to explore **data-driven patterns of common fluctuation** are principal component analysis (PCA) or independent component analysis (ICA). However, it is also possible to **explore a specific region** within the brain by defining a region of interest, which is called a *seed*, therefore assessing **which areas in the brain present common fluctuations with this selected region**.

6.2.3.1. Resting state networks (RSN) – default mode network (DMN)

At least, almost 20 different networks with synchronic fluctuation at rest have been identified (Smith et al., 2009). Importantly, they are suggested to be able to **predict the task-response properties of brain** regions (Smith et al., 2009). Some of them include **three visual systems** (medial, lateral and occipital: involved in motion perception among others), the **salience** or executive-control or cingulo-opercular network (dorsal anterior cingulate, paracingulate and insular cortices: involved in executive control, salient events, set maintenance and action-inhibition), and the default mode network (**DMN**), among others. Interestingly, this latter network has also shown to present an **anti-correlated activation with task-related networks,** although **both networks might positively couple during self-reflective cognitive demanding tasks** (Anticevic et al., 2012; Harrison et al., 2008) (see 4.3.3).

6.3. Statistical correction in sMRI and fMRI studies

6.3.1. Corrected versus uncorrected values

Given the high number of comparisons usually conducted in MRI analyses (for example, T tests between condition 1 and condition 2 in one single voxel, performed *n* times, being *n* the number of voxels in the brain), **correction for type I error is typically required**. Several methods are available to protect against it. While earlier MRI studies presented uncorrected values with more restrictive thresholds than classical statistic analyses (usually <.001), presently it is more preferred to show corrected values using either **false discovery rate** (FDR) or **family wise error** (FWE) corrections (with other methods such as Bonferroni being considered extremely stringent and increasing the probability of type II error). Other approaches include the selection of regions of interest (ROI), which restricts the number of comparisons to a smaller number of voxels; the so-called **small volume correction** is applied to only analyze selected voxels. Alternatively, within imaging analyses software using **permutation** statistics (such as FSL), a distribution of significance values obtained by chance is calculated, obtaining a good estimation of the **number of false positives in the data**, guiding the selection of the alpha value. The elevated cost of MRI studies with small samples, the stringent characteristics of the methodology used in common software used to analyse images (such as statistical parametric mapping, SPM), as well as the (usually uncorrect) assumption that an isolated unknown region will show a positive finding give rise to the need for better

correction methods or recommend giving relevance to uncorrected results under particular circumstances.

6.3.2. Voxel versus cluster significance

Another approach for statistical correction is **to consider the statistical significance of a group of voxels in contiguity (cluster)** instead of the significance of each voxel. This is a psychologically valid approach, since it is typically not expected for a task to activate one single voxel within the brain (which might be of $8mm^3$). Additionally, it is less likely for a cluster of voxels to be activated by chance, with the likelihood of a false-positive result decreasing with increasing cluster size. Although it has some limitations, cluster-based **significance allows for keeping relatively relaxed thresholds at the voxel level while setting a threshold on the number of voxels per cluster.** Available software calculate this cluster-threshold based on permutations of groups of voxels with a minimum voxel significance value within a mask containing the number of voxels that are to be analyzed [i.e. AlphaSim (Ward, 2000)]. Other software use data-driven permutations of groups of voxels to obtain significant clusters (i.e. randomize in FSL (Behrens et al., 2012).

6.4. Accounting for confounding factors in MRI studies

Neuroimaging studies in AN are putatively influenced by the low body weight (and its consequences) in (severe) underweight patients. For example, although one would predict a proportionate alteration at a whole-brain level, low weight or dehydration might produce a lost of gray/white matter in certain areas (Streitbürger et al., 2012). Similarly, a decrease in total water intake might also have a similar potential effect or either have a direct impact on MRI measurements. In addition, **severe low-weight** patients might also exhibit worse at **cognitive performance** because of their undernourished state.

Some studies attempt to control for this problem by **ensuring normal food and fluid intake for 7-10 days** before the MRI session (Alonso-Alonso, 2013). Further control has to be carefully considered, since there is a risk of proportionally ruling out some effects of the disorder itself, associated with disorder severity. Of course, **studying recovered patients** might better solve these problems. However, two problems arise from this strategy. First, 'recovery' is not well defined. For example, some authors define maintenance as at least one year of keeping weight above 90% average body weight, along with regular menstrual cycles and not presenting restrictive/bingeing/purging behaviors (Wagner et al., 2008). Other criteria, by contrast, require the maintenance between 90-110% of ideal body weight for at least 6 months (Holsen et al., 2012). Additionally, a cognitive evaluation should probably be incorporated to these criteria for recovery (Bachner-Melman et al., 2006). Second, and more importantly, some alterations not related to body weight might be **present only during the acute state**, and therefore will cease to exist in the recovered state. For example, the ability to normalize weight may be linked to improvements in different symptoms [e.g. cognitive rigidity or anxiety related to weight gain (Madsen et al., 2013)]. **Longitudinal studies** might be more appropiate to overcome these issues, although for state alterations which persist in recovery, they are not able to inform about either the preexisting nature of alterations, or their persistence as a *scar*. The combination of all these sort of studies, together with evaluations in general population and family members are thus complementary strategies to understand the effects of weight and symptoms in brain alterations.

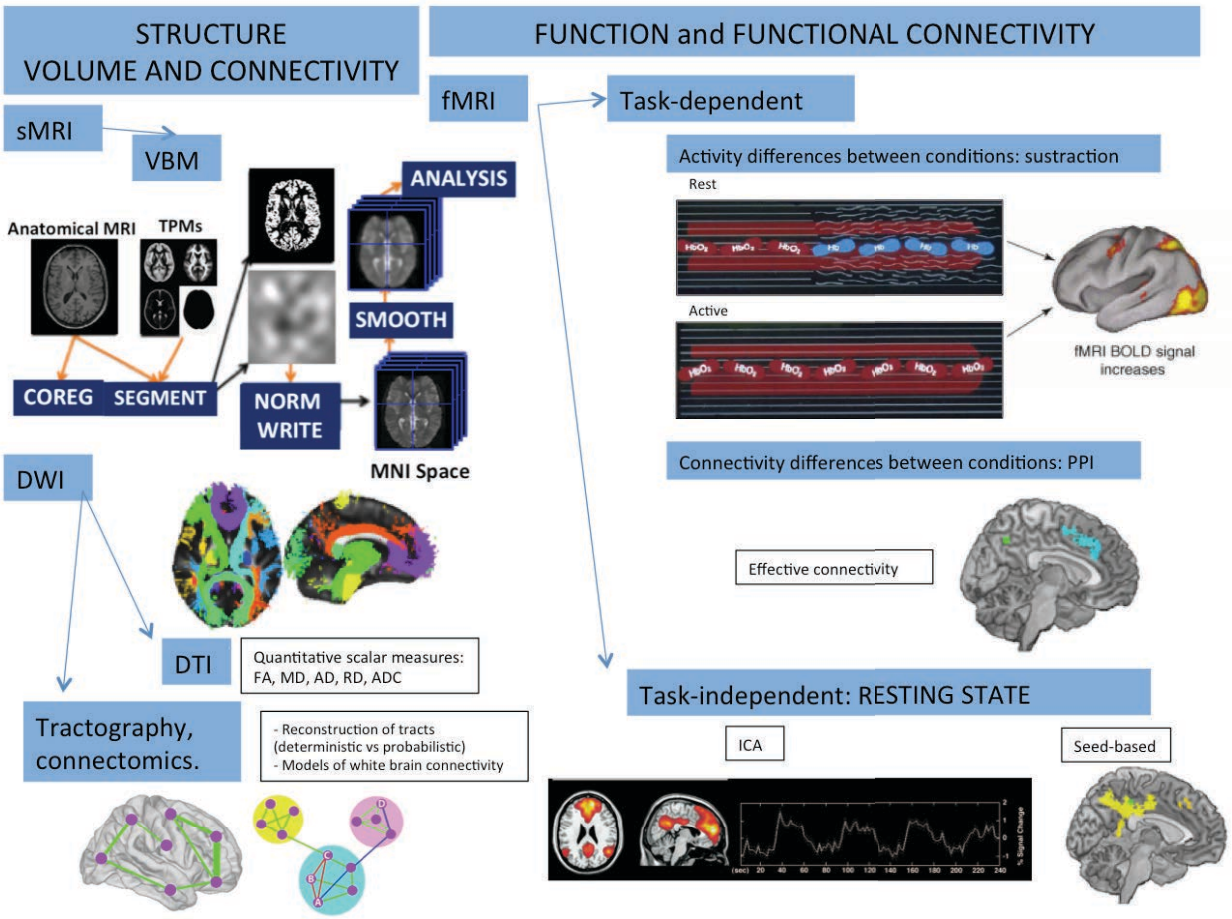

Figure 6. Representation of some available techniques with MRI images, including the ones used for this work. Partially adapted from (Fornito and Bullmore, 2012; Fornito and Bullmore, 2014; Harrison et al., 2008; Ogawa et al., 1990; Raichle, 2009). sMRI: structural magnetic resonance. fMRI: functional magnetic resonance. VBM: voxel-based morphometry. DWI: diffusion weighted imaging. DTI: diffusion tensor imaging. PPI: psychophysiological interaction. ICA: independent component analysis.

6.5. Summary and unanswered questions

Several conclusions might be drawn from the above revision of circuits involved in AN. First, there is convergence in the findings from both functional and structural studies in highlighting alterations in the fronto-parietal circuit, the limbic system and the reward system. Despite this, a scarce number of studies have evaluated the structural connections within and between these networks. Second, although the response to (and the regulation of) social interactions seems relevant in AN, only a few studies have evaluated the biological substrates involved in alterations in either self-processing or socio-emotional responses in social contexts. Moreover, within the mechanisms that shape social relationships, the reward system, or more generally, the reward-inhibition system, is probably involved in social relationships. Third, alterations in body perception most likely relate to alterations in higher-order integrative processes, which are necessary for self-evaluation processes involved in both the creation of self-identity and interaction with others in social relationships (see Figure 5).

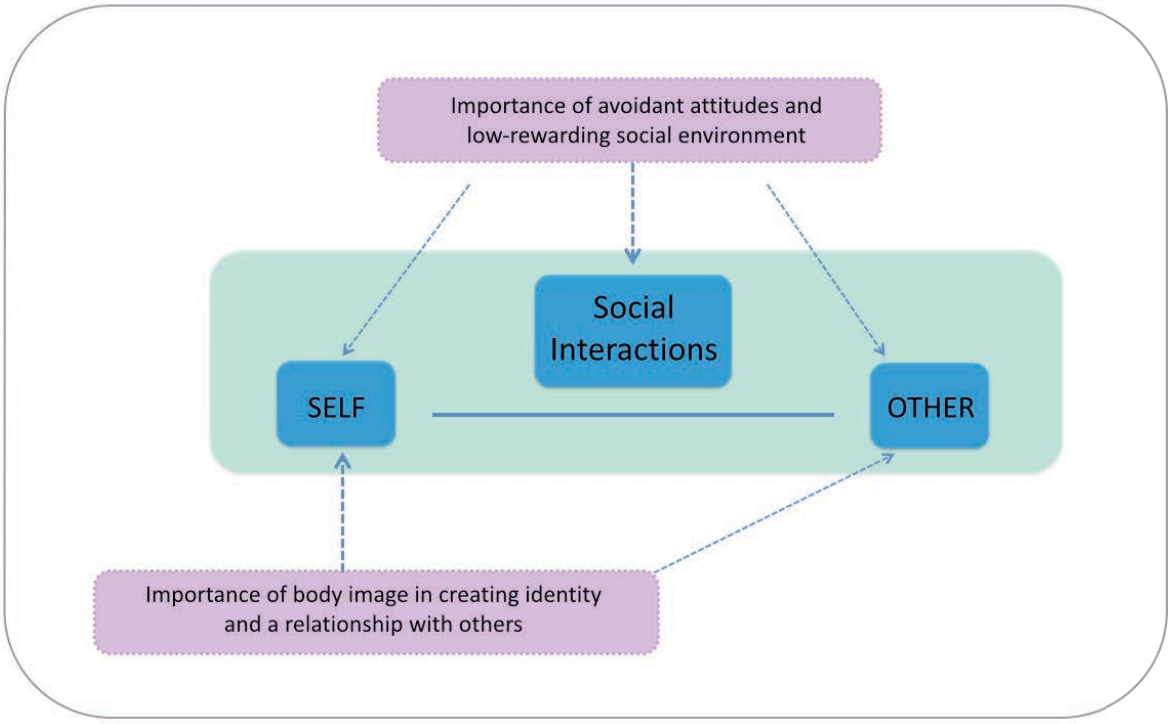

Figure 5. Representation putative factors involved in abnormal social relationships in AN.

Chapter 2

AIMS AND HYPOTHESES

Chapter 2- Aims and hypotheses

With this work we aimed to expand upon the knowledge regarding the neurobiological bases of anorexia nervosa in relation to nuclear elements of the disorder such as body evaluation and the participation of the reward system and other motivational circuits in social interactions. In addition, we also aimed to explore how these symtoms translate into structural alterations at the brain level. With this objective, a group of 20 AN adult female patients, restrictive subtype, with no comorbid disorders, were consecutively recruited from the Eating Disorders Day Unit at the Bellvitge University Hospital. These patients were matched by gender, handedness, mean age and mean educational level with a group of 20 healthy controls.

1. Aims

Main aims

- To study, in a group of consecutivety admitted anorexia nervosa (AN) patients and healthy controls, microstructural differences in white matter tracts by comparing quanitative differences in scalar measures retreived by using diffusion tensor imaging techniques.

- To study, in a group of consecutivety admitted AN patients and healthy controls, the pattern of brain responses when receiving experimentally manipulated acceptance or rejection responses by other individuals. This will be conducted using functional magnetic resonance techniques.

- To study, in a group of consecutively admitted AN patients and healthy controls, the differential response of the default mode network during the presentation of video images of their own and another's body. This will be conducted using functional magnetic resonance techniques.

- To study, in a group of consecutivety admitted AN patients and healthy controls, differences in the connectivity pattern of the default mode network during the presentation of video images of their own and another's body and at rest. This will be conducted using functional magnetic resonance techniques.

Secondary aims

- To study, in AN patients, associations between alterations in white matter microstructure and variables related to disorder severity or specific clinical features.

- To study, in patients, associations between brain responses to social acceptance and rejection and variables related to disorder severity or specific clinical features (e.g., sensibility to reward and punishment scores).

- To study, in patients, associations between brain responses to the visualization of own and another body, and variables related to disorder severity or specific clinical features.

2. Hypotheses

- Patients with AN, compared to healthy controls, will present differences in either fractional anisotropy (FA) or mean diffusivity (MD), with associated alterations in radial and axial diffusivity measures (RD, AD) in long-range connections such as the fronto-parietal circuit.

- Patients with AN, compared to healthy controls, will present a differential pattern of brain activity in response to either receiving social acceptance or rejection, involving areas associated with reward response.

- Patients with AN, compared to healthy controls, will present a different pattern of brain activity within the DMN in response to the visualization of their own and another's body.

- Patients with AN, compared to healthy controls, will present a different pattern of brain connectivity within the DMN in response to the visualization of their own and another's body and at rest.

Chapter 3

STUDY 1

“Disruption of brain white matter microstructure in women with anorexia nervosa”

J Psychiatry Neurosci

Research Paper

Disruption of brain white matter microstructure in women with anorexia nervosa

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Background: The etiology of anorexia nervosa is still unknown. Multiple and distributed brain regions have been implicated in its pathophysiology, implying a dysfunction of connected neural circuits. Despite these findings, the role of white matter in anorexia nervosa has been rarely assessed. In this study, we used diffusion tensor imaging (DTI) to characterize alterations of white matter microstructure in a clinically homogeneous sample of patients with anorexia nervosa. **Methods:** Women with anorexia nervosa (restricting subtype) and healthy controls underwent brain DTI. We used tract-based spatial statistics to compare fractional anisotropy (FA) and mean diffusivity (MD) maps between the groups. Furthermore, axial (AD) and radial diffusivity (RD) measures were extracted from regions showing group differences in either FA or MD. **Results:** We enrolled 19 women with anorexia nervosa and 19 healthy controls in our study. Patients with anorexia nervosa showed significant FA decreases in the parietal part of the left superior longitudinal fasciculus (SLF; $p_{FWE} < 0.05$), with increased MD and RD but no differences in AD. Patients with anorexia nervosa also showed significantly increased MD in the fornix ($p_{FWE} < 0.05$), accompanied by decreased FA and increased RD and AD. **Limitations:** Limitations include our modest sample size and cross-sectional design. **Conclusion:** Our findings support the presence of white matter pathology in patients with anorexia nervosa. Alterations in the SLF and fornix might be relevant to key symptoms of anorexia nervosa, such as body image distortion or impairments in body–energy–balance and reward processes. The differences found in both areas replicate those found in previous DTI studies and support a role for white matter pathology of specific neural circuits in individuals with anorexia nervosa.

Introduction

Anorexia nervosa is an eating disorder characterized by disturbing preoccupations about body self-image, weight and dieting. Patients with anorexia nervosa engage in intense food restrictions that, in some cases, are accompanied by binge eating and purging episodes (restricting subtype v. binge eating/purging subtype), with severe and enduring physical and psychological consequences.[1] Although the etiology of anorexia nervosa is unknown, there is consensus regarding its multifactorial origin and the contribution of neurobiological factors in the vulnerability, onset and maintenance of the disorder.[2,3]

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Data from neurocognitive and imaging studies suggest that patients with anorexia nervosa have impairments in neural systems implicated in executive functions, visuospatial processes, self-image perception, emotional regulation and reward processing.[2] Consistent with these data, studies with currently ill patients with anorexia nervosa have shown widespread grey matter decreases in the neocortex and in areas linked to emotion regulation and reward, such as the anterior cingulate, orbitofrontal cortex, insular cortex, hippocampus/parahippocampus, amygdala and striatum.[4–6] However, other studies have reported grey matter increases in neocortical[6–8] and limbic regions.[7,8] Moreover, although some of these alterations may normalize in recovered patients,[4] other studies have shown the persistence of volume alterations in recovered patients.[7,9,10] The distributed nature of these changes implies disturbances of interregional brain connectivity, as has been observed in most other psychiatric disorders.[11,12]

At the same time, the major reorganization in white matter that the brain undergoes during adolescence and early adulthood is thought to be relevant to the development of some psychiatric disorders, including anorexia nervosa.[3,13] Normal maturation and organization of white matter might be affected in patients with anorexia nervosa, particularly when considering that most of the identified factors contributing to the development of the disorder — including psychological, social and biological factors — have their major impact in this period. Despite all this, white matter alterations remain rather unexplored in anorexia nervosa. Of the few published studies exploring regional volumetric differences, most showed white matter decreases in fronto-temporo-parietal and sensoriomotor regions in adult patients,[7,14,15] although 3 others found either no differences[16,17] or white matter increases in temporal and hippocampus regions in adolescent patients.[8] Regional white matter alterations were also reported in recovered patients,[7] although other studies found no differences in volume.[18–20]

In this context, diffusion tensor imaging (DTI) affords a new and highly suitable approach to assess microstructural white matter alterations that may putatively characterize anorexia nervosa. It provides information of white matter organization based on the analysis of the brain's water diffusion.[21] Specifically, water diffusion is typically quantified using 2 main compound measures: fractional anisotropy (FA) and mean diffusivity (MD), or the closely related apparent diffusion coefficient (ADC). Fractional anisotropy provides information about the maximum direction of water diffusion and the degree to which it is constrained by tissue barriers, such as axonal fibres, whereas MD indexes the overall degree of water diffusion, regardless of direction.[22,23] Both measures are typically negatively correlated and are considered to be an indicator of white matter integrity (FA is decreased in pathological white matter). Nevertheless, FA and MD are broad measures that could be driven by a number of factors (e.g., axonal ordering, density, degree of myelination).[22,23] Indirect measures of these changes include axial (AD; $\lambda_{\parallel}$) and radial diffusivity (RD; $\lambda_{\perp}$), which contribute to the computation of aggregate measures, such as FA and MD, and represent relatively specific aspects of water diffusivity, such as the average diffusion parallel (AD) and perpendicular (RD) to axonal fibres.[24] For this reason, AD and RD are thought to index more specific aspects of white matter pathology, being more sensitive to changes in integrity and myelination, respectively.[21–25] Decreases in FA, for instance, might derive both from a decreased AD due to axonal impairment or an increased RD due to myelination changes, as observed in animal models.[23–25] Therefore, the combined quantification of such measurements is recommended to better characterize any putative changes in white matter microstructure.[23,25]

Two previous studies have explored white matter microstructure with DTI in adult patients with anorexia nervosa.[14,26] Kazlouski and colleagues[14] studied a group of 16 patients with anorexia nervosa with acute symptoms (10 patients with restricting subtype and 6 with binge eating/purging subtype); they found FA decreases in the bilateral fimbria-fornix, the fronto-occipital fasciculus and the posterior cingulum as well as ADC/MD increases in frontoparietal and parieto-occipital bundles. Comorbid depression and anxiety diagnoses were not excluded (8 participants per diagnosis), although both diagnoses are often comorbid with anorexia nervosa. In the second study, Frieling and colleagues[26] included a sample combining acute (n = 12) and recovered (n = 9) patients with anorexia nervosa; they found FA reductions in thalamic regions, the posterior corona radiata, the left middle cerebellar peduncle and parts of the left superior longitudinal fasciculus. Methodological limitations, such as lack of sample power or mixed samples of patients, might account for differences between these 2 studies. In this sense, although comparisons between subgroups of patients were conducted in both studies, splitting an already modest sample size may have limited statistical power.

The objective of the present study was to identify differences in white matter microstructure in a homogeneous sample of patients with anorexia nervosa. To this end, we recruited a phenotypically well-characterized group of currently ill patients with anorexia nervosa, restricting subtype. The inclusion of a homogeneous sample was designed to reduce some of the variability typically found in clinical samples, such as the one associated with a subgroup of patients with impulsive behaviours (binge/purging subtype).[6,27] Unlike previous studies, we also aimed to provide a full characterization of white matter microstructure abnormalities across the aforementioned diffusivity measures (i.e., FA, MD, AD, RD). This was conducted to derive a more comprehensive understanding of potential alterations, as suggested.[25] In addition, to explore whether the results were modulated by potential confounders or explained by symptoms and psychological factors related to anorexia nervosa, we assessed correlations between clinical variables and DTI-derived parameters. Finally, we explored whether differences in diffusivity were accompanied by differences in grey or white matter volumes.

Based on previous findings, we hypothesized that patients with anorexia nervosa would present decreases in FA and/or increases in MD in long-range connections between frontal and temporoparietal or occipital areas. We also expected these changes to correlate with clinical variables, such as duration and severity of the disease, or with personality traits thought to be associated with anorexia nervosa, such as harm avoidance.[14,28]

Methods

Participants

The study was conducted between 2011 and 2012. We consecutively recruited women with anorexia nervosa fulfilling DSM-IV-TR criteria for anorexia nervosa, restricting subtype,[1] from the Eating Disorders Unit of Bellvitge University Hospital (day hospital), Barcelona, Spain. Diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders.[29] Comorbid psychiatric disorders, any neurologic condition and abuse of any substance with the exception of nicotine were exclusion criteria. Before scanning, all patients must have had at least 1 week of supervised meals and hydration during their day hospital admission. By ensuring normal hydration, we minimized putative biases that dehydration may cause in brain measurements.[30]

We recruited healthy controls, matched for sex, mean age, handedness and mean educational level, from the same sociodemographic area as patients. Controls were screened to exclude any psychiatric or other medical condition by means of the General Health Questionnaire[31] and a clinical semistructured interview.[32] We also ensured that controls had a body mass index (BMI) within the healthy range and that they did not present unhealthy eating behaviours (e.g., constant dieting) or subthreshold symptoms of any eating disorder.

For all participants, the presence of symptoms and psychological features involved in eating disorders were assessed with the self-reported Eating Disorder Invertory-2 (EDI-2) scale.[33] We assessed depressive and anxiety symptoms using the Hamilton Rating Scale for Depression (HAM-D)[34] and the Hamilton Rating Scale for Anxiety (HAM-A).[35] The harm avoidance personality trait from the Temperament and Character Inventory—Revised[36] was also collected. The ethical committee of clinical research of the Bellvitge University Hospital approved the study protocol. All participants gave written informed consent after a detailed description of the study.

Imaging protocol — DTI

Acquisition

Scanning was performed with a GE Signa Excite scanner at 1.5 T (Medical Systems) equipped with an 8-channel phased-array head coil. We used a single-shot, spin echo, echo planar imaging sequence to obtain 26 consecutive axial diffusion-weighted images for each participant (repetition time [TR] 8300 ms; echo time [TE] 95 ms; thickness 5 mm, no gap; pulse angle 90°; field of view 26 cm; 128 x 128 acquisition matrix reconstructed to a 256 x 256 matrix). Twenty-five diffusion-weighted volumes were acquired along noncollinear directions using a b value of 1000 s/mm^2. A single non–diffusion weighted volume was also acquired.

Preprocessing

Imaging data were processed on a Macintosh computer running FMRIB's Software Library (FSL), developed by the Analysis Group at the Oxford Centre for Functional MRI of the Brain (FMRIB).[37] Diffusion-weighted images were corrected for possible eddy current distortions ("Eddy Current Correction" option in the FMRIB Diffusion Toolbox [FDT] version 2.0 in FSL), and a brain mask was applied using the FSL Brain Extracting Tool. Subsequently, we estimated FA and MD maps using FDT in FSL by fitting a tensor model to the eddy-corrected and brain-masked diffusion data. We also estimated AD and RD maps using the eigenvalues associated with the fitted tensor model. Data from 2 participants (1 patient and 1 control) were excluded owing to excessive signal loss in the orbitofrontal cortex.

Processing and statistical analyses

We used tract-based spatial statistics (TBSS)[38] in FSL to test for between-group differences in FA on a voxel-wise basis. First, all FA images were aligned to the $1 \times 1 \times 1$ mm standard space provided in FSL (FMRIB58 FA) using the FMRIB nonlinear image registration tool (FNIRT). Next, we created a mean FA skeleton map (together with a mean FA map), which represents the centre of all the tracts common to the group. Finally, the skeleton was thresholded at a standard intensity value of 0.2, which is recommended in TBSS analyses to avoid areas of high variability,[38] and each participant's FA map was projected to this skeleton. The resulting FA data were analyzed using the Randomize permutation-based program in FSL[39] with the following contrasts: controls > patients and patients > controls. The results were cluster-wise thresholded using a primary t statistic of $t > 2$ and a family-wise error (FWE)–corrected p value of $p_{FWE} < 0.05$. These preprocessing and thresholding procedures were repeated for the MD images. Anatomic localization of the clusters was based on the white matter atlas of the Johns Hopkins University White Matter Labels (1 mm) Atlas available in the FSL software library.[40]

For each cluster showing a significant group difference in FA or MD, we extracted voxel values and averaged them to obtain a summary measure of diffusion properties in these regions for each participant. We calculated Spearman correlations between these diffusion measures and demographic and clinical variables (EDI-2, duration of illness, harm avoidance, age, BMI, HAM-D and HAM-A) in the patient group alone. We also assessed between-group differences in the component AD and RD measurements, which were additionally extracted from each cluster with significant between-group differences in FA or MD. See the Appendix, available at jpn.ca, for details of the acquisition, preprocessing and analysis of structural images (voxel-based morphometry).

Results

Participants

We recruited 20 women with anorexia nervosa, but 1 had to be excluded for the technical reason of excessive signal loss in the orbitofrontal cortex, for a final patient sample of 19 women (mean age 28.37 ± 9.55 yr). Five (26%) patients were on pharmacological treatment (3 on selective serotonin reuptake inhibitors, 1 on a tricyclic antidepressant and 1 on

a combination of low doses of a sedative antipsychotic treatment plus a tricyclic antidepressant) owing to the presence of past (n = 4) or current (n = 1) depressive and anxiety symptoms. However, at the time of examination, none of the patients fulfilled criteria for any comorbid psychiatric disorder. We recruited 20 healthy controls, but 1 had to be excluded after the preprocessing of the images, leaving a final sample of 19 controls (mean age 28.63± 8.58 yr). Table 1 summarizes the demographic and clinical characteristics of the sample.

Clinical and demographic variables

There were no statistical differences in age, handedness or educational level between the anorexia nervosa and control groups. As expected, BMI and EDI-2 measures were significantly different between the groups, with lower mean BMI and higher mean EDI-2 scores in patients with anorexia nervosa. Depressive and anxiety symptoms were also higher in the patients than the controls, although differences in anxiety did not reach statistical significance after correction for multiple comparisons. Harm avoidance scores were no different between the groups (Table 1).

Group comparison of the FA and MD diffusivities

A significant FA reduction in patients relative to controls was localized to a large cluster (512 voxels; $p_{FWE} < 0.05$) that extended across the parietal region of the left superior longitudinal fasciculus (SLF), including its portion II (SLF II) and the arcuate fasciculus (AF). This area included the temporoparietal junction and surrounded the posterior insular cortex and the temporal and parietal opercula. The results extended into the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus (Fig. 1, Table 2). No significant increases in FA were identified in the patient group.

In addition, patients showed increased MD in a cluster encompassing the fornix and extending to the anterior thalamic radiations bilaterally (266 voxels; $p_{FWE} < 0.05$; Fig. 2, Table 2). There was no decrease in MD in patients.

To test if potential confounding factors (e.g., age, depression and anxiety symptoms, medication and nicotine use) accounted for a significant percentage of variability in the diffusivity results, we conducted 2 separate hierarchical multiple regression models, with mean FA and MD measures from the previously mentioned clusters as the dependent variables. The inclusion of potential confounders did not significantly increase the percentage of variability explained by group, which was the only variable that significantly predicted FA and MD. Specifically, group accounted for 62% of the variance of FA in the SLF ($p < 0.001$) and 69% of the variance of MD in the fornix ($p < 0.001$; see the Appendix, Table S1). In addition, we repeated our analyses by excluding 1 participant with a late-onset disorder (aged 48 yr at onset). All differences remained significant after excluding this participant.

Clinical correlations and component measures

There were no significant correlations between the extracted FA/MD measurements and the clinical variables examined (Appendix, Fig. S1).

Analysis of the component measures extracted from the clusters showing significant FA/MD differences indicated that SLF alterations were predominantly driven by an increase in RD accompanied by an MD increase (RD: $t_{36} = 7.24$; FA: $t_{36} = 7.73$; MD: $t_{36} = 5.54$; all $p < 0.001$). In the fornix, changes were driven by increases in both AD and RD accompanied by an FA decrease (AD: $t_{36} = 4.39$; RD: $t_{36} = 9.37$; FA: $t_{36} = 7.93$; MD: $t_{36} = 8.96$; all $p < 0.001$; Fig. 3).

Group differences in volume

There were no between-group differences in grey or white matter volumes either at the whole brain level or in specific analyses aimed at the regions of significant between-group differences in DTI measurements. Further information is provided in the Appendix.

Table 1: Demographic and clinical characteristics of the study sample

	Group; mean ± SD (range)*		Between group differences	
Variable	Anorexia nervosa, n = 19	Control, n = 19	t	p value
Age, yr	28.37 ± 9.55 (18–49)	28.63 ± 8.58 (19–52)	0.09	0.93
Handedness, no. right:left	18:1	18:1	—	—
Education level, yr	15.47 ± 3.22 (12–23)	16.58 ± 2.46 (10–21)	1.19	0.24
Age at onset, yr	21.84 ± 9.19 (12–48)	—	—	—
Duration of the illness, mo	78.32 ± 72.37 (12–240)	—	—	—
BMI	17.03 ± 1.09 (14–18)	21.09 ± 1.80 (18–25)	8.45	< 0.001†
EDI-2 total scores	66.79 ± 44.28 (13–178)	13.53 ± 7.37 (3–28)	5.17	< 0.001†
Harm avoidance (TCI-R)	106.89 ± 20.26 (75–144)	98.63 ± 10.83 (78–119)	1.57	0.13
HAM-D	3.26 ± 3.02 (0–10)	0.84 ± 1.07 (0–3)	3.30	0.003†
HAM-A	5.11 ± 5.91 (0–22)	1.63 ± 1.42 (0–4)	2.50	0.025

BMI = Body Mass Index; EDI-2 = Eating Disorders Inventory-2; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; SD = standard deviation; TCI-R = Temperament and Character Inventory, revised edition.
*Unless otherwise indicated.
†Significant p values after Bonferroni correction ($p < 0.007$).

Discussion

Using DTI in a well-characterized sample of women with anorexia nervosa, we identified axonal abnormalities that highlight the relevance of specific brain systems in the pathophysiology of this disorder. Overall, patients with anorexia nervosa demonstrated alterations of white matter microstructure in the parietal component of the superior longitudinal fasciculus as well as the fornix. The nature of these alterations varied for each fibre tract: decreased FA in the SLF was largely driven by increased RD, whereas increased MD in the fornix was driven by a combination of increased AD and RD. These results were not found to be attributable to potential confounding factors.

Changes in the left SLF

The SLF is a major association fibre, connecting frontal to parietotemporal and occipital areas. Although it comprises several portions, our results were mainly located in the parietal parts of SLF II and AF components, fibres that connect dorsolateral and ventrolateral prefrontal areas to the angular gyrus and posterior parts of the superior temporal cortex.[41]

Alterations in the structure of the SLF are consistent with grey matter decreases found in patients with anorexia nervosa in both frontal and parietotemporal regions[4] and replicate part of the findings of a previous DTI study of anorexia nervosa,[26] which found a decrease in FA in the parietal parts

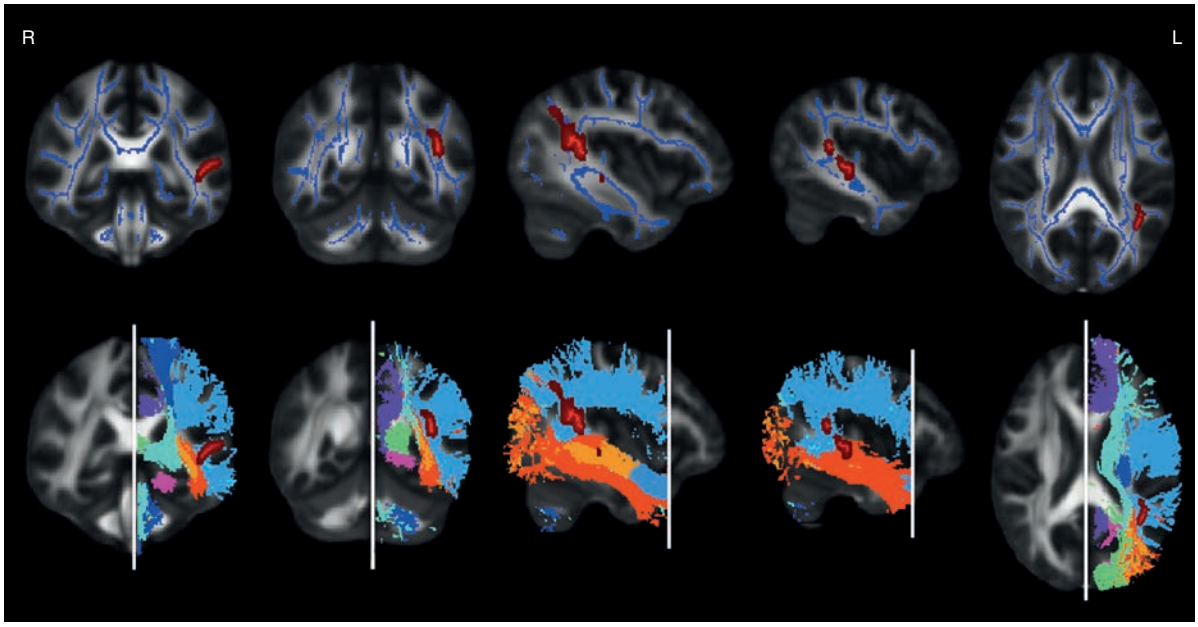

Fig. 1: Map of the fractional anisotropy (FA) differences between groups (patients < controls). The FMRIB58_FA (1 mm thick) template provided in FSL was used in all the figures. Top row: results are shown on top of the mean FA skeleton template created from all the participants' images for this study. Bottom row: results are shown on top of the atlas of tracts probability Johns Hopkins University–International Consortium for Brain Mapping (threshold 0 mm and 1 mm thick) provided in FSL; different shades correspond to specific probability tracts in the left hemisphere: superior longitudinal tract, corticospinal tract, cingulum, anterior thalamic radiation, splenium of the corpus callosum, inferior longitudinal tract and inferior fronto-occipital tract.

Table 2: Coordinates of the between-group differences in diffusion tensor measures

Diffusion measures	Geometrical centre and extension of the cluster	Pathway/region	Cluster size	MNI coordinates			
				x	*y*	*z*	*t**
FA	Patients < controls	Left superior longitudinal tract (parietal pars) extended to fibres of the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus	512	–43	–42	15	4.49
MD	Patients > controls	Fornix extended to bilateral anterior thalamic radiations	266	0	–7	11	4.92

FA = fractional anisotropy; MD = mean diffusivity; MNI = Montreal Neurological Institute.
*Corresponds to the region with maximal *t* value ($p_{FWE} < 0.05$ in all cases).

of the left SLF. Moreover, changes in this white matter tract might be present irrespective of the phase of the disorder, as suggested by findings reported in 2 recent DTI studies involving adolescent patients[8] and recovered patients.[28]

The results found in the left SLF seem functionally relevant to one of the characteristic features of anorexia nervosa, body image distortion. The medial and inferior parietal areas are involved in proprioception, size and spatial judgment, visual imagery and the integration of visual information — all of which are processes that conform the neural basis for the representation of the body self-image.[42] In turn, body-image perception is integrated in a functional network connecting prefrontal and parietal areas,[43] with the SLF being the major white matter tract connecting these regions. Accordingly, several studies have found differences between patients with anorexia nervosa and controls in the activity of the parietal cortex and prefrontal areas during the visualization of their own body image (see the review by Gaudio and Quattrocchi[42]). In addition, the unilateral location of our findings might relate to previously observed lateralization of self-image distortions in patients with anorexia nervosa to the left hemisphere.[43]

Superior longitudinal fasciculus alterations may also influence other cognitive processes. Some studies have demonstrated that both currently ill patients with anorexia nervosa and recovered patients have a specific perceptual cognitive style, the so-called "weak central coherence," which describes enhanced attention to local details at the expense of global processing.[44] These abnormalities are thought to rely on alterations of long-range connections between prefrontal and parieto-occipital areas in other disorders,[45] and these same areas also seem to be implicated in weak central coherence in patients with anorexia nervosa.[46] However, the specific role of the SLF in these deficits in patients with anorexia nervosa remains to be further investigated.

The pattern of alterations observed in the SLF, consisting of decreases in FA, increases in MD and RD and no modification of AD, seems consistent with a reduction in the degree of myelination in this area, as shown in animal models.[24] Given that long-range associative connections, such as the SLF, continue their myelination into adulthood,[47] it is possibile that these areas might be more vulnerable to factors involved in the onset and development of anorexia nervosa during adolescence and early adulthood. In turn, this vulnerability might be greater in some individuals, such as those with greater harm avoidance, given the correlation found between this personality trait and MD in this area in recovered patients.[28] Harm avoidance, however, was not correlated with either FA or MD results in our study.

Alternatively, considering that myelination is a dynamic process[48] and that changes in RD have been observed even after a short period of cognitive training[49] or meditation,[50] these white matter changes may reflect a plastic response to

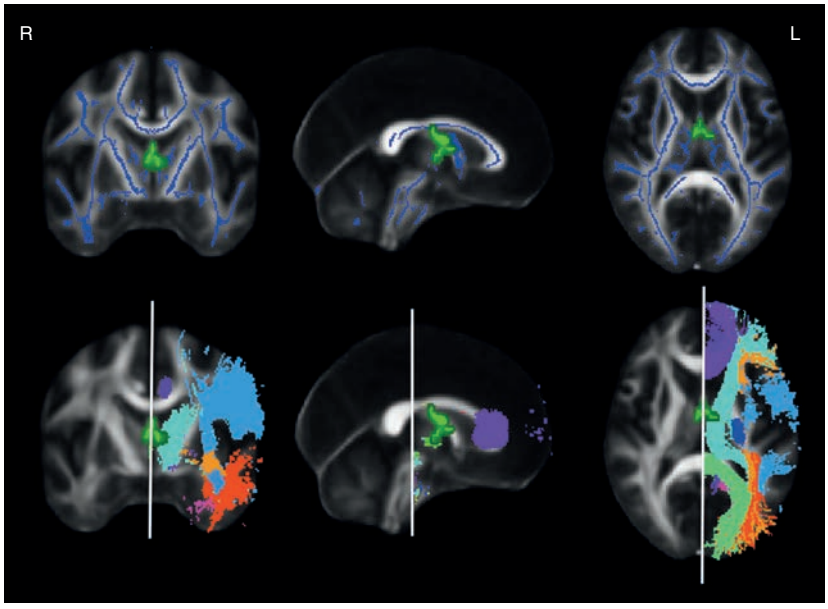

Fig. 2: Map of the mean diffusivity (MD) differences between groups (patients > controls). The FMRIB58_FA (1 mm thick) template provided in FSL was used in all the figures. Top row: results are shown on top of the mean FA skeleton template created from all the participants' images for this study. Bottom row: results are shown on top of the atlas of tracts probability Johns Hopkins University–International Consortium for Brain Mapping (threshold 0 and 1 mm thick) provided in FSL; shades correspond to specific probability tracts in the left hemisphere: superior longitudinal tract, corticospinal tract, cingulum, anterior thalamic radiation, splenium of the corpus callosum, inferior longitudinal tract and inferior fronto-occipital tract.

the cognitive distortions and symptoms of anorexia nervosa as well as to nutritional problems. However, we found no correlations with clinical variables to support these speculations. Different design approaches, such as the inclusion of a high-risk group or a longitudinal cohort, would be particularly informative in this context to further understand the nature of these alterations.

Changes in the fornix

The fornix is the main white matter tract connecting the hippocampus to the hypothalamus; it also connects the hippocampus to the ventral striatum and prefrontal areas, including the orbitofrontal and anterior cingulate cortices. Through the connections it forms between these structures, the fornix is a key structure involved in the regulation of body–energy balance and processing of reward responses.[51] Although these results should be interpreted with some caution owing to putative specific preprocessing problems of this area (i.e., misalignment),[52] it is interesting to note that they replicate the findings of several previous studies in currently ill patients with anorexia nervosa that showed either FA decreases or ADC/MD increases in the fornix[8,14] or in closely related areas, such as the mediodorsal thalamus.[26]

Two studies have reported hippocampal volume reductions in patients with anorexia nervosa,[53,54] and it is likely that some of the metabolic alterations implicated in the disorder might impair this structure and its connections. For example, the typically hyperactive hypothalamic–pituitary–adrenal axis observed in anorexia nervosa can lead to hippocampal atrophy in animal models.[3] The hippocampus has been implicated in weight-regulation processes,[55] and animal models have shown that both lesions of the hippocampus and fornix transections lead to alterations in eating behaviours.[56,57]

The reward system is also intrinsically related to body-energy regulation. This system is thought to underlie alterations in some eating behaviours,[58,59] and it has received increasing interest in recent years, being considered a key element in the development and maintenance of anorexia nervosa.[2,60] Actually, several studies have shown that patients

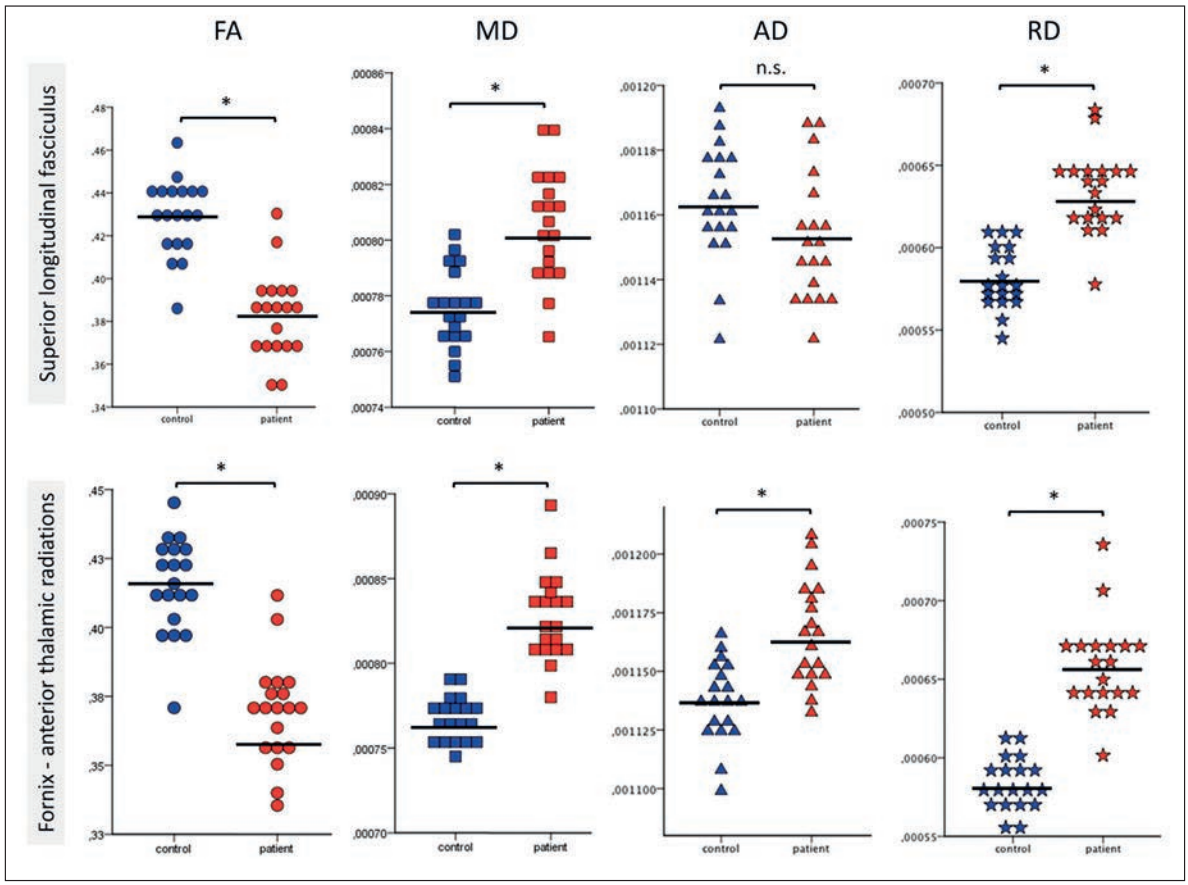

Fig. 3: Diffusivity measures' eigenvalues for patients and controls in the 2 regions with significant differences in fractional anisotropy (FA) and mean diffusivity (MD). Black horizontal lines represent the mean of the values represented in each plot. *Significant between-group differences of the extracted measures, all $p < 0.001$. AD = axial diffusivity; NS = nonsignificant comparison; RD = radial diffusivity. *$p < 0.05$.

with this disorder present deviant responses to the reinforcing characteristics of several types of disorder-relevant and nonrelevant stimuli and that such abnormal responses are probably implicated in the persistence of the pathological behaviour.[60]

While our observed MD and RD increases and FA decreases putatively relate to myelin decreases in the fornix, the biological significance of AD increases is still unclear. Some possibilities include increased extracellular water resulting from fibre atrophy, breakdown of axonal flux of water[61] and/or axonal reorganization.[62] These mixed results might reflect the effects of overlapping pathophysiological mechanisms in the fornix. It is also interesting to note that these mechanisms might be nonspecific to patients with anorexia nervosa, restricting subtype, since a similar pattern of microstructural alterations in the fornix has been found in patients with bulimia nervosa[63] and in overweight and obese individuals.[64] Even if some of these conditions have opposite behavioural consequences, some shared biological effects are suggested,[65] and it is likely that extreme weight conditions might have similar structural effects in this energy balance system.

Limitations

Our sample size was relatively modest and replication is required. However, we sought to improve on previous DTI studies in adults with anorexia nervosa by providing a more homogeneous sample, comprising currently ill patients with the restricting subtype of the disorder. Second, we included patients receiving current pharmacological treatment. Since the interaction between medications and DTI measures is still unknown, such an effect cannot be ruled out. Nevertheless, between-group differences persisted even after taking treatment status into account. Third, while the precise biological interpretations of the diffusion measures remain a topic of debate,[25] the detailed characterization of our results has provided testable hypotheses concerning regional pathophysiological alterations. In addition, the use of a 1.5 T MRI system limited our sensitivity to group differences compared with higher-field imaging techniques. In this regard, our findings may reflect a conservative estimate of the extent of white matter abnormalities in patients with anorexia nervosa. Finally, our results are limited to a cross-sectional design. It would be interesting to test whether these alterations might persist in a longitudinal assessment of the same participants — especially after recovery — or, alternatively, in comparison to a group of recovered individuals.

Conclusion

Our results provide new insight into the nature of white matter microstructural alterations in patients with anorexia nervosa. Alterations found in the SLF and the fornix were found to result from different microstructural changes, such that demyelination may be more prominent in the SLF and a combination of altered white matter myelination and integrity may characterize changes in the fornix. Taken together, alterations in these areas are consistent with previous findings and with prevailing hypotheses regarding the neurobiological basis of anorexia nervosa, as well as with core symptoms of the disorder, such as body distortion, dysfunctions in weight regulation and altered reward processing.

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Competing interests: J.M. Menchón declares personal fees from Eli Lilly, Janssen, Lundbeck, Medtronic, Otsuka, Rovi and Servier. N. Cardoner declares personal fees from AstraZeneca, Eli Lilly, Esteve, Ferrer, Pfizer and Janssen. No other competing interests declared.

Contributors: E. Via, A. Zalesky, B.J. Harrison, J. Pujol, F. Fernández-Aranda, J.M. Menchón, C. Soriano-Mas, N. Cardoner and A. Fornito designed the study. E. Via, I. Sánchez, L. Forcano, J. Pujol, F. Fernández-Aranda, C. Soriano-Mas and N. Cardoner acquired the data, which E. Via, A. Zalesky, B.J. Harrison, J.M. Menchón, C. Soriano-Mas, N. Cardoner and A. Fornito analyzed. E. Via, A. Zalesky and A. Fornito wrote the article, which all authors reviewed and approved for publication.

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Structural analyses: voxel-based morphometry (VBM)

Methods

Acquisition
A 130-slice 3-dimensional SPGR sequence in the axial plane (repetition time 11.84 ms, echo time 4.2 ms, pulse angle 15°, field of view 30 cm, matrix 256 × 256 pixels, in-plane resolution 1.17 mm^2, and section thickness 1.2 mm, without gap) was acquired.

Preprocessing
Preprocessing of SPGR images was conducted on a Macintosh platform running MATLAB 7.8 (MathWorks) and SPM8 (Wellcome Department of Imaging Neuroscience)[1]. Images were realigned, segmented using the "new segment" algorithm in SPM8[2], normalized with DARTEL tools[3] and smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel.

Analyses
Global grey matter and white matter volumes were obtained from segmented images in native space and used as covariates of no interest in the analyses. Global volumes were additionally compared between groups by means of independent samples *t* tests using SPSS (v. 20).

Whole-brain between-group differences in grey and white matter were explored at a corrected statistical threshold of $p_{FWE} < 0.05$. In addition, areas of differential fractional anisotropy or mean diffusivity were saved as masks and used in 2 separate region-of-interest (ROI) analyses to explore putative differences in volume in selected areas. In this case, we used small volume correction procedures and a statistical threshold of $p_{FWE} < 0.05$ corrected across the ROI.

Results

There were no differences in global grey and white matter volumes between controls and patients with anorexia nervosa (grey matter volume: mean 652.07 ± 43.93 in controls v mean 643.13 ± 48.73 in patients, $t_{36} = 0.59$, $p > 0.05$; white matter volume mean 474.19 ± 34.54 in controls v. mean 457.60 ± 35.22 in patients, $t_{36} = 1.47$, $p > 0.05$). Likewise, there were no regional between-group differences in grey or white matter volumes in either the whole brain or the ROI (superior longitudinal fasciculus and fornix) analyses.

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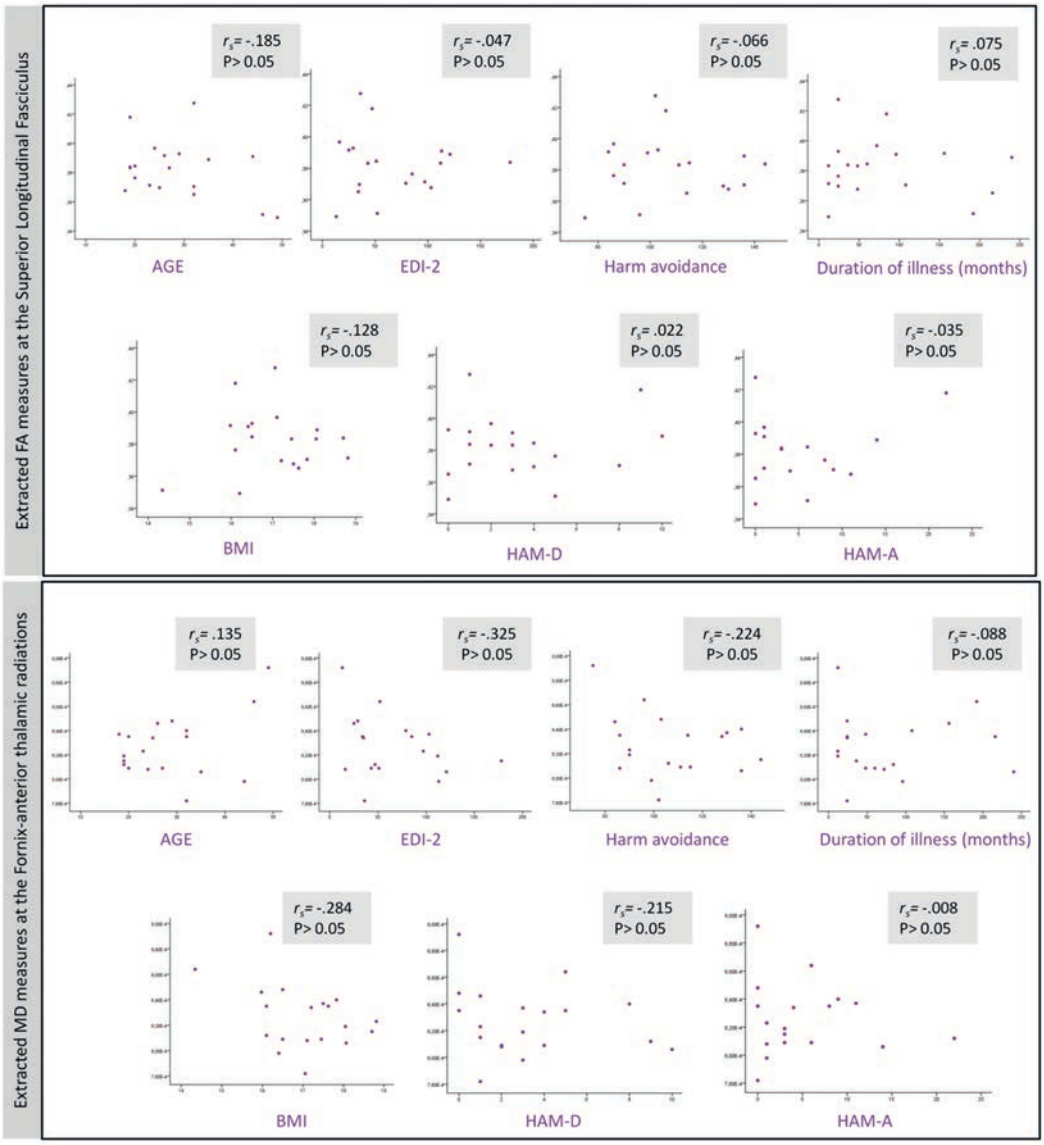

Fig. S1: Scatter plots representing the associations between diffusivity measures (fractional anisotropy [FA] at the superior longitudinal fasciculus and mean diffusivity [MD] at the fornix) and demographical/clinical variables. Light grey boxes show the statistical results of each correlation (Spearman correlation coefficients and *p* values). BMI = body mass index; EDI-2 = Eating Disorders Inventory-2; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression.

Appendix 2:

Figures in the original article are black and white and have been replaced here for the original coloured images. According to this modification, colour labels in Fig 1 and 2 are as follows:

Fig 1: Significant FA results in the SLF are shown in red in all the images, thickened for display purposes. Top row: blue color represents the mean FA skeleton template created from all the subject's images for this study. Bottom row: the atlas of tracts probability JHU-ICBM (threshold 0 and 1 mm thick) provided in FSL is partially shown in each brain slice; colors correspond to specific probability tracts in the left hemisphere: light blue: superior longitudinal tract, dark blue: corticospinal tract, purple and pink: cingulum, light green: anterior thalamic radiation, dark green: splenium of the corpus callosum, red: inferior longitudinal tract, orange: inferior fronto-occipital tract.

Fig 2: Significant MD results in the fornix are shown in bright green in all the images, thickened for display purposes. Top row: blue color represents the mean FA skeleton template created from all the subject's images for this study. Bottom row: the atlas of tracts probability JHU-ICBM (threshold 0 and 1 mm thick) provided in FSL is partially shown in each brain slice; colors correspond to specific probability tracts in the left hemisphere: light blue: superior longitudinal tract, dark blue: corticospinal tract, purple and pink: cingulum, light green: anterior thalamic radiation, dark green: splenium of the corpus callosum, red: inferior longitudinal tract, orange: inferior fronto-occipital tract.

Chapter 4

STUDY 2

"Abnormal Social Reward Responses in Anorexia Nervosa: An fMRI Study"

PLOS | ONE

RESEARCH ARTICLE

Abnormal Social Reward Responses in Anorexia Nervosa: An fMRI Study

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Abstract

Patients with anorexia nervosa (AN) display impaired social interactions, implicated in the development and prognosis of the disorder. Importantly, social behavior is modulated by reward-based processes, and dysfunctional at-brain-level reward responses have been involved in AN neurobiological models. However, no prior evidence exists of whether these neural alterations would be equally present in social contexts. In this study, we conducted a cross-sectional social-judgment functional magnetic resonance imaging (fMRI) study of 20 restrictive-subtype AN patients and 20 matched healthy controls. Brain activity during acceptance and rejection was investigated and correlated with severity measures (Eating Disorder Inventory -EDI-2) and with personality traits of interest known to modulate social behavior (The Sensitivity to Punishment and Sensitivity to Reward Questionnaire). Patients showed hypoactivation of the dorsomedial prefrontal cortex (DMPFC) during social acceptance and hyperactivation of visual areas during social rejection. Ventral striatum activation during rejection was positively correlated in patients with clinical severity scores. During acceptance, activation of the frontal opercula-anterior insula and dorsomedial/dorsolateral prefrontal cortices was differentially associated with reward sensitivity between groups. These results suggest an abnormal motivational drive for social stimuli, and involve overlapping social cognition and reward systems leading to a disruption of adaptive responses in the processing of social reward. The specific association of reward-related regions with clinical and psychometric measures suggests the putative involvement of reward structures in the maintenance of pathological behaviors in AN.

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Introduction

Anorexia nervosa (AN) is a severe and disabling psychiatric disorder. With limited evidence-based treatments available, at least 25% of patients show poor clinical outcome and high levels of functional and social impairment [1–5]. These data highlight the need for a better understanding of the underlying pathophysiological bases of AN, including the identification and precise delineation of the complex neural systems involved [6]. Current theoretical models describe AN as a multifactorial disorder [7,8] and, social factors, including both the impact of social environment and how individuals interact and process social information, are considered highly relevant to the development, maintenance and prognosis of the disorder [1,9]. Indeed, AN patients generally struggle to maintain interpersonal social relationships, with evidence of social difficulties and social anxiety symptoms, both in the premorbid state and after the disorder's onset [10,11]. However, little is known about the neural substrates responsible of these abnormal responses to social stimuli or their relevance in the disorder.

Reward-based processes have been highlighted as powerful and natural modulators of social interactions [12,13]. Indeed, social information is acquired using the same mechanisms of basic reward-based learning, (e.g. reward evaluation and associative learning) [12], such that past social experiences are used to predict future social outcomes, attempting to maximize rewards and avoid punishments [14]. At the neural level, reward- and punishment-based learning involves midbrain dopaminergic neurons sending large-scale projections to the ventral striatum, the amygdala, the ventromedial prefrontal cortex, the orbitofrontal and frontal opercula-insular cortices [12,15–19]. All these regions have been involved in reward response prediction, either to primary (e.g. the taste of food) or more complex reinforcements such social stimuli [14]. For example, the reward system has been shown to respond to gaze direction, images of romantic partners and even to the experience of being liked, among others [14,20]. Direct comparisons between social and other stimuli have also shown the overlapping nature of reward system responses to a broad variety of rewards [19,21]. Given the complex nature of social relationships, which require the integrated participation of a number of functions (e.g. social cognition, emotion processing and regulation [13,22]), these tasks have also shown to activate the reward system in conjunction with other areas, for example those involved in theory of mind and self-related regions [20].

In AN, increasing evidence has suggested altered responses of this so-called brain reward system. Early studies suggested a rewarding effect of starvation itself through an hypercortisolemic and hyperdopaminergic state [23], and, in the same line, the animal model of self-starvation/activity-based anorexia (ABA) has implicated imbalances in the brain reward system in AN, driven merely by modifications in food consumption and starvation [24]. Further development of conditioned processes based on this aberrant reward-system response have been also implicated in the pathophysiology of AN, where primary rewarding stimuli (such as food) might become aversive, and negative stimuli might become rewarding, as suggested by the *contamination reward theory* [25,26]. Biological evidences of this imbalance have come mainly from alterations in the concentrations of dopamine and its D2 receptor found both in AN patients and recovered subjects [27,28], as well as from functional magnetic resonance (fMRI) studies, which have shown abnormal responses of regions such as the ventral striatum, the anterior insula and the ventromedial prefrontal cortex [27,29,30]. For example, the ventral striatum has been found to present either a dysfunctional hyperactivation to the visualization of underweight bodies [31], an exaggerated [32,33] or a decreased [34] response to pleasant/sweet tastes, and even found to be non-discriminative between wins and losses in a monetary reward task [35]. These findings have been proposed as a potential trait marker of the disorder, given the presence of abnormal responses to disorder-specific and disorder-nonspecific stimuli [29]

in both ill and recovered AN patients [33]. In the context of social stimuli, AN patients might present similar alterations in their responses to reward. Data from behavioral studies have suggested a negative bias in social relationships: patients with AN perceive low reward from- and are avoidant of- social contexts and are oversensitive and attention-biased towards rejection [1,36–40]. These behavioral responses are modulated by the so-called approaching/avoidance systems [41,42], which in AN might be affected though alterations in personality traits linked to these systems [43]. Specifically, AN present consistent heightened scores in *sensitivity to punishment* and putative alterations in *sensitivity to reward*, thought to be vulnerability factors inherently associated with the illness [43–46]. Taken all together, the question arises as to whether altered brain reward responses are implicated in the processing of social stimuli in AN, and if present, whether they involve the same areas found to be altered for non-social rewards or expand to an extended network. Likewise, there are scarce evidences regarding the level to which sensitivity to reward and punishment might be modulating the responses to social stimuli.

We therefore investigated brain responses to social reward (acceptance) and punishment (rejection) in patients with restrictive-subtype AN in an fMRI experiment. Specifically, we used a modified version of a peer-oriented social judgment paradigm [20,47], previously shown to activate reward- and social processing- related brain regions, including the ventral striatum, the insular cortex and dorsal and ventromedial prefrontal cortices. We hypothesized that AN patients, when receiving socially rewarding peer feedback, would demonstrate reduced activity in these regions. When they received negative feedback we considered two possible outcomes. Considering AN heightened sensitivity and attention-bias to punishment and social rejection, one possibility would be to detect increased activation of regions engaged in attentional processing or in social rejection (e.g. the dorsal anterior cingulate and anterior insula cortices [48]). Alternatively, we might find evidences for a primary dysfunctional enhancement of reward-related activity, as has been found for other non-naturally rewarding stimuli in AN [31]. We also anticipated an interaction between reward brain areas and sensitivity to reward and punishment and explored whether an abnormal brain response to social reward/punishment would be modulated by the severity of the disorder.

Material and Methods

Participants

Twenty female patients with Anorexia Nervosa, restricting subtype [49] (mean age 28.40 years; SD 9.30 years) were recruited consecutively from admissions at the day patient program, Eating Disorders Unit of Bellvitge University Hospital, Barcelona between 2011 and 2012. Diagnoses were conducted by experienced psychologists/psychiatrists (E.V., I.S., F.F-A.) following DSM-IV TR criteria and using a semi-structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders) [50]. Five patients (25% of the sample) were on pharmacological treatment, as described elsewhere ([51]; Table 1). Comorbid psychiatric disorders—including any other eating disorder-, any neurological condition and abuse of any substance with the exception of nicotine were exclusion criteria. None of the patients met criteria for hospital admission at the time of scanning on the basis of physical consequences of excessive starvation.

20 healthy controls (20 females, mean age 28.15, SD 8.62) were recruited from the same sociodemographic area and matched by gender, mean age, handedness and mean educational level with the patients (Table 1). Controls were screened in order to exclude any psychiatric or other medical condition by means of the General Health Questionnaire (GHC-28, [52]) and a clinical semi-structured interview [53]. None of the controls presented subthreshold symptoms for any eating disorder and their body mass index (BMI) was within the normal range.

Table 1. Demographic and clinical description of the subjects included in the sample.

		AN patients (n = 20)	Healthy controls (n = 20)	Between group differences		
				t Statistic	p	Cohen's d
Age: mean in years (sd), range		28.40 (9.30), 18–49	28.15 (8.62), 19–52	0.09	.93	0.03
Handedness: right/left (number of subjects)		19/1	19/1	-	-	-
Educational level: mean in years of studies (sd), range		15.85 (3.56), 12–23	16.45 (2.46), 10–21	0.62	.54	0.19
Age at the onset: mean in years (sd), range		21.30 (9.26), 11–48	-	-	-	-
Illness duration: mean in months (sd), range		85.20 (76.88), 12–240	-	-	-	-
BMI: mean (sd), range*		16.94 (1.26), 14–18	20.99 (1.82), 18–25	8.47	< .001	2.59
EDI-2: mean (sd), range		66.79 (44.28), 13–178	13.53 (7.37), 3–28	5.17	< .001	1.68
	Drive for Thinness	10.35 (7.34), 0–21	0.90 (1.55), 0–6			
	Bulimia	1.25 (1.59), 0–4	0.05 (0.22), 0–1			
	Body dissatisfaction	11.20 (8.67), 0–27	2.40 (2.78), 0–9			
	Ineffectiveness	7.80 (7.95), 0–28	0.75 (1.16), 0–3			
	Perfectionism	7.10 (4.87), 1–17	3.60 (3.57), 0–12			
	Interpersonal distrust	3.40 (3.72), 0–11	0.65 (1.35), 0–5			
	Interoceptive awareness	6.45 (6.16), 0–20	0.25 (0.34), 0–2			
	Maturity fears	5.35 (4.84), 0–16	2.70 (2.89), 0–11			
	Asceticism	5.65 (3.96), 1–16	1.25 (1.12), 0–4			
	Impulse regulation	3.30 (4.52), 0–14	0.25 (0.64), 0–2			
	Social insecurity	4.95 (4.81), 0–17	0.40 (1.00), 0–4			
SPSRQ total: mean (sd), range		21.35 (7.06), 8–34	15.95 (6.95), 6–30			
SPSRQ Subscales:						
	SP	12.85 (5.45), 2–20	8.20 (4.37), 2–17	2.98	= .005	0.94
	SR	8.50 (4.22), 2–15	7.75 (4.35), 2–16	0.55	= .58	0.18
LSAS: mean (sd), range		44.60 (26.53), 9–89	25.65(16.60), 3–67	2.70	= .011	0.86
HDRS: mean (sd), range		3.30 (2.94), 0–10	0.90 (1.07), 0–3	3.43	= .002	1.08
HARS: mean (sd), range		4.95 (5.79), 0–22	1.65 (1.39), 0–4	2.48	= .025	0.78
Pharmacological treatment (n):						
	Selective serotonin reuptake inhibitors	3	-			
	Tricyclic antidepressant	1	-			
	Sedative antipsychotic +tricyclic antidepressant	1	-			

BMI: Body mass index. EDI-2: Eating Disorders Inventory-2. LSAS: Liebowitz Social Anxiety Scale. HDRS: Hamilton Depression Rating Scale. HARS: Hamilton Anxiety Rating Scale.

* Patients received at least one week of supervised meals and hydration before the MRI, and were scanned in the afternoon, 2–4 hours after lunch.

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Ethics statement

The ethical committee of clinical research (CEIC) of the Bellvitge University Hospital approved the study protocol, which was in compliance with the national legislation and the principles expressed in the Declaration of Helsinki. All participants gave written informed consent after detailed description of the study.

Clinical measures

For all participants, severity of symptoms and psychological features involved in eating disorders were assessed with the self-reported Eating Disorder Invertory-2 (EDI-2) scale [54]. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [55] and the Liebowitz Social Anxiety Scale (LSAS) [56] were also collected. Additionally, measurements of depressive and anxiety symptoms were collected by means of the Hamilton Depression Rating Scale (HDRS [57]) and the Hamilton Anxiety Rating Scale (HARS [58]).

Social Judgment Task

A modification of the task originally reported in Davey et al.[20] was used in the current study. Participants were assessed on two different days, approximately five days apart. On the first day, participants were asked to participate in a multi-center study about the influence of first impressions on deciding whether or not people would like to meet someone. They were presented a face database containing 70 people's faces with neutral expression (35 male and 35 female faces)—supposed to be study's participants from other collaborating centers- and were asked to decide if they would like to meet them or not (*acceptance/rejection*), rating their decision in a 10-point Likert-type scale—10 being the maximum for liking to meet someone (*score pre-scanning*). Likewise, participants had a photograph taken, which was supposedly sent and reciprocally scored by the database participants. This feedback was given during the fMRI scanning on the second day of assessment. In reality, the face database integrated pictures selected from a larger pre-existing and public available face database [59], and at the end of the experiment, participants were debriefed about the deception involved.

During the fMRI scanning, participants viewed a total of 54 of the 70 rated on the first assessment day. Each picture was presented for 8 seconds, and during the last 6 seconds a feedback symbol (a happy, sad or neutral draw of a face) was additionally displayed on the top right corner of the picture (Fig 1). Participants were instructed that happy face symbols indicated acceptance, and sad faces rejection. Neutral faces appeared when people supposedly could not be contacted to give feedback, which formed the control condition of the experiment. The 54 presented faces and the feedback responses were pseudo-randomly determined to ensure good balance between gender (27 male, 27 female) and between the three conditions (17 acceptance responses, 18 rejection responses and 19 control condition responses). The paradigm was presented visually on a laptop computer running E-Prime software on Windows (Psychology Software Tools, Inc., Sharpsburg, PA, USA, www.pstnet.com). Magnetic resonance imaging-compatible high-resolution goggles were used to display the stimuli.

After the scanning session, participants were presented again with the complete face database (70 faces). For each face, they were asked to recall if it appeared during the scanning and in each case what type of feedback the person had given. Participants were also asked about the first impression they had of each face on the first day (10-point Likert-type scale, *score post-scanning*). This assessment allowed exploration of potential attention and memory biases. A visual analogue scale was used to evaluate how they felt after receiving each one of the three types of feedback (scores ranging from 0 to 10). Finally, after debriefing about the nature of the

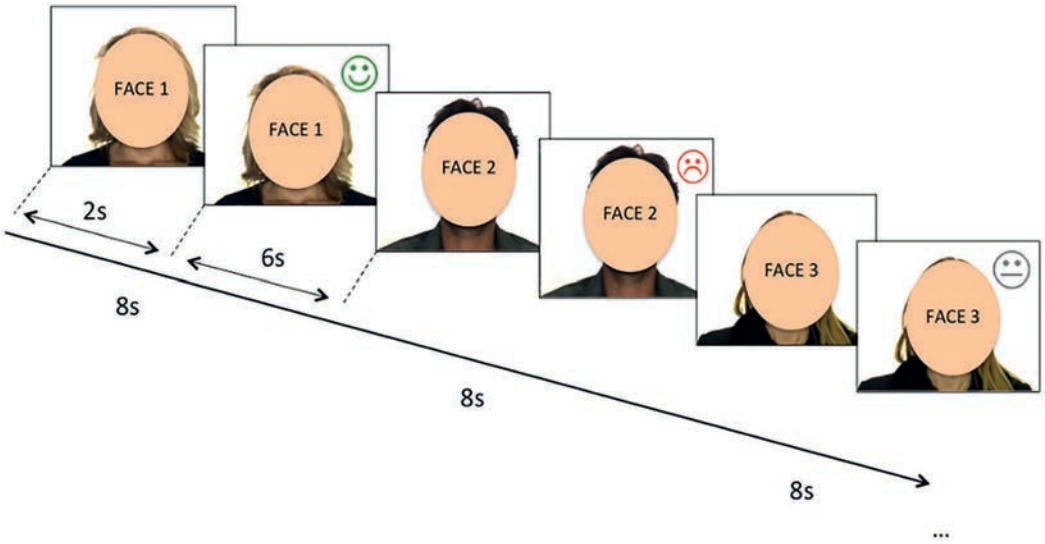

Fig 1. Diagram of the Social Judgment Task used in the fMRI session. Participants received social feedback based on the willingness to be met by other participants. Each facial stimulus (represented in by ovals instead of the originally presented faces) was presented for a total of 8 second-blocks, with an overlapping feedback symbol during the last 6 seconds. Acceptance, rejection or no-feedback (control condition) was indicated by a happy, sad, or neutral draw of a face. Originally presented images were contained in a preexisting face database: Martinez AM, Benavente R. The AR Face Database CVC Tech. Report #24 [Internet]. 1998. Available: http://www2.ece.ohio-state.edu/~aleix/ARdatabase.html.

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study, participants were asked to rate how much they believed they had received true feedback (scores ranging from 0 to 10).

Behavioral measures

Accuracy of recall on which faces had been displayed during the MRI session was compared between groups using a two-sample *t*-test. Next, the number of correctly remembered feedback responses was compared across groups and conditions by means of a mixed-design ANOVA analysis: task condition (acceptance, rejection, neutral) was included as the within-group variable and group (controls, patients) as the between-group variable (3x2 mixed ANOVA). Then, to compare, between groups, score changes across the two time points (pre-and post- scanning) and the three conditions, a second ANOVA analysis was conducted, with task condition and pre-post scores as the within-group variables, and group as the between-group factor (3x2x2 mixed ANOVA). Additionally, a similar 3x2 ANOVA was conducted to compare, between-groups and conditions, how the subjects felt when receiving each type of feedback. Finally, a two-sample t-test was conducted to compare, between-groups, how much they believed they were being truly evaluated. Behavioral analyses were performed in Statistical Package for the Social Sciences (SPSS) v20 on a Windows platform. Level of significance was set at $p<0.05$.

Imaging acquisition and preprocessing

A 1.5-T Signa Excite system (General Electric Milwaukee, WI, USA) magnetic resonance, equipped with an 8-channel phased-array head coil and single-shot echoplanar imaging software was used. The functional sequence consisted of gradient recalled acquisition in the steady

state (repetition time (TR) = 2000 ms, echo time (TE) = 50ms and pulse angle, 90°) in a 24 cm field of view, 64 x 64 pixel matrix and a slice thickness of 4mm (inter-slice gap, 1.5 mm). A total of 22 interleaved sections, parallel to the anterior—posterior commissure line, were acquired to generate 216 whole-brain volumes, excluding four initial dummy volumes to allow the magnetization to reach equilibrium.

Data were processed on a Macintosh platform running Matlab version 7.14 (The MathWorks, Inc) and statistical parametric mapping software version 8 (SPM8). Within participants, time-series of acquired images were initially realigned to the mean image by using a least squares and a 6-parameter (rigid body) spatial transformation. Images were then normalized to the standard echoplanar imaging (EPI) template in SPM and resliced in Montreal Neurological Institute (MNI) space (resulting voxel size 2 mm^3). Finally, they were smoothed with an 8 mm isotropic Gaussian filter. All image sequences were routinely inspected for potential movement or normalization artifacts.

Imaging processing and imaging analyses

For each participant, the onset and offset timing of the conditions (each 6-second block of the acceptance, rejection and neutral conditions, as well as the first 2-seconds of no-feedback), was convolved with a canonical hemodynamic response function to model the acquired BOLD signal. A high-pass filter was used to remove low-frequency noise (cut off period = 1/128 Hz). At a first single-subject level of analysis, contrasts were defined as: i) the acceptance condition *minus* the control condition; and ii) the rejection condition *minus* the control condition. Within-group contrast images were then carried to a mixed effects second-level, creating two-sample t-tests at each voxel to compare between-group brain activations.

Statistical analyses at the second level involved a combination of voxel and cluster correction methods providing a significance level equivalent to a Family Wise Error corrected p (pFWE)<0.05. Specifically, individual voxel threshold was set at an uncorrected $p<0.005$, while minimum spatial cluster extent (min. K_E) required to satisfy a pFWE<0.05 was determined by 1000 Monte Carlo simulations using the Alphasim algorithm as implemented in the SPM RESting-state fMRI data analysis Toolkit (REST) toolbox in Matlab [60]. Other input parameters included a connection radius of 5 mm and the actual smoothing value of each statistical comparison (between 13 and 16mm). Cluster extents were determined using a whole-brain mask for within-group activations and single masks containing combined (both groups) brain activations for the between-group comparisons (whole brain mask: 337,701 voxels, min. $K_E = 124$ for acceptance, min $K_E = 147$ for rejection; masks with combined brain activations: 4,568–27,851 voxels; min. K_E ranged between 29–99).

Additional analyses were conducted to explore the relationship between clinical measurements and brain activations during task performance. Firstly, to assess for potential and differential associations between sensitivity to reward/punishment and brain activations between groups, SPSRQ scores were included in two separate between-group interaction analyses (sensitivity to reward during acceptance and sensitivity to punishment during rejection). Secondly, brain activations in patients were correlated with EDI-2 scores in two separate regression analyses (acceptance, rejection). Levels of significance were set based on the same cluster correction methods used for the main analyses. For the interaction SPSRQ analyses, masks contained the combined activation of patients and controls in both the acceptance and rejection, while separate masks containing patients' activations during the acceptance and the rejection conditions were used for the correlation analyses with EDI-2 (masks contained between 4,787–36,673 voxels; min. $K_E = 4–118$). Age and depressive symptoms (see below) were included as nuisance covariates in all the analyses.

Results

Clinical and demographic variables

There were no statistically significant differences in age, handedness or educational level between patients and controls. As expected, body mass index (BMI) and EDI-2 measurements were significantly different in patients and controls, with lower mean BMI and higher mean EDI-2 scores in patients.

SPSRQ subtest scores indicated higher sensitivity to punishment in patients, with no differences in sensitivity to reward. Higher LSAS scores were also found in patients although differences did not survive Bonferroni correction for multiple testing. Similarly, depressive and anxiety symptoms were higher in patients compared to controls, but Bonferroni-corrected statistical significance was only observed for depressive symptoms (Table 1). Since anxiety and depressive symptoms were highly correlated ($r = .86$, $p < .001$), we only included depressive symptoms as a nuisance covariate in our analyses.

Behavioral measures

Both groups remembered with high accuracy which faces appeared during the fMRI task (AN patients: 69%, Controls: 65%). There were no interaction effects or between-group differences in the accuracy of recall to the different types of feedback; however, across conditions, all participants more accurately remembered being rejected in comparison to being accepted ($p < .001$) or receiving no feedback ($p < .001$; condition effect: $F(2,76) = 16.54$, $p < .001$). Similarly, there were no interaction effects or between-group differences in the *pre* and *post-scanning scores* across conditions, and all participants gave both higher *pre* and *post-scanning* ratings to faces that provided rejection feedback compared to acceptance or no feedback (both $p < .001$; condition effect: $F(2,76) = 36.43$, $p < .001$).

There were no interaction effects or between-group differences on how participants felt after receiving any type of feedback, and all of them liked more being accepted than rejected ($p < .001$) or receiving no feedback ($p < .001$; condition effect: $F(2,74) = 83.32$, $p < .001$). All participants indicated that they believed the participant ratings were genuine (mean (SD) out of 10: AN patients: 9.4 (1.30); Controls: 9.12 (1.21)). The results are summarized in S1 Table.

Imaging results

Main analyses: within-group results. In response to acceptance feedback, both groups showed an overlapping activation of the dorsal and ventral medial prefrontal cortices. Controls presented an additional activation of the ventral striatum and bilateral anterior insular cortices, whereas patients showed an additional activation of an area including the parahippocampal gyrus, hippocampus and amygdala.

Conversely, both groups presented a similar pattern of brain activation in response to rejection, with enhancement of the dorsomedial prefrontal cortex, anterior insular cortices and primary and secondary visual areas. Patients showed an additional activation of the ventral striatum, specifically in the ventral part of the caudate nucleus (Table 2, Fig 2).

Main analyses: between-group results. In response to acceptance, patients showed significantly decreased activation in a dorsomedial prefrontal cortex (DMPFC, Brodmann area 8-BA8-, extending to BA9) compared to controls. By contrast, patients showed increased activation of the left secondary visual cortex (parastriate BA18) during rejection (Table 2, Fig 2, and S1 Fig).

Interactions with clinical variables. In response to acceptance feedback, sensitivity to reward was differentially associated—between groups—with activity of bilateral frontal

Table 2. Within and between-group activations of extended brain regions during the performance of the task.

	Healthy controls	Anatomy [1]			Stats [2]		AN patients	Anatomy [1]			Stats [2]		Group comparisons	Anatomy [1]			Stats [2]	
		x	y	z	K_E	Z		x	y	z	K_E	Z		x	y	z	K_E	Z
Acceptance > neutral contrast													**Healthy controls> AN patients**					
	Medial superior frontal cortex (BA 8 and BA9, extending to BA6 and BA10)	-14	48	38	5 133	4.95	Medial superior frontal cortex (BA 8 and BA9, extending to BA10)	-10	36	60	1 104	3.92	Medial superior frontal cortex (BA8, extended to BA9)	10	32	50	127	3.38
		10	28	62		4.56		6	48	34		3.34		10	28	62		2.87
		-14	36	56		4.39		-8	54	34		3.30						
	Left dorsolateral prefrontal cortex/left anterior insular cortex	-48	14	24	2 000	4.08	Left parahippocampus, extended to hippocampus, fusiform and amygdala cortices	-34	-12	-22	330	3.75						
		-40	2	40		3.82		-30	-14	-14		3.46						
		-44	2	50		3.71		-38	-20	-26		3.45						
	Left temporo-parietal junction	-56	-56	46	696	4.01												
		-50	-60	52		3.42							**Healthy controls<AN patients**					
		-52	-58	30		3.37							No areas					
	Right frontal operculum/ right anterior insular cortex	46	32	-8	462	3.95												
		52	26	-2		3.85												
		46	26	-14		3.68												
	Bilateral ventral striatum (caudate)	8	10	10	125	3.45												
		-6	8	8		3.21												
Rejection > neutral contrast	Medial superior frontal cortex	-8	44	52	3 580	5.34	Medial superior frontal cortex	-4	52	22	2 302	4.77	**Healthy controls> AN patients**					
		-8	50	44		5.07		-8	38	58		4.54	No areas					
		12	42	50		4.59		-12	54	32		3.94						
	Left inferior frontal cortex, triangular and orbital parts/ Left anterior insular cortex.	-50	18	6	680	4.12	Right inferior frontal gyrus, operculum/right anterior insular cortex	32	24	-18	250	3.91						
		-38	26	-16		3.45	Left inferior frontal gyrus, operculum/ Left anterior insular cortex.	-30	16	-24	276	3.26						
		-44	36	-16		3.32		-28	22	-10		3.01						
	Right inferior frontal cortex, triangular and opercular parts/right anterior insular cortex	52	28	-6	292	4.00		-48	30	-14		3.00						
		60	24	20		2.82	Left ventral striatum (caudate)	-8	6	4	155	2.97	**Healthy controls<AN patients**					
		52	24	10		2.81		-6	14	-6		2.90	Visual cortex (BA18)	-30	-98	6	262	3,79
	Left middle temporal cortex	-50	-42	-2	226	3.38	Left visual cortex (BA17, BA18)	-32	-98	4	1 437	5.14						
		-52	-30	-8		2.86		-38	-58	-16		3.57						
	Visual cortex (BA17)	12	-92	4	281	3.86		-36	-74	-12		3.55						
							Right visual cortex (BA17, BA18), Fusiform gyrus	28	-98	0	1 260	4.78						
								22	-80	-14		3.50						
								12	-88	12		3.27						

[1] Activity co-ordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space.

[2] Magnitude and extent statistics correspond to a minimum threshold of $P_{FWE} < 0.05$ (cluster corrected at whole-brain).

K_E = cluster size.

BA = Brodmann area.

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opercula-anterior insula cortices (negative association in patients), and the dorsomedial and dorsolateral prefrontal cortices (BA8, BA10; positive association in controls; Fig 3, S2 Table). No areas of between-group interaction were found in response to rejection feedback.

There were no associations between symptom severity measured with the EDI-2 and brain activation observed in response to acceptance feedback. By comparison, symptom severity was both positively and negatively associated with brain activation observed in response to rejection feedback. Specifically, positive correlations were observed between symptom severity and ventral striatal-located at the ventral part of the caudate nucleus-, dorsomedial prefrontal (BA8), and visual cortical (BA17-BA18-BA19) activations, while negative correlations were observed with dorsolateral prefrontal cortex activation (Fig 4, S2 Table).

Several post-hoc analyses were conducted. First, and given the associations between illness duration and reward responses in other disorders [61], we extracted mean signal values from regions with significant results and correlated them with illness duration and age at onset, finding, however, no significant associations (S3 Table). Second, and because of the high prevalence of social anxiety in AN, social anxiety (LSAS) scores were included in correlation analyses using the same approach as for severity measures, to explore whether this putative contributing factor would be independently associated with brain responses to social acceptance and rejection. However, there were no associations emerging from these correlation analyses. Finally, to control for potential effects of treatment over brain activity during feedback presentations, we repeated all the above analyses excluding the 5 patients under pharmacological treatment (12.5% of the sample, 25% of the patients). Most of the results were replicated, except, for the patient group, the association between severity and brain activation during rejection at the dorsolateral prefrontal and visual cortices (BA19). Despite the lost of statistical power, the rest of results were replicated with reductions of the size of clusters with significant voxels-which therefore affected cluster-based corrected significance-, mainly at the level of bilateral anterior insula and dorsomedial prefrontal cortices in the sensitivity to reward interaction analysis (S2 Fig and legend).

Discussion

The results of the present study suggest that alterations in reward responses to social stimuli in AN involve an overlapping network of social cognition, attentional and reward-processing areas, highlighting the tight involvement of large-scale and distributed networks in complex processes such as social feedback evaluation [62,63]. Interestingly, the activation of reward-related structures in both conditions showed paradoxical associations with either the severity of the disorder or sensitivity to reward scores, suggesting their implication in disorder-related dysfunctional processing of social reward. Alterations in brain responses to reward and punishment, which have been implicated in the pathophysiology of AN, might also relevantly contribute to the dysfunctional social relationships experienced by AN patients. Although other factors such as social anxiety symptoms might modulate responses to reward in this context, the lack of associations between brain activations to reward/punishment and LSAS scores gives further relevance to the associations found with the severity of AN.

An extensive cluster located in the dorsomedial prefrontal cortex (DMPFC), which is commonly activated by social feedback [19], was non-specifically activated in both groups and in both conditions. Nevertheless, AN patients showed hypoactivation within this region during positive feedback. The DMPFC participates in social-cognition processes such as self-reference and reflective self-knowledge [64], making inferences about how we are viewed by others [65–68], and in inhibiting the tendency of using oneself as a reference during social judgments [68]. DMPFC hypoactivations have been observed in AN patients during the performance of related

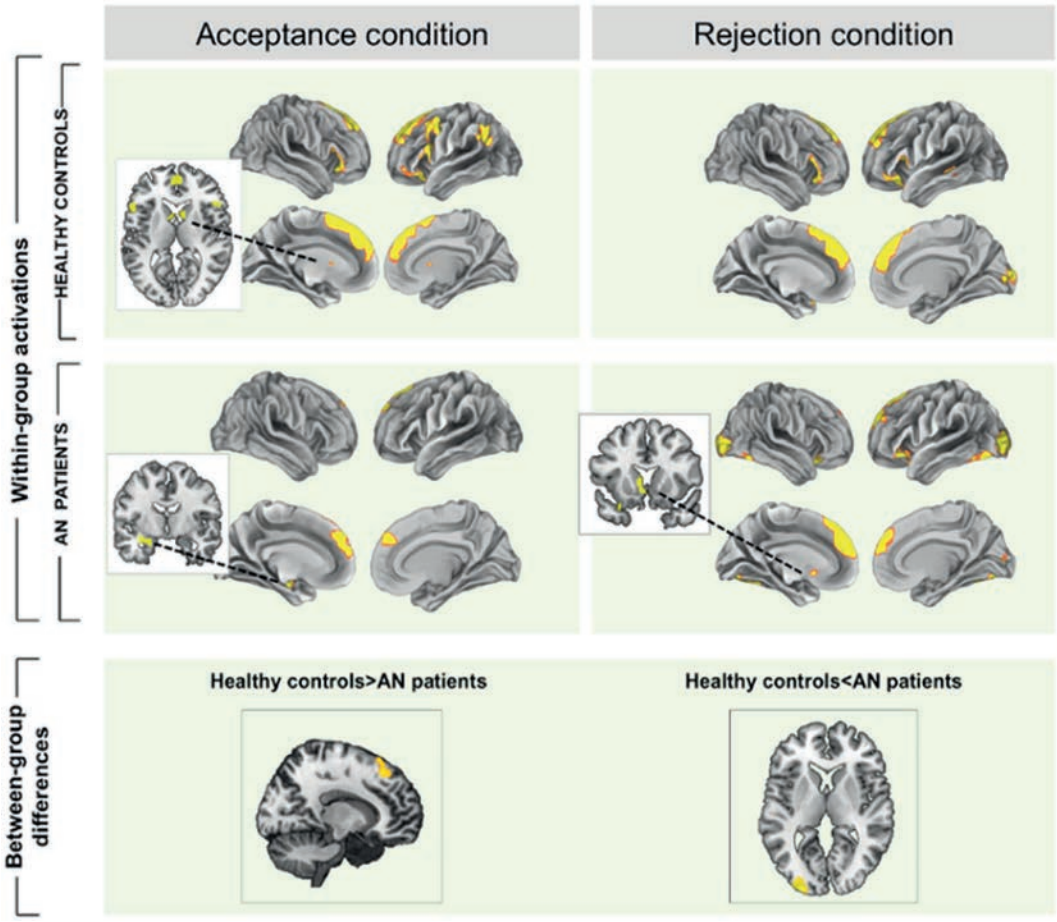

Fig 2. Within and between-group brain activations during acceptance and rejection feedback. Brain hyperactivations (i.e. contrast acceptance/rejection>control condition) are depicted in yellow and deactivations (i.e. contrast acceptance/rejection<control condition) are in blue. A and B represent within-group activations in A = controls and B = patients. Below, results for the comparison controls>AN patients and for the comparison AN patients>controls. Color bars represents T value, only for between-group comparisons. Images are displayed in neurological convention (left is left).

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tasks, such as theory of mind (attribution of intentions, BA10) [69] and self-appraisal (BA6, [70]). Additionally, the medial part of BA8 has been associated with tolerance to uncertainty [68,71,72] which, in social contexts, seems necessary for adaptively inferring other's mental state given the unpredictability of other's minds [68]. Reduced DMPFc activation in patients during acceptance suggests that self-evaluative processes and inference of other's mental states might be particularly disrupted in AN during rewarding social feedback, consistent with the reduced perception of reward value in AN [37,38], and indicating a general inhibitory-motivational response to social reward. Moreover, this response might be also associated with low tolerance to uncertainty and increased perception of lack of control in social relationships in AN patients [73], suggested to be compensated by increased control over eating, body shape and weight [10,27]. Since there was a positive association between DMPFc activity and EDI-2 scores during rejection, the opposite process—i.e increased motivational response through the engagement of the DMPFc- might be occurring when receiving negative feedback, although no between-group differences in DMPFc were found for this condition.

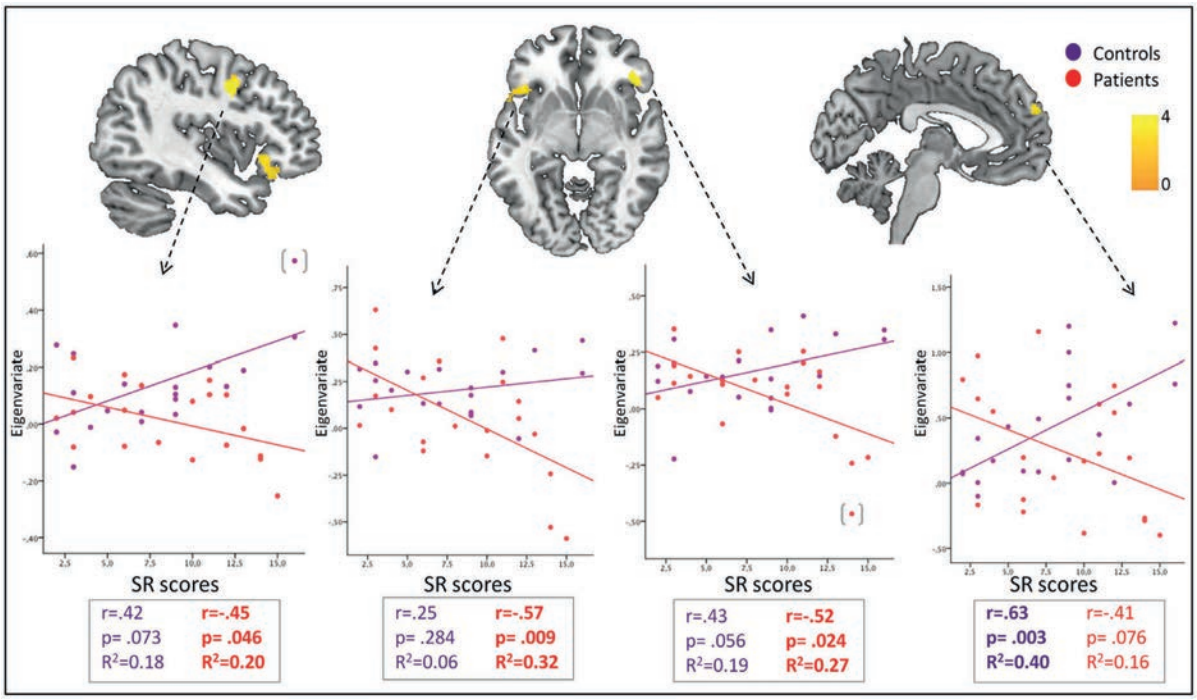

Fig 3. Interactions between Sensitivity to Reward and brain activations during the acceptance condition. Color bars represents T value. Images are displayed in neurological convention (left is left). Scatter plots represent Pearson's correlations between sensitivity to reward scores and the extracted mean eigenvalues in each relevant cluster: A. Dorsolateral prefrontal cortex. B. Left orbitofrontal-anterior insula cortex. C. Right orbitofrontal-anterior insula cortex. D. Dorsomedial prefrontal cortex. A results table is included, showing peak coordinates of each cluster and their corresponding statistics. (): Two outliers were detected based on the Tukey's Outlier Filter. Although depicted in the figure, they were removed from correlation analyses.

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During rejection, the pattern of activations was more similar between groups. Activation of the attention-network (visual cortex), together with behavioral results—rejection responses were better remembered—suggests increased attention during rejection in both groups. However, AN patients presented hyperactivation of left parastriatal visual regions, which were additionally correlated with the severity of the disorder. These results are consistent with attentional biases to negative social stimuli found in behavioral studies of AN [37,74], and might again indicate a distorted motivational drive towards negative stimuli. In other disorders, such as depression and anxiety, attentional biases towards negative stimuli have been found to increase and maintain the pathological state, but also to be modifiable [75]. Attentional bias modification strategies have been suggested in AN, and might be particularly helpful in changing cognitive biases to negative social stimuli through modification of attentional pathways [75]. Consistent with previous hypotheses, our results suggest the relevance of combined alterations in social motivation and visual orienting brain areas contributing to impaired interpersonal relationships in AN, similar to what has been observed in other disorders [10,38].

We additionally observed a between-group differential pattern of associations between brain responses and sensitivity to reward. It is worth mentioning that these differences were found even though there were no differences in sensitivity to reward scores. Indeed, while it is reasonably well established that AN patients present higher sensitivity to punishment, evidences for sensitivity to reward are mixed, and, if present, they might be more relevant in samples composed by purgative rather than restrictive subtype patients [46,76]. However, these

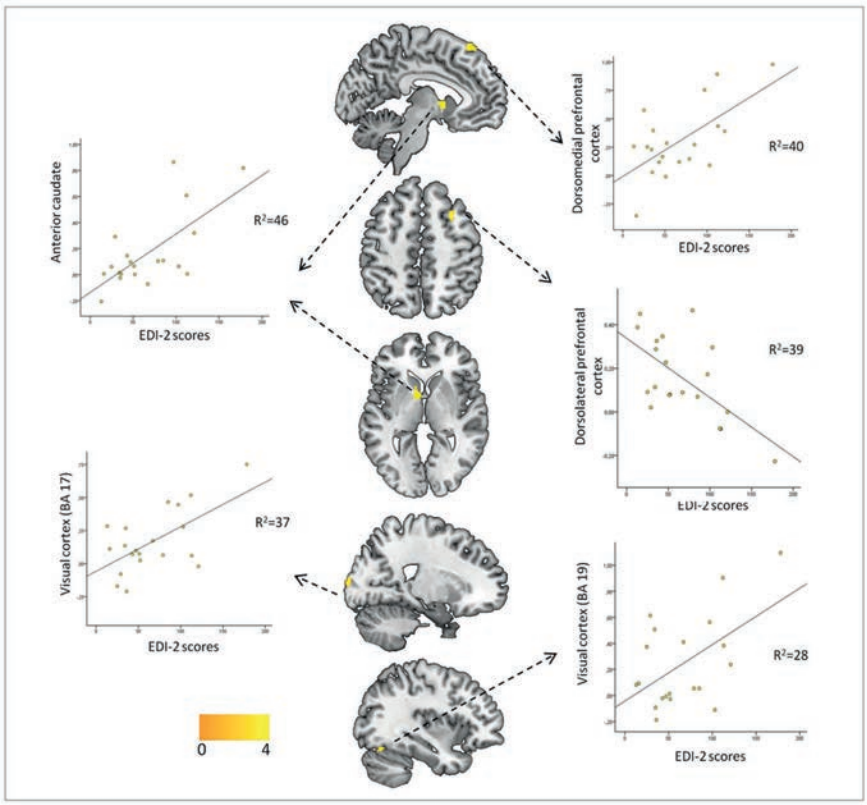

Fig 4. Associations between EDI-2 scores and brain activity in AN patients during rejection feedback. Color bars represents T value. Images are displayed in neurological convention (left is left). Scatter plots represent Pearson's correlations between EDI-2 scores and the extracted mean eigenvalues in each one of the significant clusters. A results table is included, showing peak coordinates of each cluster and their corresponding statistics.

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negative findings in the drive for rewards are not incompatible with alterations in either the reward perceived or in the interaction between the drive and perceived reward from social relationships. In our study, while control participants with high reward sensitivity engaged cognitive-control structures—possibly regulating an elevated motivational drive during positive feedback—AN patients showed a negative association between insula activation and sensitivity to reward. Neurobiological models of sensitivity to reward suggest its encoding in a cortico-limbic system including the reward loop linking the midbrain and ventral striatum with the prefrontal cortex [77], and, among them, the anterior insula has suggested to be more specifically involved in social rewards [78]. This region has been strongly hypothesized to be involved in the pathophysiology of AN [79], and some studies have found insula hypoactivation during the processing of primary rewarding stimuli both in ill [80] and recovered AN patients [34,81]. Indeed, these results suggest that in AN patients there is a disruption of the expected association between incentive motivation and the hedonic insular involvement in reward [82,83]. Such uncoupling of *wanting* from *liking* has been previously proposed in AN in other contexts [84] and might indicate here a dysfunctional compensatory response to a natural motivational drive for social rewards [85]. According to our results, besides its implication in altered

processing of basic rewards in AN, anterior insula may also lose control over more complex reward-related responses, such as those dependent on social feedback.

Finally, the ventral striatum (VS) activation during rejection feedback was associated with the EDI-2 scores. This association was only found during rejection, and might be evidence of aberrant functioning of this system during social interactions in AN, similar to the observed VS activation when patients viewed emaciated bodies [31], or received losses in a monetary task [35]. Interestingly, the results were mainly located in the ventral part of the caudate nucleus, which has shown its involvement in reward processing particularly when feedback is involved and in the context of social learning [86]. In any case, while the above findings seem to imply that the suggested aberrant response of this structure to a range of rewards might be also mediating altered social reward-based responses, other explanations should be also taken into account. For example, VS activity might be compensating for emotional pain associated with rejection, similar to VS activation in placebo-induced analgesia [87]. The specific contribution of these factors, however, requires further investigations.

Limitations

Our sample size was relatively modest and replication is required. However, we assessed for the first time brain responses in AN patients during social feedback, as well as their association with clinical and personality variables. Secondly, we included patients on current pharmacological treatment. Although it is unclear the direction in which treatment might bias these specific results, the exclusion of the 5 medicated participants—and despite the lost of statistical power- did not substantially modified our main results. However, medication effects cannot be ruled out, suggesting there is a need for further evaluation of this issue. Thirdly, we did not conduct a metabolic study in our protocol, which could have allowed a better characterization of the sample and the investigation of putative associations between altered metabolic variables and our findings. However, Day Unit recruitment—patients with BMI$\geq$14 in our centre, with better metabolic profiles-, was conducted in order to minimize possible confounding effects of malnutrition on both task performance and BOLD signal. Fourthly, our study was restricted to low-weight adult AN females, with no comorbidities, and used a cross-sectional design. It will be interesting for future studies to test our results in other populations, such as patients with comorbidities, men, or adolescent samples. Moreover, although we did not find associations between our results and age at onset or illness duration, it would be equally interesting to assess the involvement of these alterations in the onset of the disorder, as well as their impact on the prognosis and outcome of patients, and whether they persist after weight restoration and symptom recovery. Longitudinal studies, the study of patients who have recovered, or intermediate phenotypes, might be of particular interest in answering these questions.

Conclusions

Our results suggest a possible link between altered patterns of social relationships in AN and dysfunctional reward-related brain responses. These alterations might be of relevance in the maintenance of social maladaptive responses and eventually in the persistence of the disorder, and might help to explain the elevated resistance to change in patients with AN. Although alterations to functioning of the reward system have been highlighted recently in several psychiatric disorders, given the rewarding nature of food and the involvement of the reward circuit in food consumption (i.e. insula and frontal operculum, ventral striatum and amygdala, midbrain and frontal cortex) [88], these associations are of particular relevance for eating disorders such as AN [27]. In view of our findings it would be interesting for future studies to test the effectiveness of reward-processing-focused treatments, which might be easily included in

therapies such as cognitive remediation or fMRI-based neurofeedback training. For example, patients with anorexia nervosa might be trained to engage specific structures (e.g. DMPFc, ventral striatum) in front of social rewarding contexts such as social approval [89], which might ultimately improve their social responses and functional impairment. However, to our knowledge, there have been no studies using neurofeedback in AN, and the use of neurofeedback with complex stimuli such as social responses is still a field in development [90]. Additionally, it would be also of interest to examine other aspects of reward processing in social settings, such as the influence of reward expectations and prediction error in social relationships. Similar paradigms might also be interesting in the context of current trials on oxytocin [91], to evaluate treatment-mediated changes in the processing of social stimuli in AN.

Supporting Information

S1 Fig. Parameter estimates (β values) of the main conditions. Footnote: Bar charts represent parameter estimates at the medial prefrontal cortex (x,y,z = 10,32,50) and visual cortex-BA18 (x,y,z = -30, -98, 6).
(DOC)

S2 Fig. Overlapping maps of between-group differences including and excluding patients on pharmacological treatment. Footnote: [A] Main task comparisons: Acceptance: vmPFC: 68voxels, Z = 3.01, PFWE-equivalent = .04; Rejection: visual cortex (paraestriate BA18): 31voxels, Z = 2.90, PFWE-equivalent = .05. [B] Correlations: Acceptance-sensitivity to reward interaction: dorsolateral prefrontal cortex: 61voxels, Z = 3.17, PFWE-equivalent = .04; DMPFc: 5 voxels, Z = 2.92, PFWE-equivalent>.05; right frontal opercula-insula: 9 voxels, Z = 2.69, PFWE-equivalent>.05; left frontal opercula-insula: 1 voxel, Z = 2.59, PFWE-equivalent>.05. Rejection-severity correlation: DMPFc: 82 voxels, Z = 3.30, PFWE-equivalent = .01; anterior caudate (ventral striatum): 7voxels, Z = 2.69, PFWE-equivalent = .05; visual cortex (BA17): 10voxels, Z = 2.87, PFWE-equivalent = .05) (Dorsolateral prefrontal cortex and visual cortex (BA19) were not present even when lowering the voxel threshold to .01). PFWE-equivalent indicates the Alphasim cluster-based corrected significance, with a minimum threshold of p>.005 uncorrected at the voxel-level.
(DOC)

S1 Table. Behavioral responses of the subjects included in the study. Footnote: *Recall of rejection>recall of acceptance>recall of no feedback, all p <.001. ‡ Scores to faces giving rejection> scores to faces giving acceptance; Scores to faces giving rejection> scores to faces giving no feedback, both for pre and post scores and all p <.001. † Accepted>no feedback given>rejected, all p <.001.
(DOC)

S2 Table. Coordinates and statistics of correlation and interaction analyses.
(DOC)

S3 Table. Correlations between extracted eigenvalues of significant regions and clinical variables of interest.
(DOC)

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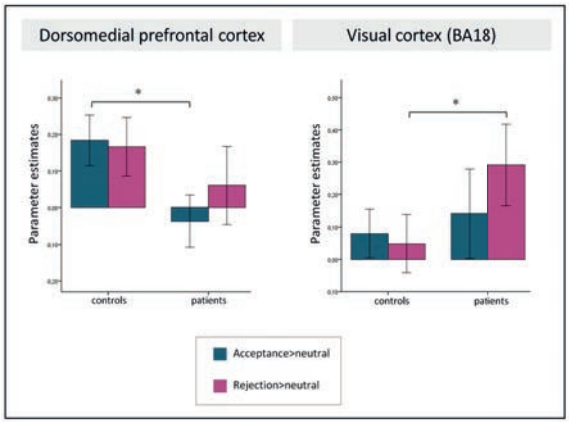
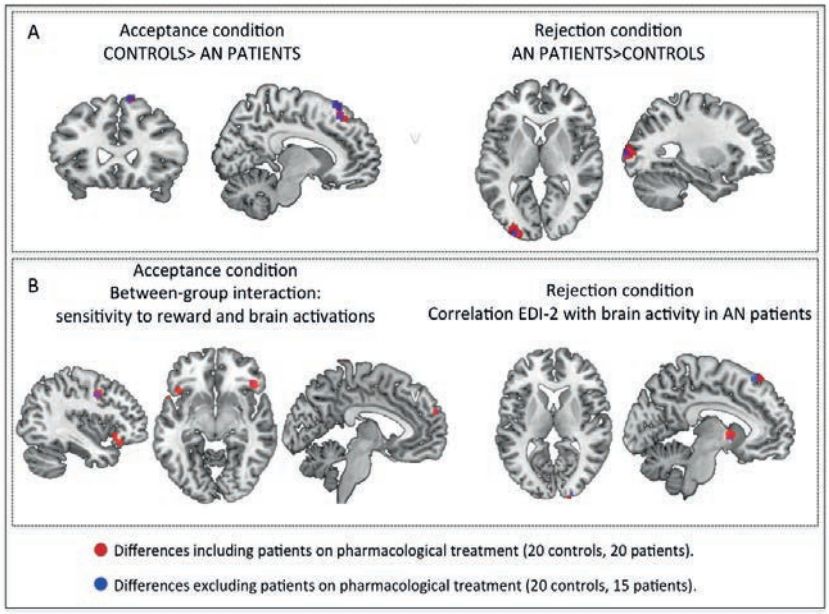
S1 Fig. Parameter estimates (β values) of the main conditions.



Bar charts represent parameter estimates at the medial prefrontal cortex (x,y,z=10,32,50) and visual cortex-BA18 (x,y,z=-30,-98, 6).

S2 Fig. Overlapping maps of between-group differences including and excluding patients on pharmacological treatment.



[A] Main task comparisons: **Acceptance:** vmPFC: 68voxels, Z= 3.01, P_{FWE}-equivalent= .04; **Rejection**: visual cortex (paraestriate BA18): 31voxels, Z= 2.90, P_{FWE}-equivalent= .05. [B] Correlations: **Acceptance-sensitivity to reward interaction**: dorsolateral prefrontal cortex: 61voxels, Z=3.17, P_{FWE}-equivalent=.04; DMPFc: 5 voxels, Z= 2.92, P_{FWE}-equivalent>.05; right frontal opercula-insula: 9 voxels, Z=2.69, P_{FWE}-equivalent>.05; left frontal opercula-insula: 1 voxel, Z=2.59, P_{FWE}-equivalent>.05. **Rejection-severity correlation**: DMPFc: 82 voxels, Z=3.30, P_{FWE}-equivalent=.01; anterior caudate (ventral striatum): 7voxels, Z=2.69, P_{FWE}-equivalent=.05; visual cortex (BA17): 10voxels, Z=2.87 , P_{FWE}-equivalent=.05) (Dorsolateral prefrontal cortex and visual cortex (BA19) were not present even when lowering the voxel threshold to .01).

P_{FWE}-equivalent indicates the Alphasim cluster-based corrected significance, with a minimum threshold of *p*>.005 uncorrected at the voxel-level.

S1 Table. Behavioral responses of the subjects included in the study.

Behavioural-task related measurements, mean (SD)		AN patients (n=20)	Healthy controls (n=20)	t/F statistics	p	*Partial eta squared*
Number of correctly classified faces (appearing or not during the fMRI task) (out of 70 faces)		48.20 (7.62) (69%)	45.79 (8.80) (65%)	t(37)=0.92	.37	.02
Accuracy in the recall of feedback responses (out of 54 faces)		18.60 (7.18) (34%)	18.80 (8.48) (35%)			
	Recall of acceptance responses (out of 17)	6.05 (2.50)	5.75 (2.77)			
	Recall of rejection responses (out of 18)	7.75 (2.77)	7.40 (3.25)			
	Recall of no feedback responses (out of 19)	4.80 (2.78)	5.65 (3.92)			
	Group effects			F(1,38)=0.01	.94	~0
	Condition effects			F(2,76)=16.54	<.001*	.30
	Interaction effects			F(2,76)=1.30	.28	.03
Scores given to face database (pre and post-scanning) (0-10)						
	To faces giving acceptance -pre	5.06 (0.65)	5.29 (0.02)			
	To faces giving acceptance -post	5.17 (0.71)	5.19 (0.07)			
	To faces giving rejection -pre	5.44 (0.05)	5.59 (0.54)			
	To faces giving rejection -post	5.41 (0.72)	5.44 (0.70)			
	To faces giving no feedback –pre	5.02 (0.78)	5.11 (0.53)			
	To faces giving no feedback –post	5.07 (0.71)	5.11 (0.56)			
	Group effects			F(1,38)=0.29	.59	.01
	Condition effects			F(2,76)=36.43	<.001‡	.49
	Scores by condition effects			F(2,76)=0.51	.54	.01
	Interaction (scores by condition by group) effects			F(2,76)=0.27	.69	.01
Scores of “how did you feel when being…” (0-10)		(N=19)	(N=20)			
	Accepted	8.05 (1.54)	7.63 (1.05)			
	Rejected	4.05 (1.81)	3.65 (1.35)			
	No feedback given	4.90 (0.46)	5.16 (1.09)			
	Group effects			F(1,37) =0.99	.32	.03
	Condition effects			F(2,74) =83.32	<.001†	.69
	Interaction effects			F(2,74) =0.77	.43	.02
Believe of being rated (0-10)		(N=15) 9.4 (1.30)	(N=16) 9.12 (1.21)	t(29)=0.62	.54	.01

*Recall of rejection>recall of acceptance>recall of no feedback, all p<.001. ‡ Scores to faces giving rejection> scores to faces giving acceptance; Scores to faces giving rejection> scores to faces giving no feedback, both for pre and post MRI scores and all p<.001. † Accepted>no feedback given>rejected, all p<.001.

S2 Table. Coordinates and statistics of correlation and interaction analyses.

Correlation in AN patients between EDI-2 scores and brain activation in response to the rejection condition					
Anatomy	**Coordinates**			**Stats**	
	x	**y**	**z**	K_E	**Z**
Dorsomedial prefrontal cortex (BA 8)	-8	38	60	71	3.70
Dorsolateral prefrontal cortex (BA 8)	30	14	50	40	2.97
Anterior caudate	-10	4	0	67	3.70
	-10	14	0		2.75
Associative visual cortex (BA 19)	-34	-68	-20	22	3.18
Primary visual cortex (BA 17 extending to BA18)	18	-100	10	16	3.00
Interactions between Sensitivity to Reward and brain activations in AN patients and controls in response to the acceptance condition.					
Anatomy	**Coordinates**			**Stats**	
	x	**y**	**z**	K_E	**Z**
Right frontal opercula-anterior insula complex / Inferior frontal-lateral orbitofrontal cortex	44	30	-10	144	3.76
	-56	12	12	312	3.12
	-42	22	-6		3.11
	-44	30	-16		3.08
Dorsolateral prefrontal cortex (BA6)	-42	0	40	120	3.67
Dorsomedial prefrontal cortex (BA10)	-6	62	28	120	3.49
	6	60	26		3.03

S3 Table. Correlations between extracted eigenvalues of significant regions and clinical variables of interest.

		Illness duration (months)	Age at the onset
Acceptance condition	Dorsomedial prefrontal cortex	r=.10 *p*=.68	r=.19 *p*=.42
	Right frontal opercula- anterior insula	r=-.09, *p*=.72	r=.31, *p*=.19
	Left frontal opercula-anterior insula	r=-.01, *p*=.95	r=.30, *p*=.19
	Dorsolateral prefrontal cortex	r=-.15 *p*=.52	r=.39 *p*=.09
Rejection condition	Visual cortex (BA18)	r=-.20 *p*=.39	r=.18 *p*=.46
	Ventral striatum (anterior caudate)	r=-.36 *p*=.15	r=-.45, *p*=.07
	Dorsomedial prefrontal cortex	r= -.14 *p*=.56	r=.03 *p*=.91
	Dorsolateral prefrontal cortex	r=.18 *p*=.46	r=-.22 *p*=.35
	Visual cortex (BA19)	r=-.004 *p*=.99	r=-.18 *p*=.44
	Visual cortex (BA17)	r= -.41 *p*=.08	r=-.12 *p*=.63

Author Contributions

Conceived and designed the experiments: EV CSM BJH CGD JP IMZ JMM FFA NC. Performed the experiments: EV CSM IS LF IMZ NC. Analyzed the data: EV CSM NC. Contributed reagents/materials/analysis tools: EV CSM IS LF BJH CGD JP IMZ JMM FFA NC. Wrote the paper: EV CSM IS LF BJH CGD JP IMZ JMM FFA NC.

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Chapter 5

STUDY 3

"Default Mode Network alterations during self-other body perception and resting-state in anorexia nervosa"

Chapter 5- Study 3: Default Mode Network alterations during self-other body perception and resting-state in anorexia nervosa

(In review)

Default Mode Network alterations during self-other body perception and resting-state in anorexia nervosa

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Running title: Body evaluation in anorexia nervosa.

Key words: anorexia nervosa, fMRI, rest, self-evaluation, body image.

Abstract

Body image distortion is a core symptom of anorexia nervosa (AN), which involves alterations in self- (and other) evaluative processes arising during body perception. At a neural level, self–related information is thought to rely on areas of the so-called default mode network (DMN), which, additionally, shows prominent synchronized activity at rest. Twenty female patients with AN and 20 matched healthy controls were scanned using magnetic resonance imaging when: a) viewing video clips of their own-body and another's body; and b) at rest. Between-group differences within the DMN during task performance were evaluated and further explored for task- and resting-state related functional connectivity alterations. In AN patients, alterations were observed in the posterior cingulate cortex (PCC) and precuneus during either the processing of own's or another's body image. Task-related connectivity alterations were found between PCC –dorsal anterior cingulate cortex and precuneus - mid temporal cortex. Further, resting-state connectivity between the PCC and the angular gyrus was decreased in AN patients. The PCC and the precuneus are suggested as key components of a network supporting self-other evaluative processes implicated in body distortion, while the existence of DMN alterations at rest might reflect a sustained, task-independent breakdown within this network in AN.

WORD COUNT

Abstract: 200 Text: 4,635

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Supplementary information: Text: 1, Figures 3, Tables: 3

Introduction

Body image distortion is a core symptom of anorexia nervosa (AN)(American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000), which often precedes the onset of the disorder(Jacobi et al., 2004) and contributes to the relapse of symptoms(Keel et al., 2005). It is considered a multidimensional construct encompassing alterations in the integration of body perception, the affective response to one's own body and the higher-order cognitive appraisal of body image(Fernández-Aranda et al., 1999; Gaudio and Quattrocchi, 2012). This latter feature is suggested to involve self-evaluative processes arising from a system of perceptions, attitudes and beliefs, as well as the mental representation of one's own body, and has been argued as the most relevant component of body image distortion(Benninghoven et al., 2007; Kaye, 2008; Legrand, 2010). Alterations in self-evaluative processes involved in body distortion extend to other areas in AN, being a core domain of its psychopathology(American Psychiatric Association and Association, 2000; Stein and Corte, 2007). For example, AN patients display impairments in emotional self-knowledge (alexithymia)(Beadle et al., 2013), low interoceptive awareness (Kaye, 2008), alterations in identity development and fewer self-schemas(Stein and Corte, 2007), increased self-reflection(Philippi and Koenigs, 2014), and overdependence on self-evaluation(American Psychiatric Association and Association, 2000; Zanetti et al., 2013). Moreover, body perception is a relevant component of the self-concept(Ainley et al., 2014; Seth, 2013; Stowers and Durm, 1996; Webster and Tiggemann, 2003), and serves as our interface with others (Adolphs, 2009), establishing a link between body and the understanding of other's mind, and social cognition(Bosbach et al., 2005; Cavanna and Trimble, 2006; Tsakiris et al., 2010). Self-related processes during body perception seem a key element to the self -and through it, to the relationship with others- in AN; however, their biological bases are not well established.

In the last years, neuroimaging studies have suggested that self-referential and self-evaluative mental activity processes rely on the so-called default mode network (DMN). The DMN involves a set of areas that show synchronized increased activation during resting periods compared to tasks, and which actively respond to self-related processes such as autobiographical memory recall, prospective thinking and self-judgments(Harrison et al., 2008; Northoff et al., 2006; Preedy, 2011; Raichle et al., 2001; Zhu et al., 2012), including the evaluation of one's own body and the sense of body-ownership(Northoff et al., 2006; Tsakiris et al., 2010). This network has also shown to present an anticorrelated activation with task-related networks, although both networks might positively couple during self-reflective cognitive demanding tasks(Anticevic et al., 2012). These areas include the posterior cingulate cortex and precuneus, the inferior parietal cortices, bilateral lateral temporal cortex, the insula, and dorsal and

ventral areas of the medial frontal cortex(Raichle et al., 2001). In AN, a few studies have found resting-state alterations in the connectivity of DMN regions, including between the anterior cingulate and the precuneus(Lee et al., 2014; Mcfadden et al., 2014), and between the DMN and frontal and parietal cortices(Cowdrey et al., 2014), which were suggested to imply a dysfunctional self-referential network involved in rumination about body shape, weight and eating(Cowdrey et al., 2014).

Body perception has been shown to activate an extensive network, with its integrative processes for the self thought to rely on a prefronto (lateral, medial, inferior)-parietal (inferior and superior) network (Hodzic et al., 2009a; Hodzic et al., 2009b; Pfeifer and Peake, 2012; Serino et al., 2013). Relevantly, when body ownership was evaluated separately from other features of body evaluation, midline cortical structures highly overlapping with the DMN emerged (Tsakiris et al., 2010). Studies that have directly assessed the neural basis of body processing alterations in AN patients, however, have rarely evaluated this self-evaluative component (Berlucchi and Aglioti, 2010; Gaudio and Quattrocchi, 2012). Additionally, the experimental designs used (i.e. the comparison of distorted versions of the participants' bodies with their real bodies or with other neutral images such as houses) might have favored the emergence of other areas involved in emotion (e.g., the fear network) and visuo-attentional processes(Castellini et al., 2013; Miyake et al., 2010; Mohr et al., 2010; Seeger et al., 2002; Wagner et al., 2003). Instead, comparing one's own body image with the body image of another has been suggested to be less emotionally driving(Sachdev et al., 2008), and to provide more specific information about self-related body processing(Berlucchi and Aglioti, 2010). With this approach, both Sachdev. et al(Sachdev et al., 2008) and Vocks et al. (Vocks et al., 2010) found that AN patients presented decreased activation in prefrontal (middle(Sachdev et al., 2008) and medial, superior, inferior(Vocks et al., 2010) prefrontal gyri) and parietal (precuneus(Sachdev et al., 2008; Vocks et al., 2010), inferior parietal cortex(Vocks et al., 2010)) areas when looking at their own body image; other areas of decreased activity were only present in one or the other study (insula and occipital regions(Sachdev et al., 2008), parahipppocampus and fusiform gyrus(Vocks et al., 2010)). In Vocks et al. (Vocks et al., 2010), however, the self condition was compared to a cross-fixation baseline, with no direct comparison between self and other. Similarly, in McAdams et al.(McAdams and Krawczyk, 2014), the comparison of adjectives referring to the participants' own personalities and bodies with those of their friends' resulted in decreased activation in the precuneus and the dorsal anterior cingulate but increased in the left middle frontal gyrus in patients during the self-related condition.

The aim in the present study was to assess the links between DMN self-evaluative processes and body image perception in AN patients. We used a functional magnetic resonance imaging (fMRI) experiment that allowed us to explore differences in activation and connectivity in a group of 20 AN patients compared to 20 matched healthy participants during the presentation of video clips of their own bodies, and while they were at rest. Unlike prior studies, we used short video clips instead of static images to create more immersive and salient stimuli. We tested our hypothesis that patients with AN would show impaired DMN activity and connectivity while viewing their own bodies, as well as impairment connectivity of those regions during the resting-state. A primary disturbance of this system was hypothesized, which would suggest a more general alteration of self-evaluative processes in AN beyond those stemming from own-body processing. Specifically, and in view of previous studies, alterations of DMN fronto-parietal connectivity were hypothesized to be generally present.

Methods:

Subjects

Twenty female patients fulfilling DSM-IV TR criteria for Anorexia Nervosa, restricting subtype(American Psychiatric Association and Association, 2000) were consecutively recruited from the Eating Disorders Unit (Day Hospital) of Bellvitge University Hospital, Barcelona, Spain (Table 1). Diagnoses were performed using the Structured Clinical Interview for DSM-IV Axis I Disorders(First et al., 2002). Exclusion criteria included the presence of other psychiatric disorders, neurological conditions, abuse of any drug other than nicotine, and the presence of contra-indications to fMRI scanning. Five patients (25% of the sample) were receiving pharmacological treatment (described elsewhere(Via et al., 2014), and Table 1). None of the patients met criteria for hospital admission at the time of scanning, on the basis that they were not manifesting severe physical consequences of excessive starvation.

Twenty healthy controls were recruited from the same socio-demographic area and were matched with the patients by gender, mean age, handedness and mean educational level (Table 1). Controls were screened in order to exclude any psychiatric or other medical condition by means of the General Health Questionnaire(Lobo et al., 1986) and the Structured Clinical Interview for DSM-IV Axis I Disorders-Non patient edition(First et al., 2007). None of the controls presented lifetime or current subthreshold symptoms for any eating disorder or unhealthy eating behaviors (i.e. they did not engage in recurrent dieting); their body mass index (BMI) was within the normal range. The ethical committee of clinical research (CEIC) of the Bellvitge University Hospital approved the study protocol, which was in compliance with the national legislation and the principles expressed in the Declaration of Helsinki. All subjects gave and signed written informed consent after detailed description of the study.

Clinical measures

For all subjects, the presence and severity of symptoms and psychological features involved in eating disorders were assessed with the self-reported Eating Disorder Invertory-2 (EDI-2) scale(Garner, 1991). Participants also completed the harm avoidance personality trait measure from the Temperament and Character Inventory Revised -TCI-R(Cloninger, 1999)- and ratings on self-perceived and ideal body shape from the Cross-cultural Questionnaire (CCQ, section 5)(Penelo et al., 2011). Finally, depressive and anxiety symptoms were assessed with the Hamilton Rating Scales for Depression (HDRS(Hamilton, 1960)) and Anxiety (HARS(Hamilton, 1959)).

Demographical and clinical measures were compared between groups by means of Student's T or χ^2 tests. Additionally, clinical measures of interest were correlated by means of Spearman's correlations with extracted imaging values. These variables included age of onset, duration of the illness, EDI-2 scores of interest for the task (drive for thinness, body distortion, interoceptive awareness), harm avoidance and self-perceived and ideal body shape ratings from the CCQ. Analyses were conducted in Statistical Package for the Social Sciences (SPSS) v20 on a Windows platform. Significance thresholds were set at $p<0.05$.

Body perception task

Prior to scanning, subjects were video-recorded in three static positions (front-facing, lateral, back) and under strictly standardized conditions. They were asked to wear tight black clothes, showing the silhouette contour and the same proportion of body skin, similar to previous descriptions using video-distortion confrontation protocols(Fernández et al., 1994; Fernández-Aranda et al., 1999). Edited clips

sequentially zooming body parts and finishing with a general view for each position were presented at the scanning session. Specifically, six 20-seconds blocks consisting of video clips of the participants' own bodies (2 front-facing, 2 lateral and 2 back view) were presented in alternation with the same six 20-seconds blocs of video clips of a healthy subject's body. Each block was preceded by 4 seconds of instructions (in Spanish): 'look at your own body' (*self*) or 'look at another's body' (*other*). The paradigm was presented visually on a laptop computer running E-Prime software on Windows (Psychology Software Tools, Inc., Sharpsburg, PA, USA, www.pstnet.com). Magnetic resonance imaging-compatible high-resolution goggles were used to display the stimuli (VisuaStim Digital Googles, Resonance Technology Inc., Northridge, CA, USA, www.mrivideo.com).

Resting state

Participants were instructed to lie still with the eyes closed but to remain awake, and to relax without focusing on any particular thought. This sequence was acquired prior to the body perception task.

Imaging acquisition and preprocessing

A 1.5-T Signa Excite system (General Electric) magnetic resonance, equipped with an 8-channel phased-array head coil and single-shot echoplanar imaging (EPI) software was used. The functional sequence consisted of gradient recalled acquisition in the steady state (repetition time (TR) = 2000 ms, echo time (TE) = 50ms and pulse angle, 90º) in a 24 cm field of view, with a 64 x 64 pixel matrix and a slice thickness of 4mm (inter-slice gap, 1.5 mm; voxel size, 3.75 x 3.75 x 4mm). For both the body perception task and resting sequences, a total of 22 interleaved sections, parallel to the anterior–posterior commissure line, were acquired to generate 144 (body perception) and 180 (resting) whole-brain volumes, excluding four initial dummy volumes to allow the magnetization to reach equilibrium (total duration body perception: 4'48'' and rest: 6'). A high quality 3-D SPGR sequence was also acquired in order to improve the registration process.

Data were processed on a Microsoft Windows platform running Matlab version 7.8(The MathWorks, Inc) and statistical parametric mapping software version 8(SPM8). Within subjects, motion correction was performed by aligning each time series to the mean image volume using a least-squares minimization and a 6-rigid-body parameter spatial transformation. These realigned functional sequences were then co-registered to the SPM-EPI template, and subsequently to their own co-registered T1 image(co-registered and segmented to the SPM-T1 template). Finally, images were normalized to the Montreal Neurological Institute(MNI) template and smoothed with an 8 mm isotropic Gaussian filter. All image sequences were routinely inspected for potential movement or normalization artifacts.

Imaging processing and imaging analyses

As the main analysis of interest, between-group differences during the body perception task were first evaluated within the DMN(see later for how the mask was defined). Next, psychophysiological interaction analyses were conducted to assess the influence of the task on the functional coupling between the areas identified in our main analysis and other areas within the DMN. Finally, we assessed

resting-state connectivity between the areas resulting from our main analysis and the rest of the DMN regions.

Body perception task - main analysis

For each subject, each task condition was convolved with a canonical hemodynamic response function to model the acquired BOLD signal. A high-pass filter was used to remove low-frequency noise (cut off period = 1/128 Hz). At a first level of analysis, the contrast of interest was defined as *self versus other*. Within-subject images were then carried to a second-level model, creating two-sample t tests at each voxel to compare brain activations between the groups and for the contrast of interest. Both within and between-group analyses were explored, including age and depression (see further) as covariates of no-interest in all the analyses.

Statistical results at the within and between-group analyses were thresholded using a combination of voxel- and cluster- level significance thresholds that provided a significance level equivalent to a Family Wise Error corrected p (p_{FWE})<0.05. Specifically, individual voxel threshold was set at an uncorrected p<0.005, while minimum spatial cluster extent (min. K_E) required to satisfy a p_{FWE}<0.05 was determined by 5000 Monte Carlo simulations using the Alphasim algorithm as implemented in the SPM Resting-state fMRI data analysis Toolkit (REST) toolbox in Matlab(Ward, 2000). The REST input parameters included a connection radius of 5 mm and the smoothing values for each statistical comparison (which ranged between 11 and 13mm). Cluster extent was determined within a predefined DMN mask provided in the NeuroSynth platform(Yarkoni et al., 2011). The mask contained 11,853 voxels (out of 87,121 voxels activated either during the *self* or the *other* conditions, Supplementary Figure 1), requiring a min K_E=23 voxels.

Given the overlap between areas processing for *self* and *other*, and the nature of our task (*self* vs *other*), we expanded our DMN analysis to include areas involved in social cognition processes. The mask was retrieved from the NeuroSynth platform. The total DMN-social cognition mask contained 18,769 voxels, requiring a K_E=42 voxels for cluster-corrected significance (Supplementary Figure 1, see legend for regions included in the social cognition mask).

Body perception task - Psychophysiological interaction analyses.

For regions identified in our main analysis, we planned to evaluate any specific task-based increase in functional connectivity between their activity and any other area in the brain. This approach was conducted by means of the psychophysiological interaction (PPI) analysis in SPM8(Friston et al., 1997) and following the same standard procedure as in prior studies(Cardoner et al., 2011). Briefly, an interaction (PPI) factor was included as a regressor in first-level analyses for each subject, with the psychological and physiological factors included as covariates of no interest. Next, first-level maps representing each cluster's PPI effect for each subject were carried to second-level random-effects analyses, to test between-group results. Statistical thresholds were calculated to satisfy a p_{FWE}<0.05 and using the same approach as above (DMN mask, min K_E=24-28 voxels depending on the selected region).

Resting State - Functional connectivity analyses

For the same regions, we performed seed-based cross-correlation analyses of the subjects' resting-state imaging sequences. First, preprocessed and temporally high-pass filtered images (cut off period=1/128 Hz) were used to extract mean signals across time series for each region. Next, extracted mean signals would be included in a regression analysis to investigate inter-regional correlations in neuronal variability

across individual BOLD time points during the resting-state. Estimates of white matter, cerebrospinal fluid, and global brain signal fluctuations were extracted and included in the regression analyses as covariates of no interest, together with movement parameters(Harrison et al., 2009). This process was performed for each subject. The obtained first level images were next carried to a second between-group level of analysis. Statistical threshold was calculated to satisfy a $p_{FWE}<0.05$ and using the same approach as above (DMN mask, min K_E=32-36 voxels depending on the region).

Clinical correlations

Peak eigenvalues of the significant clusters obtained from the main task comparison, PPI and resting-state connectivity analyses were correlated with the clinical variables of interest described above.

Results:

Clinical and demographic variables

There were no statistical differences in age, handedness or educational level between patients and controls. As expected, body mass index (BMI) and EDI-2 measurements were significantly different in patients and controls, with lower mean BMI and higher mean EDI-2 scores in patients. Ideal and self-perceived body shape scores from the CCQ questionnaire were lower in patients (i.e. thinner body shape preferred), with only a trend for the self-perceived score. There were no differences in harm avoidance scores. Depressive and anxiety symptoms were higher in AN patients compared to controls (Table 1). Given that these two measures were highly correlated (Pearson's r= .86, *p*< .001), only depressive symptoms were included as a nuisance covariate in the reported analyses.

Imaging results

Main analyses

Several common areas of increased activation in the *self versus other* were observed across patients and controls in the anterior insula, inferior parietal cortex and inferior temporo-occipital cortex. Instead, when looking at another's body, common neural activity increases were found within the posterior cingulate-precuneus, bilateral angular gyrus and medial prefrontal cortex in both groups. Group comparison revealed that AN patients presented greater activity in three clusters when looking at their own body image compared to another's: in the precuneus, ventral posterior cingulate cortex (vPCC) and dorsal posterior cingulate cortex (dPCC) (Table 2, Figure 1). The analysis of the extracted eigenvalues of the regions (Figure 1, Supplementary Figure 2, and Statistics in Supplementary Figure 2 Legend) allowed us to better characterize the nature of these between-group differences. In the case of dPCC, they were mostly driven by an increased activation to the self in AN patients. Instead, differences in the precuneus were driven by a lack of differential activation between conditions in patients, whereas controls presented greater activation of this region for the *other*. At the level of the vPCC, both of the aforementioned situations for dPCC and precuneus favored between-group differences.

When analyses were extended to the social cognition mask, the same three regions emerged, although precuneus was at a subthreshold level (dPCC: x,y,z=0,-34,44, K_E=58, Z=2.95; vPCC: x,y,z=6,-48,36, K_E=42, Z=2.97; precuneus: x,y,z=0,-60,42, K_E=24, Z=2.76).

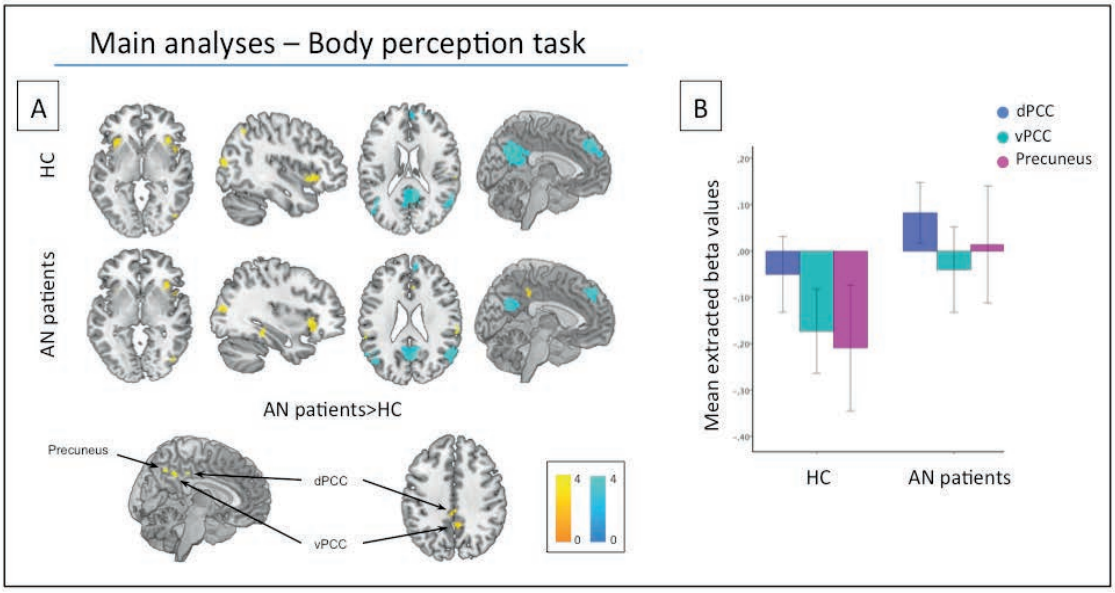
Based on these results, three ROIs (peak coordinates of each cluster at the center of 5mm-radius spheres) were built on MarsBar region-of-interest toolbox (Brett et al., 2002), which were used as *seeds* for the subsequent PPI and resting-state seed-based analyses.

Table 1. Demographic, clinical and behavioural measurements of the subjects included in the sample.

	AN patients	Healthy controls	Between group	
			t Statistic	*p*
Age: mean in years (sd), range	28.40 (9.30) 18-49	28.15 (8.62) 19-52	0.09	=.930
Handedness: righ/left (number of subjects)	19/1	19/1	-	-
Educational level: mean in years of studies (sd), range	15.85 (3.56) 12-23	16.45 (2.46) 10-21	0.62	=.539
Age at the onset: mean in years (sd), range	21.30 (9.26) 11-48	-	-	-
Illness duration: mean in months (sd), range	85.20 (76.88) 12-240	-	-	-
BMI: mean (sd), range	16.94 (1.26) 14-18	20.99 (1.82) 18-25	8.47	<.001*
EDI-2: mean (sd), range	66.79 (44.28) 13-178	13.53 (7.37) 3-28	5.17	<.001*
Drive for Thinness	10.35 (7.34) 0-21	0.90 (1.55) 0-6		
Bulimia	1.25 (1.59) 0-4	0.05 (0.22) 0-1		
Body dissatisfaction	11.20 (8.67) 0-27	2.40 (2.78) 0-9		
Ineffectiveness	7.80 (7.95) 0-28	0.75 (1.16) 0-3		
Perfectionism	7.10 (4.87) 1-17	3.60 (3.57) 0-12		
Interpersonal distrust	3.40 (3.72) 0-11	0.65 (1.35) 0-5		
Interoceptive awareness	6.45 (6.16) 0-20	0.25 (0.34) 0-2		
Maturity fears	5.35 (4.84) 0-16	2.70 (2.89) 0-11		
Asceticism	5.65 (3.96) 1-16	1.25 (1.12) 0-4		
Impulse regulation	3.30 (4.52) 0-14	0.25 (0.64) 0-2		
Social insecurity	4.95 (4.81) 0-17	0.40 (1.00) 0-4		
Harm avoidance (TCI-R)	104.45 (22.55) 58-144	96.90 (13.08) 64-119	1.30	=.205
Body shape-CCQ mean (sd), range				
Self-perceived (1-10)	3.05 (1.81) 1-8	3.95 (0.96) 2-5.5	1.95	=.059
Ideal (1-10)	2.63 (1.01) 1-5	3.38 (0.58) 2-4	2.87	=.007*
HDRS : mean (sd), range	3.30 (2.94) 0-10	0.90 (1.07) 0-3	3.43	=.002*
HARS : mean (sd), range	4.95 (5.79) 0-22	1.65 (1.39) 0-4	2.48	=.025*

BMI: Body mass index (range of normal BMI: 18-24). EDI-2: Eating Disorders Inventory-2. TCI-R: Temperament and Character Inventory Revised. CCQ: Cross-cultural Questionnarie. HDRS: Hamilton Depression Rating Scale. HARS: Hamilton Anxiety Rating Scale. *Significant *p* values <0.05.

Figure 1. Within and between-group brain activations for the main analyses of the body-perception task.



Legend: HC: Healthy controls. AN: anorexia nervosa patients. dPCC: dorsal posterior cingulate cortex, vPCC: ventral posterior cingulate cortex. **A**. Activations are displayed on brain templates. Yellow color indicates areas of increased activation for the *self* condition, blue color represents activated areas for the *other* condition. Color bars represent T values. **B**. Bar chart displaying the extracted eigenvalues from the areas showing between-group differences in activation for the contrast *self* >*other*. Positive values indicate greater activations for *self* compared to *other*, while the opposite is indicated by negative values. Error bars represent +/- 2 standard error deviations.

Finally, to allow comparison with prior studies of body image processing in AN, whole-brain analyses were also performed. Two areas of significant cluster-corrected results emerged in the superior parietal cortex-precuneus and in the parieto-occipital transition zone. Results are shown as supplementary material (Supplementary Text 1, Supplementary Figure 2, and Supplementary Table 3).

Psychophysiological interaction analyses.

The specific seed located at the dPCC (x,y,z=0,-34,44) showed increased task-related functional connectivity in AN patients with the dorsal anterior cingulate cortex (dACC) for the *self* condition. Additionally, the precuneus seed (x,y,z=0,-60,42) showed increased task-related functional connectivity in AN patients with a cluster located in the posterior part of the left mid temporal lobe during the *other* condition. There were no areas of different connectivity for the vPCC seed (x,y,z=6,-48,36) (Figure 2, Supplementary Table 1, Supplementary Figure 2).

Functional connectivity at rest

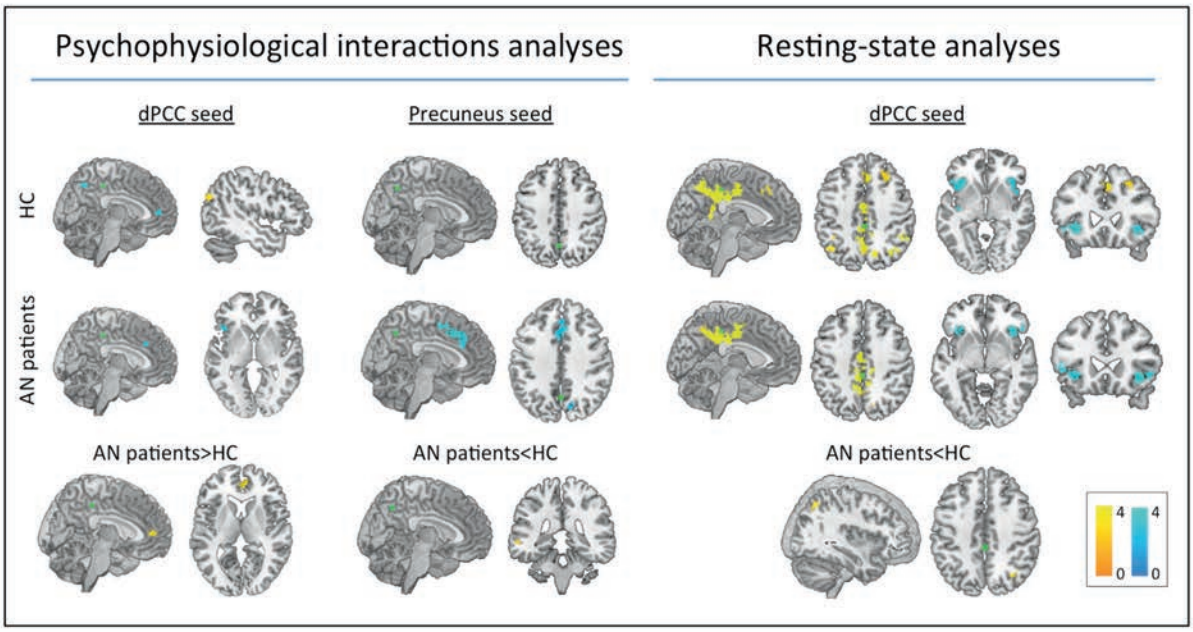
The dPCC seed (x,y,z=0,-34,44) showed decreased functional connectivity with the left angular gyrus in AN compared to controls. There were no between-group differences in functional connectivity in any of the other two seeds at rest (Figure 2, Supplementary Table 1).

Additionally, to control for potential effects of treatment on the results, the three analyses were repeated excluding the five participants who were receiving pharmacological treatment. These analyses reproduced essentially the same findings.

Clinical correlations

Task-related functional connectivity between the precuneus and left mid temporal lobe was correlated in patients with illness duration (ρ=0.59; p=0.01), although it did not survive Bonferroni correction for multiple comparisons. There were no other correlations between imaging and clinical data (Supplementary Table 2).

Figure 2. Results of the psychophysiological interactions analyses and functional connectivity at rest.



Legend: Seeds are depicted in green color (dPCC cingulate seed located at; x,y,z: 0,-34,44; precuneus seed: x,y,z: 0,-60,42). Yellow color indicates areas of increased activation when 'looking at my own body' contrast, blue color represents activated areas when 'looking at another's body'. HC: Healthy controls. AN: anorexia nervosa patients. Color bars represent T value.

Table 2. Within and between-group activations of extended brain regions during the performance of the task.

	Healthy controls	Anatomy[a]			Stats[b]			AN patients	Anatomy[a]			Stats[b]			Group comparisons	Anatomy[a]			Stats[b]		
		x	y	z	K_E	mm^3	Z		x	y	z	K_E	mm^3	Z		x	y	z	K_E	mm^3	Z
Looking at my own body>looking at another's body															Healthy controls> AN patients						
	Supramarginal gyrus	62	-22	26	25	200	4.98	Parietal inferior gyrus	46	-42	52	95	760	4.85							
	Inferior parietal lobe	56	-34	50	25	200	4.33		56	-34	50			4.52	No regions						
		50	-42	50			3.00	Supramarginal gyrus	-60	-34	26	65	520	4.72							
	Inferior parietal lobe	44	-42	46	40	320	4.22	Supramarginal gyrus	62	-22	26	24	192	4.62							
	Angular gyrus	36	-60	50	36	288	4.12		60	-30	26			4.10							
		28	-66	42			3.43	Temporal inferior gyrus	-46	-64	-14	49	392	4.55							
	Inferior temporal cortex	44	-60	-10	30	240	3.85	Temporal inferior gyrus	44	-62	-10	30	240	4.43							
		-64	-32	28	50	400	3.80	Inferior parietal lobe	-36	-50	46	105	840	4.35							
	Supramarginal gyrus	42	10	-8	223	1784	3.80		-30	-54	52			4.15							
		30	18	-2			3.50	Inferior temporal lobe	46	-66	-8	65	520	4.19							
		36	30	-4			2.99		42	-76	-6			3.25							
	Middle occipital gyrus	36	-90	12	84	672	3.70	Insula	40	16	-10	244	1952	4.09							
	Inferior occipital gyrus	46	-66	-8	47	376	3.15		48	10	0			3.37							
		46	-80	0			3.06		30	18	-2			3.18							
	Insula	-36	14	-4	105	840	3.14	Inferior parietal lobe	-54	-38	42	23	184	4.02							
		-34	22	0			2.90		-52	-42	50			3.05							
								Precuneus	16	-64	48	57	456	3.66							
									16	-72	40			3.09							

Looking at my own body>looking at another's body								Inferior frontal lobe	-44	42	16	25	200	3.43								
								Parietal superior lobe	32	-86	12	70	560	3.28								
									38	-82	8			2.89								
								Middle and anterior cingulate gyrus	4	26	30	27	216	3.28								
								Parahippocampus/hippocampus gyrus, fusiform gyrus	34	-34	-16	46	368	3.17								
									30	-40	-4			3.00								
								Insula	-34	14	0	25	200	2.99								
								Posterior cingulate gyrus	-8	-34	36	57	456	2.89								
									-12	-42	40			2.80								
									0	-36	44			2.72								
Looking at another's body>looking at my own body	Precuneus and posterior cingulate cortex	0	-70	34	1404	11232	4.88	Precuneus and posterior cingulate cortex	8	-54	20	440	3520	3.87	**AN patients > Healthy controls**							
		2	-62	36			4.69		6	-62	22			3.85	Ventral posterior cingulate cortex	6	-48	36	41	328	2.97	
		8	-50	32			4.58	Angular gyrus	-50	-68	40	531	4248	4.99	Dorsal posterior cingulate cortex	0	-34	44	52	416	2.95	
	Angular gyrus	-52	-64	36	764	6112	5.26		-46	-62	24			4.38		-4	-34	34			2.85	
		-46	-62	24			4.06		-54	-62	26			4.30	Precuneus	0	-60	42	24	192	2.76	
		-38	-70	44			3.74	Angular gyrus/Middle temporal gyrus	56	-62	36	305	2440	4.31								
	Angular gyrus	56	-62	36	558	4464	5.21		60	-58	28			4.25								
		60	-58	28			5.04	Middle temporal gyrus	60	-10	-22	71	568	3.64								
		52	-56	28			4.79		64	-14	-16			3.21								
	Middle temporal gyrus	64	-12	-10	137	1096	5.51	Middle and superior frontal gyrus	20	38	42	91	728	5.19								
		60	-14	-22			4.24		20	28	52			2.76								
		60	-20	-8			4.05	Middle and superior frontal gyrus	-18	34	44	54	432	3.85								

Looking at another's body>looking at my own body	Middle temporal cortex	-58	-40	-12	80	640	4.00		-20	26	38			3.58								
		-60	-32	-10			3.82	Superior frontal gyrus/anterior cingulate	10	58	24	87	696	3.69								
	Superior frontal gyrus	10	46	38	488	3904	4.60		10	46	38			2.95								
		0	46	44			4.51	Frontal superior gyrus	8	58	2	23	184	2.82								
		-10	42	38			3.73	Medial superior frontal gyrus	-10	42	40	131	1048	4.54								
	Middle and superior frontal gyrus	-18	22	48	169	1352	4.77		-8	50	32			3.07								
	Middle and superior frontal gyrus	20	34	40	156	1248	5.21		-4	34	46			2.92								
		20	28	52			4.73															
		22	26	40			4.30															
	Inferior frontal cortex	-42	14	34	25	200	3.65															
	Anterior cingulate cortex	10	52	8	68	544	3.34															
		-58	-16	-14	40	320	3.10															
		60	-6	4	26	208	3.09															
		26	58	12	28	224	3.02															
		18	58	16			2.93															

Footnote: [a] Activity co-ordinates (x. y. z) are given in Montreal Neurological Institute (MNI) Atlas space. [b] Magnitude and extent statistics correspond to a minimum threshold of $P_{FWE} < 0.05$ (cluster corrected at whole-brain). K_E = cluster size. BA= Brodmann area.

Discussion:

Our results suggest a central role for the posterior cingulate cortex (PCC)/precuneus in maladaptive self-other body evaluation in patients with AN. Connections originating in PCC/precuneus are additionally proposed to be the hub of an altered network of interconnected midline-anterior and posterior DMN components during body evaluation. Furthermore, the posterior DMN subnetwork is suggested to present a more general alteration, given its common impairment during the task and at rest. Specifically, the results showed a hyperactivation of dPCC during the processing of one's own body image in patients, as well as a failure to activate the precuneus in response to processing another's body, while a mixed altered response was found in the vPCC. A pattern of increased functional task-related connectivity with the dorsal anterior cingulate (dACC) for the *self*, and with mid temporal areas for the *other* condition was also observed. Additional decreases in connectivity between PCC and the angular gyrus were evidenced at rest.

Precuneus and PCC are the most interconnected areas within the DMN and are thought to comprise a key node of this network(Fransson and Marrelec, 2008). The precuneus integrates multiple sources of information for the representation of the body and peri-personal space(Cavanna and Trimble, 2006) and the posterior cingulate cortex is mostly known for its function in self-referential processes(Brewer and Garrison, 2014). Importantly, both areas are involved in higher-level visuo-spatial and semantic representation of the body, the self, autobiographical memory, and experience of body ownership(Berlucchi and Aglioti, 2010; Cavanna and Trimble, 2006; Northoff et al., 2006; Tsakiris et al., 2010). All these functions are particularly relevant in the context of the integration of body perception, and some authors have specifically suggested a link between parietal areas and engagement in self-referential processes during the visualization of the own body(Kaye, 2008; Lee et al., 2014; Preedy, 2011). Parietal areas are thought to play an important role in body distortion and generally in the pathophysiology of AN(Gaudio and Quattrocchi, 2012; Kaye, 2008). Accordingly, neuroimaging studies have found rather consistent volume decreases in parietal gray matter (Van den Eynde et al., 2012), and in some cases alterations in parietal white matter volume and architecture (including previously published results from this sample(Via et al., 2014)). Using a similar task, Sachdev et al. (Sachdev et al., 2008) also found differences in the precuneus during the visualization of the patients' own bodies compared to another's body, although in that study, patients presented an hypoactivation in this area. Even though further exploration would be required given the modest sample sizes usually recruited in AN studies (i.e. 10 AN patients in Sachdev et al.(Sachdev et al., 2008) and 20 AN patients here), differences between our results and the studies of Sachdev et al.(Sachdev et al., 2008) might relate to the stimuli used. Specifically, the researchers presented images of headless bodies, which might induce a decreased sense of body ownership and a less self-referential emotional processing mediated by medial parietal areas and the PCC(Cavanna and Trimble, 2006; Pujol et al., 2008). On the opposite, the general activity increases to self and other bodies in AN patients in our study, may relate to increased attention to (female) bodies(Watson et al., 2010). Additionally, the posterior regions of the DMN, such as PCC/precuneus have been shown to extend self-perception beyond the individual, being as well implicated in perspective taking and thinking about the other(Pfeifer and Peake, 2012; Tsakiris et al., 2010). This is particularly true for the precuneus, part of the mirror neuron system, which underlies empathy and social insight(Rizzolatti and Fabbri-Destro, 2010). The different patterns of responses at the dPCC, vPCC and precuneus might suggest alterations emerging both during the processing of the self and of another's body image in AN, with an hypersensitive inward attentional system to their own body image, and difficulties in processing and understanding information from other people co-occurring

during body image processes. Eventually, this may have implications both for self-evaluation and others during social interactions.

Additionally, an increase in task-related connectivity was found between the dPCC and the dACC in AN patients during the visualization of their own bodies. The ACC is another key region of current models of AN pathophysiology (Kaye, 2008), implicated in error detection, conflict monitoring, interoceptive awareness and emotional evaluation(Etkin et al., 2011; Medford and Critchley, 2010). Increased functional connectivity between the PCC and ACC has previously been associated with self-reflection (Andrews-Hanna et al., 2010; van Buuren et al., 2010), self-relevant affective decisions (Andrews-Hanna et al., 2010; Philippi and Koenigs, 2014), rumination(Berman et al., 2011; Philippi and Koenigs, 2014), focus on one's own duties(Johnson et al., 2006), and attributing causes to the self(Cabanis et al., 2013). Thus, our results might relate to increased rumination about body shape during the visualization of one's own body in AN, while this coupling might be adaptive, as observed in controls, for the evaluation of the other's body. Although we did not specifically measured rumination in patients, these data might fit with the results of Lee et al. 2013 (Lee et al., 2014) showing an association between increased resting functional connectivity between dACC and retrosplenial cortex and body distortion. Moreover, additional increases in task-related connectivity were found between precuneus-mid temporal cortex in AN patients during the visualization of the other's body. Together with the precuneus, the middle temporal cortex is an area of the social cognition network, and it is involved in motion perception(Billeke and Aboitiz, 2013). Within the DMN, the connections between precuneus and lateral temporal areas conform a dorsal system of this network, associated with mentalizing and autobiographical tasks, and are suggested to participate in retrieving stored conceptual knowledge about the self or other people (Andrews-Hanna et al., 2014a; Andrews-Hanna et al., 2014b). Speculatively, our results in precuneus-mid temporal might be associated with disturbances in social relationships in AN, involving aspects of one's and other's physical appearance and the comparison between the two(Kelly et al., 2014; Watson et al., 2010; Zucker et al., 2007). Interestingly, these alterations might be modulated by illness duration, given the trend-level association found between these variables. The differential behavior of our results may thus highlight the complexity of the different self-other disturbances arising during body perception, integrating two distinct domains of self-referential processing(van Buuren et al., 2010; Harrison et al., 2008; Northoff et al., 2006).

Finally, posterior areas of the DMN presented further between-group differences in connectivity during the resting state. In particular, AN patients showed decreased connectivity between dPCC and the angular gyrus, the latter area also being implicated in visuo-spatial and attentional functions, and in sense of agency(Seghier, 2013). Similar decreases in activation have been previously observed in the resting-state in AN patients(Mcfadden et al., 2014), and together with our task-related results further highlight the role of parietal and posterior DMN areas in AN. In addition, these results suggested the persistence of alterations in the posterior DMN component at rest, extending beyond those found during own-body visualization. In the context of differential subnetworks within the DMN(Andrews-Hanna et al., 2010; van Buuren et al., 2010; Harrison et al., 2008), these alterations of the posterior-parietal DMN in both conditions are in contrast to alterations of the anterior-posterior (PCC-dACC) DMN connections, which were only triggered by body perception and not replicated in the resting state. Given the suggested intrinsic properties of rest connectivity measures(Shehzad et al., 2009), this contrast might indicate some level of *tonic* (sustained, task-independent) alterations in posterior areas versus *phasic* (transient, task-related or stimuli-triggered) alterations in posterior-anterior connections. Importantly, these results would suggest the presence of a sustained posterior DMN breakdown during self-related processes in AN.

Limitations

Generalization of the results is limited by the modest sample size, although to our knowledge, it is the largest sample of restrictive-type AN patients engaged in a body image perception fMRI task. Furthermore, for the first time, we provide an integrative view of the involvement of self-referential areas during the processing of one's own body image and at rest. Secondly, we included patients receiving pharmacological treatment. Although it is unclear as to what direction treatment might bias these results, the exclusion of the 5 medicated participants did not modify our findings. Fourth, our study was restricted to low-weight AN patients, and used a cross-sectional design. It will be interesting for future studies to assess if these changes persist after weight restoration and symptom recovery, as well as if they precede the onset of the disorder, and therefore predict it. In addition, AN patients had a wide range of age at onset; although it would be interesting to study putative differences between early and late onset subgroups, we did not find associations between age at onset or illness duration and our results, and literature findings have suggested similar clinical profiles and psychopathological features between these two groups(Bueno et al., 2014; Joughin et al., 1991). Subgroup analyses, longitudinal studies, the study of recovered patients or intermediate phenotypes might be of particular interest in answering all these questions. Finally, and given some evidences of a relationship between failure of DMN deactivation and attentional or behavioural performance(Anticevic et al., 2012), further studies might also specifically evaluate putative deficits in deactivation and anticorrelation properties of this system in AN patients.

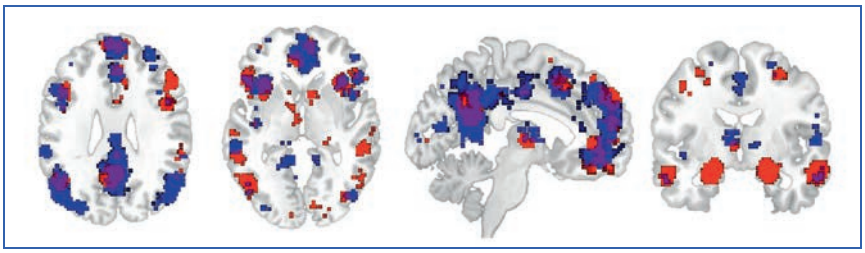
Conclusion

In conclusion, these results provide new insights into the neurobiological substrates of AN, and highlight the influence of alterations in regions supporting self-other evaluation of body perception, establishing a putative neural link between these processes and body image distortion. AN is a disorder with limited evidence-based treatment, a particularly poor outcome in adults(Park et al., 2011), and a clear lack of understanding of its neuroanatomical basis. In this respect, a recent debate has emerged about treatments based on neuromodulation therapies (e.g. transcranial magnetic stimulation or deep brain stimulation), which urges a better understanding of the neural systems involved in AN(Treasure and Schmidt, 2013b). In this context, we believe studies such as the one presented here offer new relevant perspectives to the field.

Moreover, it would be equally appealing to assess the effects produced by other more traditional approaches over DMN functioning. For example, evoking changes in body processing has been used in therapies such as video confrontation and mirror exposure therapy(Fernández and Vandereycken, 1994). Interestingly, the latter is known to improve a DMN–related process such as interoceptive awareness(Ainley et al., 2012), and thus, it would be of relevance to test whether its improvement after mirror exposure therapy might translate to a normalization of DMN alterations found in our study in AN patients.

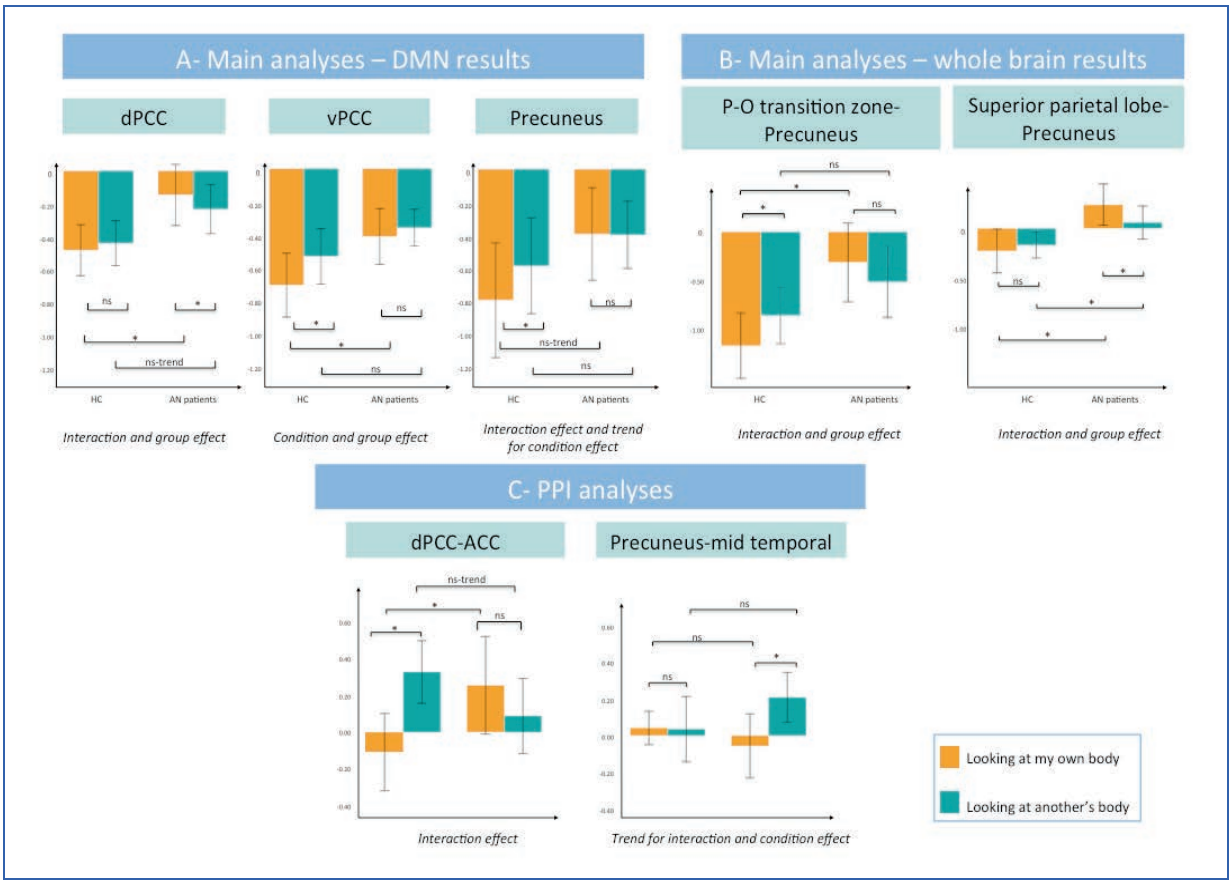
SUPPLEMENTARY INFORMATION

Supplementary Figure 1. Areas of the Neurosynth Default Mode Network and social cognition masks used in the analyses.



Legend: Areas included in the default mode network mask (blue): posterior cingulate cortex and precuneus, inferior parietal cortices, bilateral lateral temporal cortex, insula, dorsal and ventral areas of the medial frontal cortex. Areas included in the social cognition mask (red): ventromedial prefrontal cortex, anterior and posterior cingulate cortices, precuneus, anterior insula, orbitofrontal cortex, superior temporal sulcus, temporo-parietal junction, premotor cortex, inferior parietal cortex (supramarginal gyrus), amygdala-hippocampus, associative occipital cortex, fusiform area, striatum, thalamus-hypothalamus. In purple, overlapping regions.

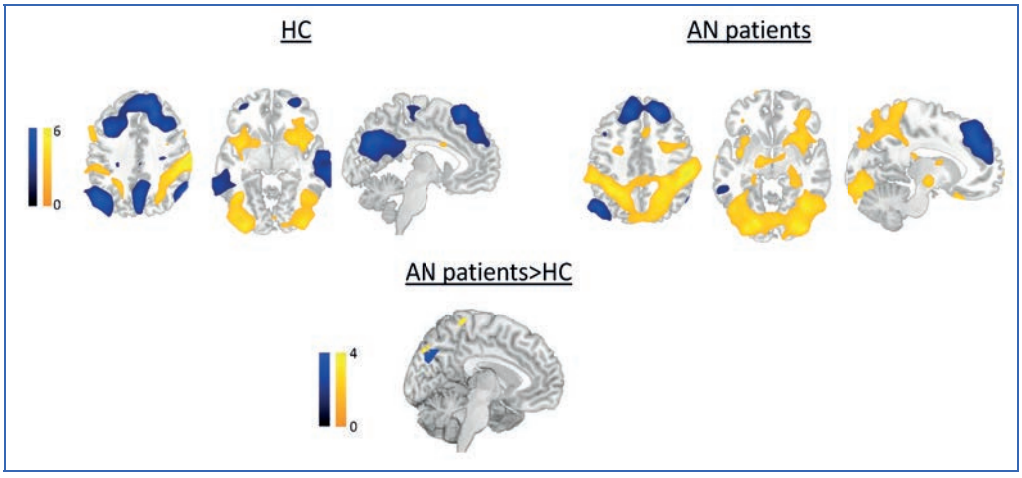
Supplementary Figure 2. Extracted beta-values for the main and PPI analyses to 'looking at my own body' and 'looking at another's body' compared to baseline in controls and AN patients.



Legend: dPCC: dorsal posterior cingulate cortex; vPCC: ventral posterior cingulate cortex. P-O: parieto-occipital. Column bars represent the activation of each region in each condition. The implicit baseline of the model used to retrieve the eigenvalues is the instruction's period, in which subjects might have engaged in reflexive, self-directed attention thus activating the DMN; this is evidenced by the negative values of the column bars. Although this baseline comparison was not the purpose of this study, it provides information about

Statistics of the repeated ANOVA analysis for each region: A. **1. dPCC:** Interaction effects: F(1,38)=5.37, p=.026, η^2_p=. 12. Condition effect: F(1,38)=0.61, p=.44, η^2_p=.02, Group effects: F(1,38)=6.35, p=.016, η^2_p=. 14. Post-hoc: between-group comparison *self* condition: t(38)=2.78, p=.008, Cohen's d=. 88; *other* condition: t(38)=2.05, p=.047; Cohen's d=.65. Control group: *self* vs *other*: F(1,19)=1.03, p=.323, η^2_p=.05. AN patients, *self* vs *other*: F(1,19)=5.60, p=.029, η^2_p=.23. **2. vPCC:** Interaction effects: F(1,38)=2.93, p=.095, η^2_p=.07. Condition effect: F(1,38)=10.40, p=.003, η^2_p=.22. Group effects: F(1,38)=4. 56, p=.039, η^2_p=.11. Post-hoc: between-group comparison *self* condition: t(38)=2.29, p=.027, Cohen's d=.73; *other* condition: t(38)=1.73, p=.092, Cohen's d=.55. Control group: *self* vs *other*: F(1,19)=13.24, p=.002, η^2_p=. 41. AN patients, *self* vs *other*: F(1,19)=1. 06, p=.316, η^2_p=.05. **3. Precuneus:** Interaction effects: F(1,38)=4.62, p=.038, η^2_p=.11. Condition effect: F(1,38)=4.26, p=.046, η^2_p=.10, Group effects: F(1,38)=2. 26, p=.141, η^2_p=. 06. Post-hoc: between-group comparison *self* condition: t(38)=1.79, p=.081, Cohen's d=.57; *other* condition: t(38)=1.06, p=.297; Cohen's d=.33. Control group: *self* vs *other*: F(1,19)=8.81, p=.008, η^2_p=. 32; AN patients, *self* vs *other*: F(1,19)=0.004, p=.95, η^2_p=. 32. B. **P-O transition zone-Precuneus:** Interaction effects: F(1,38)=10.65, p=.002, η^2_p=. 22. Condition effect: F(1,38)=0.49, p=.49, η^2_p=.01, Group effects: F(1,38)=6.49, p=.02, η^2_p=.15. Post-hoc: between-group comparison *self* condition: t(38)=3.27, p=.002, Cohen's d=1.03; *other* condition: t(38)=1.47, p=.15; Cohen's d=.47. Control group: *self* vs *other*: F(1,19)=9.55, p=.006, η^2_p=.33. AN patients, *self* vs *other*: F(1,19)=2.79, p=.11, η^2_p=.13. **2. Superior Parietal cortex-precuneus:** Interaction effects: F(1,38)=7.63, p=.009, η^2_p=.17. Condition effect: F(1,38)=1.92, p=.17, η^2_p=.05, Group effects: F(1,38)=7.76, p=.01, η^2_p=.17. Post-hoc: between-group comparison *self* condition: t(38)=3.07, p=.004, Cohen's d=.97; *other* condition: t(38)=2.11, p=.04; Cohen's d=.67. Control group: *self* vs *other*: F(1,19)=0.89, p=.36, η^2_p=.05. AN patients, *self* vs *other*: F(1,19)=9.19, p=.01, η^2_p=.33. C. **1. dPCC-ACC:** Interaction effects: F(1,38)=7.84, p=.01, η^2_p=. 17. Condition effect: F(1,38)=1.56, p=.22, η^2_p=.04, Group effects: F(1,38)=0.33, p=.57, η^2_p=. 01. Post-hoc: between-group comparison *self* condition: t(38)=2.15, p=.04, Cohen's d=.68; *other* condition: t(38)=1.80, p=.08; Cohen's d=.57. Control group: *self* vs *other*: F(1,19)=9.07, p=.01, η^2_p=.32. AN patients, *self* vs *other*: F(1,19)=1.09, p=.31, η^2_p=.06. **2. Precuneus-mid temporal:** Interaction effects: F(1,38)=3.49, p=.07, η^2_p=.08. Condition effect: F(1,38)=3.13, p=.09, η^2_p=.08, Group effects: F(1,38)=0.24, p=.63, η^2_p=.01. Post-hoc: between-group comparison *self* condition: t(38)=1.00, p=.32, Cohen's d=.32; *other* condition: t(38)=1.54, p=.13; Cohen's d=.49. Control group: *self* vs *other*: F(1,19)=0.01, p=.94, η^2_p=.00. AN patients, *self* vs *other*: F(1,19)=6.35, p=.02, η^2_p=.25.

Supplementary Figure 3. Whole-brain within and between-group brain activations for the main analyses of the body-perception task.



Legend: Yellow color indicates areas of increased activation when 'looking at my own body' contrast, blue color represents activated areas when 'looking at another's body'. Results are depicted at an uncorrected p value=0.005. HC: Healthy controls. AN: anorexia nervosa patients.

Supplementary Table 1. Within and between-group results for PPI and seed-based resting state analyses.

		Healthy controls	Anatomy [a]			Stats [b]			AN patients	Anatomy [a]			Stats [b]			Group comparisons	Anatomy [a]			Stats [b]		
			x	y	z	K_E	mm^3	Z		x	y	z	K_E	mm^3	Z		x	y	z	K_E	mm^3	Z
PPI ANALYSES	Looking at my own body > looking at another's body	**SEED COORDINATES (x,y,z): 0,-34,44**																				
		Angular gyrus	-50	-70	30	49	392	3.10	No areas							**AN patients > Healthy controls**						
																Anterior cingulate cortex	4	46	4	53	424	3.20
		SEED COORDINATES (x,y,z): 0,-60,42																				
		No areas							No areas							No areas						
		SEED COORDINATES (x,y,z): 6,-48,36																				
		No areas							No areas							No areas						
	Looking at another's body > looking at my own body	**SEED COORDINATES (x,y,z): 0,-34,44**																				
		Medial superior frontal gyrus- Anterior cingulate cortex	4	46	4	58	464	3.37	Precuneus	12	-68	46	53	424	3.49							
		Precuneus	4	-62	44	61	488	3.02	Inferior frontal cortex-Insula	-44	22	-2	71	568	3.29							
									Middle -anterior cingulate cortex	2	28	32	34	272	3.01							
									Middle temporal gyrus	-60	-36	-4	38	304	2.93							
		SEED COORDINATES (x,y,z): 0,-60,42																				
		No areas							Superior frontal gyrus	0	0	52	376	3008	4.30	**AN patients > Healthy controls**						
										2	10	40			4.11	Middle temporal gyrus	-60	-36	0	37	296	2.90
										4	20	40			3.81							
									Middle temporal gyrus	-62	-36	0	65	520	3.58							
									Cuneus/Precuneus	14	-74	34	52	416	3.16							
										14	-66	32			2.96							
										12	-66	40			2.81							
		SEED COORDINATES (x,y,z): 6,-48,36																				
		Inferior parietal cortex	-26	-50	52	21	168	4,09	Supplementary motor area/Mid cingulate gyrus	0	0	52	286	2288	4,17	No areas						
		Supramarginal gyrus	62	-26	24	22	176	3,10		2	8	44			3,51							
		Temporal inferior gyrus	44	-62	-10	30	240	2,98		4	22	38			3,43							
									Mid temporal gyrus	-64	-36	0	43	344	3,42							
									Parietal inferior cortex	-42	-48	50	21	168	3,01							
									Mid-anterior cingulate cortex	8	30	28	23	184	2,88							
										2	26	34			2,87							
									Precuneus/Cuneus	12	-66	38	28	224	2,85							

RESTING STATE ANALYSES	Looking at my own body> looking at another's body	**SEED COORDINATES (x,y,z): 0,-34,44**																						
																			Healthy controls> AN patients						
		Middle and superior frontal gyrus	24	38	40	108	864	4.39		Precuneus	18	-72	34	96	768	3.65		Angular gyrus	34	-62	48	42	336	3.09
			24	20	48			3.35			12	-70	44			2.69								
			30	30	42			3.07																
		Inferior parietal cortex- angular gyrus	56	-48	44	165	1320	4.37																
			42	-52	48			3.75																
			50	-42	44			3.66																
		Inferior parietal cortex	-40	-48	50	52	416	4.08																
			-28	-52	52			2.69																
		Precuneus	10	-66	48	120	960	3.93																
			12	-66	36			3.07																
			12	-74	38			3.06																
		Angular gyrus	32	-64	44	92	736	4.74																
			38	-58	50			4.31																
		Angular gyrus	-46	-60	42	101	808	3.23																
			-38	-66	42			2.79																
		Superior frontal gyrus/Mid cingulate cortex	4	24	44	109	872	3.53																
			-4	22	42			3.37																
		SEED COORDINATES (x,y,z): 0,-60,42																						
		Angular gyrus	42	-70	38	570	4560	5,24		Mid frontal gyrus	26	26	38	123	984	5,43		No areas						
			46	-72	24			4,26		Mid occipital gyrus	-38	-78	24	176	1408	4,62								
			44	-62	32			4,04			-44	-74	20			3,84								
		Angular gyrus	-40	-76	24	553	4424	4,93			-28	-78	30			3,80								
			-34	-78	42			4,43		Mid occipital gyrus	42	-70	30	208	1664	4,02								
			-34	-78	30			4,31			44	-62	32			3,83								
		Mid-Superior frontal gyrus	28	28	40	144	1152	4,78			44	-70	20			3,76								
			24	38	40			3,32		Angular gyrus	38	-60	44	38	304	3,37								
		Angular gyrus	34	-72	42	80	640	4,60			34	-66	40			3,08								
			42	-66	44			3,55																
		Mid frontal gyrus	32	14	52	44	352	3,93																
		Mid frontal gyrus	-24	6	50	57	456	3,87																
		Mid frontal gyrus	-22	18	46	122	976	3,72																
			-28	26	48			3,65																
		SEED COORDINATES (x,y,z): 6,-48,36																						
		Mid and superior frontal gyrus	26	34	40	156	1248	6,95		Mid-Superior frontal gyrus	28	28	40	131	1048	5,28		No areas						
		Angular gyrus	44	-68	36	687	5496	6,46		Angular gyrus	44	-70	28	679	5432	4,64								
			44	-64	28			6,02			44	-62	32			4,43								
			58	-60	20			5,38			58	-56	20			4,37								
		Angular gyrus	44	-66	44	94	752	5,05		Mid occipital gyrus	-42	-82	26	134	1072	3,46								
			34	-72	42			5,02			-42	-70	22			3,04								
		Angular gyrus	-46	-78	28	826	6608	4,80																
			-34	-78	42			4,80																
			-38	-76	32			4,57																
		Superior frontal gyrus	0	58	0	929	7432	4,22																
			12	50	36			4,10																
			6	52	22			3,88																

		Mid frontal gyrus	-20	22	46	174	1392	4,14																
			-24	34	48			3,09																
		Mid temporal gyrus	58	-14	-20	89	712	4,09																
		Mid temporal gyrus	-60	-14	-18	56	448	3,80																
	Looking at another's body > looking at my own body	**SEED COORDINATES (x,y,z): 0,-34,44**																						
		Superior temporal gyrus	-44	-24	4	179	1432	4,83		Insula	38	24	-10	217	1736	5,44		No areas						
			-42	-10	0			4,77			46	24	-4			3,93								
			-40	-16	8			3,99		Inferior frontal gyrus	-34	26	-8	202	1616	3,67								
		Insula	-38	26	-4	284	2272	4,39			-46	22	8			3,54								
			-42	18	2			3,77			-46	28	-4			3,39								
			-50	22	-4			3,63																
		Insula	34	28	-8	150	1200	4,19																
			46	8	-4			3,11																
			38	16	-6			2,70																
		SEED COORDINATES (x,y,z): 0,-60,42																						
		Superior temporal gyrus	54	-4	4	40	320	5,61		Superior temporal gyrus	56	-2	6	40	320	5,73		No areas						
		Superior temporal gyrus	-50	-12	2	214	1712	4,88		Superior temporal gyrus	-46	-10	10	196	1568	5,17								
			-50	-30	8			4,77			-52	-10	4			4,98								
			-42	-14	14			4,72			-50	-22	12			4,39								
		Insula	-40	22	4	365	2920	4,63		Insula- Inferior frontal gyrus	44	8	-8	347	2776	5,17								
			-38	14	4			4,45			38	22	-10			5,08								
			-44	14	-6			4,04			30	18	-2			4,42								
		Insula	46	8	-8	261	2088	4,25		Insula-Inferior frontal gyrus	-36	14	0	355	2840	4,99								
			46	22	-10			4,21			-44	14	-6			4,95								
			30	16	2			4,08			-34	26	-6			4,55								
		Parahippocampus-hippocampal gyrus	24	-24	-18	56	448	4,11																
		Supplementary motor area-Mid cingulum	-4	-6	52	126	1008	4,09																
			6	-2	50			4,06																
			-4	-14	54			3,51																
		Hippocampus	-26	-18	-14	89	712	4,01																
		Inferior temporal gyrus	46	-66	-8	77	616	3,85																
			44	-76	-2			3,65																
		SEED COORDINATES (x,y,z): 6,-48,36																						
		Insula	44	8	-8	322	2576	5,80		Insula	44	10	-8	282	2256	4,94		No areas						
			34	26	0			4,64			46	14	0			4,59								
			38	12	0			4,52			38	12	0			4,22								
		Insula	-44	14	-6	398	3184	5,69		Superior temporal gyrus/Insula	-58	-16	8	215	1720	4,92								
			-46	22	-6			5,41			-44	-22	10			4,30								
			-34	14	2			4,86			-46	-10	6			3,97								
		Superior temporal gyrus	54	-4	4	40	320	5,06		Superior temporal gryus	58	-2	8	40	320	4,58								
		Superior temporal gyrus	-52	-18	10	193	1544	4,95			54	-10	6			4,11								
			-40	-10	0			4,54		Insula	-48	24	-6	356	2848	4,50								
			-48	-22	2			3,89			-32	24	-4			4,42								
		Supplementary motor area/Mid cingulum	-4	-2	52	364	2912	4,89			-34	16	0			4,16								

			0	16	48			4,49		Inferior temporal gyrus	46	-68	-8	46	368	3,62									
			-4	6	48			4,45			42	-76	-6			3,41									
		Inferior frontal gyrus	-54	10	24	52	416	4,12																	
			-50	14	34			3,00																	
		Inferior parietal cortex	-38	-44	50	45	360	3,71																	
			-30	-48	56			3,62																	
		Inferior temporal cortex	48	-76	-4	73	584	3,69																	
			46	-66	-8			3,26																	
			38	-76	0			2,98																	
		Hippocampus	-26	-16	-12	42	336	3,36																	
			-24	-26	-12			3,18																	

Footnote: [a] Activity co-ordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. [b] Magnitude and extent statistics correspond to a minimum threshold of $P_{FWE} < 0.05$ (cluster corrected at whole-brain). K_E = cluster size. BA= Brodmann area. To avoid smoothing-induced correlations, resting state reported coordinates were only those located outside a 16mm tridimensional radius distance from the seed coordinate (2xFWHM of the Gausian filter used in the smoothing=16mm).

Supplementary Table 2. Spearman's correlations between extracted eigenvalues of the main results and clinical variables.

	Main analysis Areas, coordinates (x,y,z)			PPI analysis Areas, coordinates (x,y,z)		Resting state Areas, coordinates (x,y,z)
	dPCC (0, -34,44)	Precuneus (0,-60,42)	vPCC (6,-48,36)	Anterior cingulate cortex (4,46,4; seed: dPCC)	Middle temporal gyrus (-60,-36,0; seed: precuneus)	Angular gyrus (34,-62,48; seed: dPCC)
Age at onset	ρ=-0.32; p=0.17	ρ=-0.10; p=0.68	ρ=-0.07; p=0.76	ρ=-0.01; p=0.98	ρ=-0.28; p=0.24	ρ=-0.05; p=0.82
Illness duration	ρ=0.20; p=0.41	ρ=-0.07; p=0.76	ρ=-0.11; p=0.65	ρ=0.03; p=0.89	ρ=0.59; p=0.01*	ρ=0.39; p=0.09
Drive for thinness (EDI-2)	ρ=0.03; p=0.90	ρ=0.30; p=0.21	ρ=0.16; p=0.50	ρ=-0.21; p=0.37	ρ=0.05; p=0.84	ρ=-0.14; p=0.54
Body distortion (EDI-2)	ρ=0.03; p=0.90	ρ=0.26; p=0.26	ρ=0.24; p=0.31	ρ=0.09; p=0.72	ρ=-0.01; p=0.98	ρ=-0.19; p=0.42
Interceptive awareness (EDI-2)	ρ=0.14; p=0.57	ρ=0.29; p=0.21	ρ=0.24; p=0.31	ρ=-0.04; p=0.86	ρ=-0.10; p=0.68	ρ=-0.37; p=0.10
Harm avoidance (TCI-R)	ρ=-0.10; p=0.69	ρ=-0.17; p=0.47	ρ=-0.32; p=0.17	ρ=-0.11; p=0.65	ρ=0.31; p=0.18	ρ=0.16; p=0.50
Self-perceived body-shape (CCQ)	ρ=-0.18; p=0.50	ρ=-0.13; p=0.61	ρ=-0.22; p=0.37	ρ=-0.19; p=0.42	ρ=0.10; p=0.68	ρ=-0.09; p=0.73
Ideal body-shape (CCQ)	ρ=0.34; p=0.14	ρ=0.06; p=0.79	ρ=0.14; p=0.56	ρ=-0.08; p=0.74	ρ=0.18; p=0.44	ρ=0.11; p=0.65

* p value<0.05. Bonferroni correction: p<.001. dPCC: dorsal posterior cingulate cortex, vPCC: ventral posterior cingulate cortex.

Supplementary Table 3. Between-group differences at the whole brain level.

		Anatomy			Stats		
Self>other	**AN patients>Healthy controls**	**x**	**y**	**z**	**K_E**	**mm^3**	**Z**
	Parieto-occipital transition zone, Precuneus	-2	-80	40	192	1,536	4.02
		-12	-78	32			2.98
	Post-central gyrus, Superior parietal cortex, Precuneus	-10	-40	70	245	1,960	3.60
		6	-44	68			2.78
		-14	-48	42			2.77
Other>self	**AN patients>Healthy controls**						
	Parieto-occipital transition zone, Precuneus	-2	-80	40	545	4,360	4.02
		0	-60	42			2.76

Footnote: Self>other: Looking at my own body> looking at another's body. Other>self: Looking at another's body> looking at my own body.

Supplementary text 1. Methods and results for the whole-brain analyses.

Methods:

Between-group differences were explored for either the self>other or the other>contrasts. The same voxel threshold and cluster-correction statistics were applied for these analyses. The masks applied in AlphaSim were either the combined activations for both groups to the self>other (46,650 voxels, min K_E=184) or the other>self condition (29,740 voxels, min K_E=184).

Results:

Whole brain analyses showed activations to the *self* condition, for both groups, in occipital and lateral superior parietal cortices and anterior insulae; activations extended to medial parietal cortices including precuneus and orbitofrontal cortices, brainstem and caudate nucleus in patients. Activations to the *other* condition were found in the dorsomedial prefrontal and the lateral parietal cortices in both groups; in controls there was an additional activation in an area comprising the retrosplenial and posterior cingulate cortices, precuneus, parieto-occipital transition zone and associative visual regions, and additionally in the premotor cortex. Between-group differences were located in the parieto-occipital transition zone-precuneus and in an area comprising the post-central gyrus- superior parietal cortex and precuneus (P_{FWE}<0.5, cluster corrected). At the parieto-occipital transition zone-precuneus, controls showed differential activation between *self* and *other*, with increased activation for the *other,* while patients failed to differenciate between conditions. Instead, at the superior parietal cortex-precuneus, patients showed an hyperactive response to the *self* condition. Results are shown in Supplementary Figures 3 and Supplementary Table 3.

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Chapter 6

SUMMARY OF RESULTS

Chapter 6- Summary of results

CLINICAL AND NEUROPSICOLOGICAL VARIABLES:

- No between-group statistical differences in age, handedness or educational level.
- Significantly lower mean BMI and higher mean EDI-2 scores in patients.
- Significantly higher depressive and anxiety symptoms in patients, measured with Hamilton depression (Hamilton, 1960) and anxiety (Hamilton, 1959) scales.
- No between-group differences in the harm avoidance personality trait.
- Significant higher sensitivity to punishment in patients, and no differences in sensitivity to reward, as measured by the SPSRQ
- Significant higher social anxiety scores in AN, as measured by the Liebowitz Social Anxiety Scale (LSAS)
- There were significant between-group differences in the ideal body shape scores –but not in the self-perceived scores- of the cross-cultural questionnaire (CCQ)(Penelo et al., 2011) (i.e. thinner ideal body shape preferred in patients).

STUDY 1:

- Between-group differences in the **left Superior longitudinal fasciculus**, partietal region: **FA reductions**. Driven by an increased RD accompanied by an increased MD.

- Between-group differences in **fornix-bilateral anterior thalamic radiations**: **MD increases**. Driven by an increased AD and RD accompanied by a decreased FA.

- Confounding variables (e.g., age, depression and anxiety symptoms, medication and nicotine use) did not account for the differences in the results.

- **No significant correlations** between the extracted FA/MD measurements and the clinical variables examined: age, EDI-2, harm avoidance, duration of illness, BMI, anxiety and depressive symptoms measured by the respective Hamilton anxiety and depression scales.

- **No between-group differences in grey or white matter volumes** either at the whole brain level or in specific analyses aimed at the regions of significant between-group differences in DTI measurements.

STUDY 2:

- At a behavioral level, both groups showed **greater accuracy remembering being rejected** in comparison to being accepted or receiving no feedback. They considered the evaluations of the other people allegedly involved in the experiment to be as equally genuine as their own.

- In response to the **acceptance condition**, patients showed **decreased activation in the dorsomedial prefrontal cortex** (BA8 and BA9).

- In response to the **rejection condition**, patients showed **increased activation in the left secondary visual cortex**.

- Interaction analyses: During the **acceptance feedback**, **sensibility to reward** was differentially associated, between groups, with activity of **bilateral frontal opercula-anterior insula cortices (negative association in patients**), and **dorsomedial and dorsolateral prefrontal cortices** (BA8, BA10) (**positive association in healthy controls**).

- During rejection feedback, there were no areas of between-group interaction with sensitivity to punishment.

- In patients, there were no associations between EDI-2 scores and brain responses during acceptance feedback.

- In patients, **during rejection feedback**, AN severity, as measured by the EDI-2, was associated with the **activation of the ventral striatum** (caudate), **dorsomedial prefrontal** (BA8), and **visual** (BA17-BA18-BA19) cortices (positive correlation), and with **dorsolateral prefrontal cortex activations (negative correlation**).

- There were no associations between brain activity and illness duration or age at onset.

- There were no associations between brain activity and LSAS social anxiety scores.

STUDY 3:

- When looking at their own body compared to another's, patients presented hyperactivation of the precuneus, ventral posterior cingulate cortex (vPCC) and dorsal posterior cingulate cortex (dPCC). In the **dPCC,** patients showed an **increased activation to the 'self' condition**, while in the **precuneus,** patients **did not differentially respond to the 'other' condition,** as healthy controls did. At the level of the vPCC, both of the aforementioned situations were found.

- Patients showed **increased task-related functional connectivity** between the **dPCC** and the **ACC** during the ***self*** **condition**.

- Patients showed **increased task-related functional connectivity** between the **precuneus** and the left **mid temporal cortex** during the ***other*** **condition**.

- At **rest**, in patients, the **dPCC** showed **decreased functional connectivity with the left angular gyrus**

- There was an association between task-related precuneus-temporal lobe functional connectivity and illness duration, which did not survive correction for multiple testing.

- There were **no associations between imaging results and clinical variables of interest** [age at onset, illness duration, drive for thinness (EDI-2), body distortion (EDI-2), interceptive awareness (EDI-2), harm avoidance (TCI-R), self-perceived body-shape (CCQ), ideal body-shape (CCQ)].

- Whole brain results showed specific hyperactivation, in patients, in the **superior parietal cortex-precuneus and in the parieto-occipital transition zone**, during the visualization of their own body.

Chapter 7

GENERAL DISCUSSION

Chapter 7- General discussion

Within the present thesis, we have evaluated neuroanatomical and neurofunctional alterations in a group of 20 adult patients with anorexia nervosa, restrictive subtype. In the first study, which evaluated structural alterations, we found microstructural changes in the parietal parts of the superior longitudinal fasciculus and the fornix, with no alterations in either global or regional gray or white matter volumes. In the second study, differences in brain response to social acceptance and rejection suggested an abnormal motivational drive in AN for social stimuli, with joint alterations in the social cognition network and the reward system. The third study showed, in a body perception task, altered responses of posterior medial parietal areas in AN patients, associated with either the evaluation of the self or another's body. These functional alterations were associated with changes in functional connectivity between posterior and anterior parts of the DMN and within regions of the posterior subnetwork itself. Given that only the latter were also present at rest, we suggested differential DMN subnetwork responses involved in the underlying biological process affected in AN.

In conjunction, the results of the three articles highlight the relevance of prefrontal-parietal regions and their connections, as well as the important role played by regions involved in reward (such as the ventral striatum and the anterior insula) and in motivational drive in social contexts, in AN. Our findings suggest the existence of important alterations in a circuit underpinning self-appearance, understanding of others and social relationships, and, therefore, in the mutual connections between these elements, as discussed below. In the following paragraphs, the results of these studies will be integrated, and, thereafter, a complementary new approach to current models of the neurobiological bases of AN will be presented.

1. Prefronto-parietal system

Parietal areas, both medial and lateral, have been largerly implicated in the pathology of AN, with evidences coming from structural and functional studies. Lateral regions, such as the somatosensory cortex, the supramarginal gyrus, the intraparietal sulcus, the angular cortex and superior parietal lobe, are involved in proprioception, size and spatial judgment, visual imagery, and the integration of visual information. Medial parietal areas, such as the precuneus and the posterior cingulate cortex, share some of the integrative properties with lateral areas, and are additionally involved in self-reference cognitive processes (see section 4.3.3). Importantly, all of these processes are relevant to the mental representation of one's own body image and may play a role in one of the core symptoms of AN: body image distortion. Two of the studies presented in this work support the existence of alterations in parietal and fronto-parietal areas and suggest that this will be relevant for body processing. In Study 1, we found microstructural changes located in the major fasciculus connecting parietal with frontal areas. Specifically, FA decreases and MD/RD increases were found in the parietal parts of the superior longitudinal fasciculus- fibers SLF-II and AF, which connect dorsolateral and ventrolateral prefrontal areas to the angular gyrus and posterior parts of the superior temporal cortex (Makris et al., 2005). In Study 3, we identified alterations in medial parietal areas being involved in differential self-other body perception processes. Specifically, within the DMN, and in relation to self-body perception, a hyperresponsive PCC

arose during self-evaluative body perception processes, which, together with the results of functional connectivity analyses (increased coupling between PCC and ACC during self-body processing in AN) suggest an increased self-reflective attentional response to own body processing in patients with AN. However, alterations found in this fronto-parietal system in both studies may be associated with different processes being altered during body perception in AN. Specifically, while the connections between lateral posterior parietal and premotor (lateral) cortex reported in Study 1 have been suggested to underlie general alterations of body processing (possibly more related to sensory integration, see 5.5.2), the more specific sense of body ownership is suggested to be associated with medial parietal and frontal regions –Study 3-. Medial regions are connected through a different tract within the SLF, the SLF-I (Makris et al., 2005) instead of SLF-II (Study 1); however, both SLF I and II have a shared origin in associative visual areas of the occipito-parietal region (Makris et al., 2005) -relevant areas for the processing of body perception-. More importantly, the SLF-II (Study 1) has been suggested to integrate information from both the SLF I and II, representing a direct communication between the dorsal and ventral attention networks (Thiebaut de Schotten et al., 2011). Additionally, the connections of the SLF have a bidirectional nature (Petrides and Pandya, 1984), which may be relevant for the integration of bottom-up and top-down body-related information conveyed during body perception (Tsakiris, 2010). All together may suggest the complexity of body perception and the putative alterations of its components linked to different aspects of body distortion in AN.

In both studies, we additionally suggested a link between alterations of the SLF or body perception and its influence in interpersonal relationships. In Study 1, we hypothesized the involvement of the SLF in the suggested trait feature of *weak central coherence* [increased focus to detail at the expense of global processing, (Lopez et al., 2009; Treasure, 2013), see sections 5.2.3. and 5.4.1]. This specific cognitive style has been associated with deficits in the appropriate identification of emotions in both eyes and faces as well as contributing to poor contextual understanding, which naturally affects social abilities and relationships (Happé and Frith, 2006). In AN in particular, this cognitive style might be linked to both increased hyperattention to the body (Watson et al., 2010) and to social impairments (Treasure, 2013). In Study 3, the association between body perception and social comprehension was specifically suggested by a lack of response in the precuneus during the visualization of the other's body, together with an increased functional coupling between this region and the mid temporal cortex. Importantly, the precuneus is a central area of overlap between self-related and social cognition functions (Cavanna and Trimble, 2006; Herold et al., 2015); a 'self-centred mental imagery' region, involved in the stable representation of space and the world (Land, 2014). Moreover, its altered connections with mid temporal areas seem relevant in the link between self and other for social relationships by their involvement in recovering stored conceptual knowledge about the self and others, in turn important to the self-schema and mentalizing (Andrews-Hanna et al., 2014a; Andrews-Hanna et al., 2014b). Although the strong connection between self-body image, self-body concept, the concept of others, and interpersonal relationships has long been established (van der Velde, 1985), we emphasize the relevance of these notions in AN, as well as the need to seek putative neurobiological substrates of alterations in the processing of this information in affected patients. More importantly, and driven by the results of Study 3, we specifically suggest a central role for medial parietal regions in the link between the disturbance of self-perception and relationships with others in AN.

Unfortunately, it is not possible to arrive to conclusions about the direction of these changes. For example, individuals with high vulnerability to develop AN might be those with weak coherence cognitive

style, poor self-integrative and social abilities, in turn associated to parietal or SLF alterations. On the contrary, these fronto-parietal alterations may develop, in vulnerable individuals, with the onset of AN throughout adolescence, a period in which this tract undergoes substantial growth (Alexander et al., 2007; Giorgio et al., 2010), and which is associated with the improvement of visuo-spatial capacities (Darki and Klingberg, 2015; Klingberg, 2006) and the establishment of the self and social interactions (Pfeifer and Peake, 2012). Additionally, it is possible that cognitive distortions of AN itself might be associated with alterations of these fronto-parietal connections. Preoccupation with physical appearance associated with a learned (motivational) and overtrained attentional bias to body parts (detail-focused trained), might influence these modifications, in the context of white matter plasticity and the association of white matter changes with learning (Zatorre et al., 2012). Some evidences in the literature favor the first hypothesis (vulnerability), at least for structural findings. For example, genetic factors explain about 75–90% of the variation in fractional anisotropy in frontal and parietal lobes, but not of other areas (Zatorre et al., 2012). In addition, in AN, SLF white matter alterations are present in adolescent (temporo-peri-insular region, (Frank et al., 2013b)) and recovered patients (frontal and parietal areas (Bischoff-Grethe et al., 2013)) and have been associated with higher scores in the harm avoidance personality trait (Yau et al., 2013). However, although vulnerability factors might be an important contributor to fronto-parietal alterations, it is highly possible that both vulnerability and state processes are involved in the alterations of these connections.

2. Reward-inhibition system and social motivation

The results of Studies 1 and 2 suggested, in AN, alterations in areas within the reward network and related to motivational responses. Specifically, alterations were associated with two different types of reward, relevant to the psychopathology of AN: food and social feedback. In Study 1, microstructural alterations (increased MD, RD and AD, decreased FA) were found in the fornix, a relevant structure involved in feeding, emotion and reward processing; a key tract linking basic primitive functions of reward associated with eating behaviors (Kelley and Mittleman, 1999). Importantly, microstructural alterations in the fornix have been replicated in most of the DTI studies conducted in AN (Frank et al., 2013b; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014), but have been also observed in other conditions associated with food intake, such as bulimia and obesity (Mettler et al., 2013; Metzler-Baddeley et al., 2013), suggesting a non-specific effect of this alteration. Instead, Study 2 provided interesting information about reward responses in an experimentally-created social setting, complementing information of previous studies, which focused in reward responses to either food/taste or monetary stimuli. Specifically, an alteration in the motivational drive to social stimuli was suggested by hypoactivation of the dorsomedial prefrontal cortex when being socially accepted and hyperactivation of visual areas during rejection, while reward related areas such as the ventral striatum and anterior insula appeared to be correlated with clinical and personality measures, respectively (severity and sensitivity to reward), likely modulating social relationships in AN. These differences in the response of either structures directly responsible for the evaluation of rewards and in structures reflecting altered motivational drive is in agreement with current theories of the dysfunctional responses to reward and social relationships in AN (Harrison et al., 2010b; Keating, 2010).

Regarding reward, changes in structures such as the ventral striatum and fornix might be driven both by molecular/hormonal imbalances associated with starvation and by learned conditioned responses (in the

ventral striatum, commented in 4.2.3), the latter being associated with the value attributed to weight in societies with a great availability of food, where weight loss is encouraged but rarely achieved (Frank, 2013; Kaye, 2008; Keating, 2010; Walsh, 2013). Interestingly, these alterations of the reward system have been implicated in mechanisms of symptom resistance in AN (Walsh, 2013). The persistence of anorexic behaviors and the intermittent and unanticipated reinforcement (weight loss, social response) would favour an habitual behaviour, with associations, that once learned, are difficult to eradicate (Walsh, 2013). These associations and the involvement of habit formation processes would be relevant to the resistance to improve found in AN, which, in turn, are suggested to be particularly relevant in populations with long duration of the disorder (Walsh, 2013). At a neurobiological level, this pattern of habit formation might behave similarly to the model for long-term course of drug addiction: the initial rewarding response of voluntary behaviour is associated with the ventral striatum, while a switch to the posterior striatum develops with habit formation and compulsive drug seeking (Everitt and Robbins, 2013; Jog et al., 1999; Walsh, 2013; Yin et al., 2004). While it is possible that certain alterations of this system might be already present in vulnerable individuals, as suggested in AN and similar to the model for addiction disorders (Kaye et al., 2009; Volkow and Morales, 2015), the development of further alterations might be more associated with the persistence of the symptoms.

Although, in AN, a response of posterior striatal areas has been evidenced in prior studies (Bischoff-Grethe et al., 2013; Oberndorfer et al., 2013; Sanders et al., 2015; Wagner et al., 2007; Wagner et al., 2008), and we did include some patients with long illness duration, we only observed an involvement of the ventral striatum –but not the posterior- in the response to social feedback and dependent on clinical severity in Study 2. Alterations in the ventral striatum might persist in their influence in social relationships over the course of the disorder, as it is likely that habit formation is less involved in social contexts, given the high variability and the high degree of uncertainty of these scenarios (Adolphs, 2001). Moreover, the idea alterations in the reward system are associated with long-term course of symptoms, as well as with resistance mechanisms in several disorders may also fit with the non-specific alterations found in the fornix (Study 1). It would be interesting for future studies to test these hypotheses in a transdiagnostic manner.

With regard to models of altered social responses in AN, we framed our results within the attentional negative bias observed in AN for social relationships (see 4.3.1). Importantly, these responses are in close relationship with responses of the reward system and as a result modulate them. For example, during social settings in which previous knowledge is assumed, prefrontal structures -including the medial prefrontal cortex- as well as visual associative regions, among others, exercise a bias on the response of the ventral striatum (Delgado et al., 2005). This fits with the participation of a different integration of networks associated with AN response to social feedback, as suggested in Study 2. Within the context of these results, it is interesting to highlight the powerful social-related motivational drive in AN, which overruns above basic needs such as feeding (Maslow, 1943), and despite the natural motivation for eating associated with fasting (Goldstone et al., 2009). Powerful changes in this primitive reward system, and other networks modulating its response, might be thus relevantly important in the development and, relevantly, in the maintenance of the disorder.

3. Body, self, other, reward and social relationships. Integration within previous models and the new contribution of the present results.

Although the relevance of the self-concept has already been proposed in eating disorders (Stein and Corte, 2003; Stein and Corte, 2007; Stein and Corte, 2008; Williams and Reid, 2012), with earlier theories coming from psychoanalysis (Brunch, 1973), it has received scarce attention in AN. Indeed, to our knowledge, we are the first to support the connections between body perception, self-evaluation, social interactions and reward in AN, at a theoretical level, but, in the frame of our results, as an important construct for neurobiological alterations in AN. The abstract concept of the self refers to a developmental process resulting in a stable but evolving set of memory structures about the self, referred to as the self-concept, and greatly developed during adolescence but updated through life (Pfeifer and Peake, 2012). This construct evolves based on personal needs and objectives, but it is importantly shaped by the social environment, and determined by how we think others perceive us and their actual perception (Pfeifer and Peake, 2012). Once established, self-schemas serve as organizing templates that influence inferential processes and motivate and regulate behavior (Kendzierski and Whitaker, 1997; Sheeran and Orbell, 2000; Stein and Corte, 2008). They are associated with a better understanding of the actions of others (Markus et al., 1985) and, at the same time, the body image of others becomes inseparable from the notion of others (van der Velde, 1985). The combination of different self-schemas conform our self-concept, and individuals with decreased capacity to interrelate them are as less likely to tolerate challenging social feedback and to respond with effective strategies, but to react to stressors with low mood and deacreased self-steem (Stein and Corte, 2007). Indeed, AN patients seem to have a low interrelatedness of self-schemas (Stein and Corte, 2007) and all of these factors involved in the construction of the self-concept seem to be relevantly modulating the emergence and persistence of AN in vulnerable individuals, either in adolescence or at an adult age. In addition, the shaping process of the self by social relationships is greatly built upon perceived reward and punishment, and most likely by an interaction of fear and reward which contributes and perpetuates an already biased (or vulnerable) self-schema in AN system (Strober, 2004; Wierenga et al., 2014). This was specifically highlighted by the results of Study 2. Moreover, in this proposed imbalance between reward and inhibiton (Wierenga et al., 2014) we have mainly discussed about alterations of the reward response, although some of these hypotheses might also be relevant to the other end of this system, namely, inhibition and anxiety. For example, it is interesting, that, while there are many commonalities in the personality and cognitive style or the fear and anxiety processes associated with anorexia nervosa and anxiety disorders, a distinctive feature could be related to the involvement of *inhibition* resposes in the self-concept and identity development, and vice-versa. The high value attributed, in AN, to the body and the self in social relationships is evidenced by the avoidance of social situations related to, for example, avoiding being seen physically. This is suggested in our results by the negative bias in social response and by previous models for the involvement of reward-inhibition systems and fear learning processes in AN (Strober, 2004; Wierenga et al., 2014).

Another factor to be considered is the contribution of interoceptive awareness to self-construction, which is the link between the internal milieu, the perception and regulation of emotions and social empathy (Brugger and Lenggenhager, 2014), commented in 5.2.5. In this context, other structures such as the ventral prefrontal cortex and the anterior cingulate are suggested to link interoceptive and exteroceptive information, in a network involving the amygdala and the ventral striatum (Adolphs, 2001; Cavada and Schultz, 2000). More importantly, the insula (mostly anterior but the posterior as well) is a

classical structure involved in interoceptive awareness (Craig, 2009), and some authors have suggested either its involvement in a mismatch between actual and anticipated body arousal (Wierenga et al., 2014) or its central role in alterations of body perception (Frank, 2015). Although in our studies we suggested a higher integrative role for medial and lateral parietal areas in these alterations (Serino et al., 2013; Tsakiris, 2010), different aspects of interoception are linked to the insula and the PCC-precuneus (Vogt and Laureys, 2005), and the hierarchy of parietal and insular responses associated with the body, self and others remains to be further clarified.

The results of this work fit with current neurobiological models of AN. They highlight the higher-level cognitive (attitudinal) component involved in body perception (Cash and Deagle, 1997; Fernández et al., 1994; Fisher and Cleveland, 1958; Gaudio and Quattrocchi, 2012; Skrzypek et al., 2001), support the involvement of a cognitive bias for social relationships in the response of social reward and punishment (Study 2 (Treasure and Schmidt, 2013a)), and of reward structures in the disorder (Study 1, Study 2, (Bergh and Södersten, 1996; Frank, 2013; Kaye et al., 2011; Keating et al., 2012)). The results of our Study 2 might also be understood in the frame of the imbalance of the reward and inhibitory system (Wierenga et al., 2014). Other important models that we did not discuss, have additionally suggested anorexia nervosa as a disorder of emotion dysregulation (Haynos et al., 2015a; Haynos et al., 2015b; Wildes et al., 2014), or have contextualized the disorder in a close relationship with anxiety disorders, emphasizing the presence of fear conditioning processes (Strober, 2004). Importantly, and in addition to existent models, we introduce the relevance of self-schema construction, its link with body image and social relationships, and suggest mechanisms for the maintenance of these altered social responses at a brain level.

4. Global considerations

All together, in a multimodal but integrative approach, we have suggested the relevance of prefrontal-parietal and reward and social motivation-related networks in the development and persistence of AN. We have emphasized how alterations in these circuits are relevant to the evaluation of the body, self-schema, the perception of other's and social relationships. Importantly, our results emphasize the link between body perception and social interactions as a putative centrepiece in AN. In view of previous literature, we have suggested that, while certain vulnerabilities seem to be present in relation to both the prefrontal-parietal and reward systems, the former might be more influenced by vulnerability factors which are possibly enhanced by changes in adolescence, while in the latter, alterations are suggested to be associated with the development and resistance to improvement of the disorder. A schematic representation of our results, framed in a theoretical approach, is represented in Figure 7.

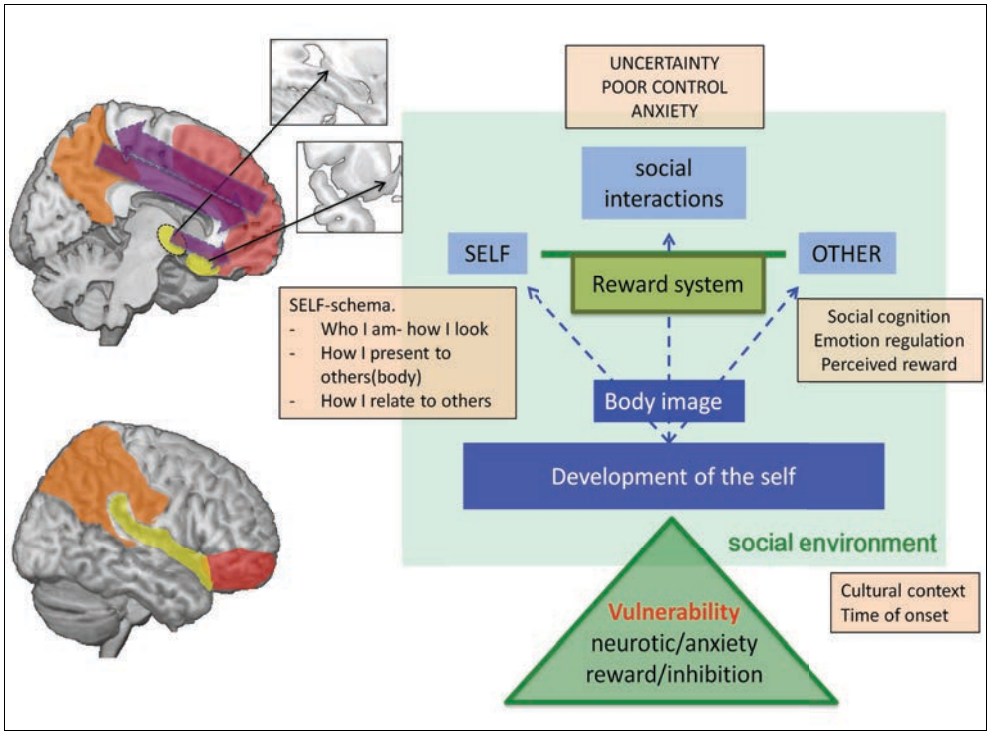

Figure 7. Schematic representation of our results and the contribution to previous models.

5. Future investigations

From the above exposed considerations, several questions arise to be tested in experimental settings for future studies. For example, as we briefly mentioned in Study 3, taping into a simple and basic part of all these components, such as body awareness (i.e. training patients for different body sensations) might have a beneficial influence over this complex system. Improving the awareness of body sensations and one's own emotions might improve the self-schema, decrease uncertainty about oneself and the world, and improve social interactions; it might possibly improve the acceptance of one's own body as an exposure-like therapy. Second, it would be interesting to study the differential contribution of different reward phases (e.g. anticipation, outcome) in social responses and other stimuli, to better characterise alterations in this system. Moreover, it would be also interesting to evaluate the 'inhibitory' response, as part of the other extreme of the reward-inhibition system imbalance. For example, it would be interesting to evaluate fear and anxiety brain system with a classical conditioning paradigm; in this respect, it is somewhat surprising the little involvement of amygdala in the literature of functional MRI studies. Third, at a structural level, multimodal approaches including animal models would improve the unclear understanding of some of the mechanisms involved in the onset and maintenance of pathological behaviours affecting brain networks. Furthermore, the greater sensitivity of new techniques -such as new diffusion imaging methods- to specific cellular features might greatly contribute to this understanding (Zatorre et al., 2012).

In clinical settings, and given that interpersonal social relationships can be targeted in treatment strategies (Treasure et al., 2012), it would be interesting to evaluate the effectiveness of including the discussed elements possibily involved in the self-concept and of dysfunctional social relationships in therapies, aimed at recognizing, in patients, the processes involved in the disorder and its maintenance.

Finally, and from a sociological point of view, there may exist some cultural influences in the (un)healthy development of some of the elements discussed above. For example, some authors have suggested the difficulty for identity development in western cultures, associated with the presence of little symbolic references for its construction (Sollberger, 2014). Implementing and testing educative protocols aiming at improving emotional, cultural and social aspects in general population should have an impact in the evolution and course of some psychiatric symptoms and disorders, such as AN.

6. Limitations

Generalization of the results is limited by the modest sample size, and replication would be required. However, to our knowledge, we are the first to evaluate alterations in brain reward responses in social contexts and within the DMN during body perception in AN. Second, we included patients receiving pharmacological treatment. Although it is unclear as to what direction treatment might bias functional or structural results, we did not find any relationship between our findings and the use of pharmacological treatment. Third, our study was restricted to low-weight AN patients, and used a cross-sectional design. It would be interesting for future studies to assess if these changes persist after weight restoration and symptom recovery, as well as if they precede the onset of the disorder, and therefore predict it. In addition, AN patients had a wide range of ages at onset; although it would be interesting to study putative differences between early and late onset subgroups, we did not find associations between age at onset or illness duration and our results, and literature findings have suggested similar clinical profiles and psychopathological features between these two groups (Bueno et al., 2014; Joughin et al., 1991). Subgroup analyses, longitudinal studies, the study of recovered patients or intermediate phenotypes might be of particular interest in answering all these questions.

Chapter 8

GENERAL CONCLUSIONS

Chapter 8- General conclusions

1. Patients with anorexia nervosa, restrictive subtype, presented structural and functional alterations in a fronto-parietal circuit, which we suggest to be involved in body distortion.
    a. In Study 1, AN patients, compared to controls, showed alterations in the microstructure of the left superior longitudinal fasciculus (decreased FA).
    b. In Study 3, AN patients, compared to controls, showed an increased response in the dorsal posterior cingulate, together with increased functional coupling with the anterior cingulate cortex during the perception of their own body.

2. Patients with anorexia nervosa, restrictive subtype, presented functional alterations in the response to the visualization of another's body, which we suggest to be involved in deficits for the understanding of the self and others.
    a. In Study 3, in AN patients compared to controls, the precuneus showed deficits in activation in response to the visualization of another's body, without a self-other discrimination within this area.
    b. In Study 3, in AN patients compared to controls, the functional connectivity between precuneus and mid temporal lobe was increased during the visualization of another's body.
    c. In Study 1, AN patients, compared to controls, presented alterations in the microstructure of the left superior longitudinal fasciculus (decreased FA), which might be associated with a particular cognitive style of AN patients important for social relationships.

3. Patients with anorexia nervosa, restrictive subtype, presented structural and functional alterations in structures of the reward system.
    a. In Study 1, in AN patients compared to controls, the fornix presented microstructural alterations (increased MD).

b. In Study 2, in AN patients compared to controls, bilateral anterior insular cortices were differently associated with sensibility to reward during the acceptance condition.
c. In Study 2, in AN patients, the ventral striatum was associated with disorder severity during social rejection.

4. Patients with anorexia nervosa, restrictive subtype, presented functional alterations when being accepted or rejected in a social task, which is suggested to be related to motivational aspects of patients during social relationships.
    a. In Study 2, AN patients compared to controls, showed hypoactivation of the dorsomedial prefrontal cortex during acceptance feedback.
    b. In Study 2, AN patients compared to controls, showed hyperactivation of visual areas during rejection feedback.

Chapter 9

SUMMARY IN CATALAN

Resum en català

Chapter 9- Summary in Catalan- Resum en català

Introducció

L'anorèxia nerviosa (AN) és un trastorn relativament poc freqüent [prevalença per vida entre 0.4 i 1.7% (Bulik et al., 2006; Preti et al., 2009; Smink et al., 2014)], però sever i debilitant (Steinhausen, 2002), i amb la taxa més alta de mortalitat d'entre tots els trastorns psiquiàtrics (Sullivan, 1995). Els pacients afectats presenten preocupacions al voltant de la pròpia imatge corporal, el pes, la dieta i realitzen restriccions alimentàries importants, freqüentment en combinació amb exercici intens, que poden comportar la mort per inanició. En alguns casos, aquest comportament s'acompanya d'episodis d'afartament i de purga, el que diferencia el subtipus *restrictiu* del *purgatiu* (American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000). El trastorn afecta a dones en 1 de cada 8 pacients i normalment s'inicia en l'adolescència o l'edat adulta jove, tot i que en els últims anys s'ha observat un increment de casos en pacients més joves, en grups d'edat més gran i en homes (Favaro et al., 2009; Mangweth-Matzek et al., 2014; Núñez-Navarro et al., 2012; Steinhausen and Jensen, 2015; Swanson et al., 2011).

Actualment s'accepta un component multifactorial en el desenvolupament del trastorn, amb una clara participació de factors genètics i neurobiològics que o bé predisposen o són fruit del propi desenvolupament del trastorn. El model del llindar multifactorial (*multifactorial threshold model*) (Connan et al., 2003; Kaye et al., 2009), suggereix l'herència d'un contínuum de factors predisponents en subjectes vulnerables, que juntament amb factors ambientals, faran sobrepassar un llindar a partir del qual es precipitaran els símptomes. Entre els factors ambientals, els socials i culturals són ben reconeguts, tot i que s'ha evidenciat que el trastorn no es troba únicament associat a les societats occidentals, sinó que ha estat reconegut en totes les cultures (Keel and Klump, 2003). Entre els factors predisponents, els trets de personalitat ansiosos i obsessius s'han relacionat d'una manera molt important amb el trastorn (Anderluh et al., 2003; Friederich and Herzog, 2011; Kaye et al., 2013; Lilenfeld et al., 2006), però altres factors de vulnerabilitat que s'hi han vinculat inclouen una pobra capacitat interoceptiva, alexitímia, necessitat d'estar prim (*drive for thinness*, EDI-2) i inoperància (aquest últim defineix

sentiments de inseguretat, baix control sobre la vida, inutilitat (McLaughlin et al., 1985)) (Beadle et al., 2013; Espina, 2003; Kaye et al., 2013; Lilenfeld et al., 2006).

Determinats períodes tenen un especial risc per al desenvolupament de AN, com l'adolescència, moment en què el cervell experimenta canvis importants en les connexions cerebrals, especialment les que determinen la integració de funcions cognitives i emocionals, sobretot en àrees i connexions frontoparietals i límbiques (Connan et al., 2003). A més, és un període d'importants canvis psicològics, com els que desenvolupen la construcció de la imatge d'un mateix i en els que participen, de forma important, els aspectes socioculturals que envolten l'individu i que modulen tots aquests aprenentatges, a nivell psicològic i neurobiològic (Pfeifer and Peake, 2012). En l'AN, i en relació amb aquests circuits en formació, els estudis estructurals i funcionals que s'han realitzat, sobretot, mitjançant tècniques de ressonància magnètica (RM), suggereixen alteracions en àrees com l'escorça cingulada anterior i l'escorça orbital frontal (ACC i OFC respectivament, per les sigles en anglès), així com a l'ínsula, àrees parietals laterals i medials, l'hipocamp/parahipocamp, i als nuclis estriats (Van den Eynde et al., 2012; Kaye et al., 2009). Les tècniques de RM, desenvolupades de forma exponencial en els últims 25 anys, han destacat com una eina molt important per avaluar tots aquests canvis en les xarxes neuronals dels pacients amb AN, canvis encara poc coneguts. En aquest sentit, un dels reptes actuals és aconseguir millor models neuroanatòmics i funcionals de l'AN (Coman et al., 2014; Oudijn et al., 2013).

Una de les característiques nuclears del trastorn és la distorsió de la imatge corporal. Es tracta d'una sobreestimació de la representació mental del propi cos en pacients amb AN (American Psychiatric Association, 2013; American Psychiatric Association and Association, 2000). A més, la distrosió de la imatge corporal és un potencial marcador associat als trastorns alimentaris en general i un predictor de recaiguda (Gardner and Bokenkamp, 1996; Jacobi et al., 2004). Malgrat això, la naturalesa d'aquest concepte està poc definida (de Vignemont, 2010), tot i que, generalment, s'accepta la participació de dos components: un de purament *perceptiu*, relacionat amb la percepció de la mida del cos i estimació del pes, i un altre *actitudinal*, relacionat amb les actituds i sentiments envers el cos (Cash and Deagle, 1997; Fernández et al., 1994; Fisher and Cleveland, 1958; Skrzypek et al., 2001). No obstant, i en base als diferents circuits neurals possiblement implicats en aquest segon component, s'ha proposat la seva subdivisió en un component emocional i un altre de cognitiu (Cash and Deagle, 1997; Gaudio

and Quattrocchi, 2012). En concret, aquest component 'cognitiu' s'ha vinculat a processos d'autoavaluació relacionats amb les percepcions, actituds i creences, així com amb la representació mental del propi cos (Gaudio and Quattrocchi, 2012). Els experiments conductuals i neuropsicològics realitzats fins ara han estudiat principalment les possibles alteracions del component perceptiu, tant directament durant tasques d'estimació de pes i/o tamany corporal, com indirectament avaluant possibles alteracions en habilitats visuoespacials en tasques no relacionades amb el cos. D'aquests estudis, se n'ha criticat el fet que és molt difícil diferenciar el component perceptiu d'un possible component cognitiu que estigui esbiaixant la percepció (Stein and Corte, 2003). A més, algunes de les troballes en tasques visuoespacials no directament relacionades amb la percepció corporal podrien reflectir alteracions en altres dominis; per exemple, podrien evidenciar un estil cognitiu de tipus 'weak central coherence' (coherència central feble, o el millor processament dels detalls a expenses del processament global, (Lopez et al., 2009)). Així doncs, la majoria d'autors coincideixen en el fet que l'AN no és un trastorn perceptiu *per se*, i de fet, el component cognitiu es considera el més important en relació a la distorsió de la imatge corporal (Benninghoven et al., 2007; Kaye, 2008; Legrand, 2010; Skrzypek et al., 2001). Igualment, i en relació amb aquest component component cognitiu més relacionat amb processos d'auto-avaluació, és important reconèixer la funció de la imatge corporal en el desenvolupament del concepte d'un mateix, de com entén els altres i com un creu que és percebut per ells, com es relaciona socialment i com aquests processos poden estar alterats en AN (Stein and Corte, 2008; Stowers and Durm, 1996; Webster and Tiggemann, 2003). En conseqüència, el vincle entre el cos, un mateix, la comprensió dels altres i el món social podria ser més estret i rellevant per l'AN del que fins ara ha estat reconegut.

A nivell cerebral, el processament de la informació sobre el propi cos es genera en diverses àrees responsables de les diferents modalitats sensorials, sent integrada en les regions posteriors de l'escorça parietal i en àrees frontals (Hodzic et al., 2009b; Serino et al., 2013; Tsakiris et al., 2010). Un dels fluxos d'informació relacionats amb el percepció del propi cos és el que té a veure amb processos d'identitat corporal, que s'ha vinculat a l'activitat d'àrees parietals i frontals medials, i que té un solapament molt evident amb la xarxa neuronal per defecte (DMN), la xarxa neuronal més coneguda i estudiada relacionada amb funcions autoreferencials (Tsakiris et al., 2010). En AN, els estudis de RM funcional que han avaluat la

resposta cerebral en relació a la imatge corporal generalment ho han fet d'una manera general, sense una avaluació diferenciada dels diferents components de la distorsió corporal abans esmentats (Gaudio and Quattrocchi, 2012). A més, els dissenys experimentals utilitzats probablement hagin contribuït més a la identificació dels components perceptiu i emocional, però no del cognitiu (Gaudio and Quattrocchi, 2012; Sachdev et al., 2008). En aquest sentit, la comparació de la imatge no distorsionada d'un mateix envers la d'una altra persona s'ha suggerit com més adient per valorar aquest constructe cognitiu (Sachdev et al., 2008).

Una altra de les característiques més sorprenents del trastorn és la capacitat egosintònica dels pacients per mantenir la restricció alimentària, malgrat la gana i les propietats intrínsecament reforçadores del menjar (Kaye et al., 2009). En relació amb aquest fet, diversos estudis han suggerit la participació de respostes alterades de la resposta al reforç (i al càstig), així com alteracions en aquest sistema neuronal. Les primeres hipòtesis van destacar els efectes reforçants que els nivells de cortisol i dopamina podrien tenir en un estat de restricció alimentària (Bergh and Södersten, 1996) i, de fet, estudis en models animals havien evidenciat possibles propietats reforçadores dels canvis en la dieta i l'estat d'inanició (Kim, 2012; Routtenberg and Kuznesof, 1967). A més, altres processos de condicionament actuarien modulant la resposa alterada del sistema del reforç; és el que es coneix com la teoria de la *contaminació del reforç,* que emfatitza el canvi de valència en certs estímuls relacionats amb l'aparença física i l'alimentació (els estímuls positius es converteixen en aversius i els negatius en reforçants) (Keating, 2010; Södersten et al., 2008). De forma semblant, a nivell social s'han observat biaixos cognitius en el reforç percebut: els pacients mostren una tendència a percebre poc reforç en les interaccions socials, evitant-les; alhora, estan excessivament atents i mostren una alta sensibilitat a les situacions de rebuig social (Cardi et al., 2013; Schmidt and Treasure, 2006; Watson et al., 2010). Donat que els processos d'aprenentatge social es construeixen i són modulats de forma important pel sistema del reforç i les respostes condicionades associades (Daniel and Pollmann, 2014), una alteració en aquests processos pot contribuir a un aprenentatge poc adaptatiu i al desenvolupament de relacions socials disfuncionals, les quals contribueixen de forma significativa al manteniment i pronòstic de l'AN (Rieger et al., 2010).

El sistema del reforç és un dels més estudiats i coneguts dels sistemes cerebrals. Consisteix, principalment, en el flux dopaminèrgic entre l'àrea tegmental ventral i l'estriat ventral, amb importants projeccions a àrees frontals i límbiques/paralímbiques, com l'amígdala, l'escorça

prefrontal ventromedial, la OFC, i les escorces insulars (Berridge and Kringelbach, 2015; Knutson and Cooper, 2005; O'Doherty, 2004). Aquest sistema respon a estímuls reforçadors bàsics, però també a formes més complexes de reforç com les de tipus social; per exemple, en resposta a la direcció de la mirada, imatges de companys sentimentals, o l'experiència d'agradar o tenir una bona reputació, entre d'altres (Daniel and Pollmann, 2014; Davey et al., 2010; Fareri and Delgado, 2014; Izuma et al., 2008; Lin et al., 2012). Aquest sistema, a més, es pot subdividir en dos components coexistents però diferenciats, el component motivacional, voler (wanting), o l'experiència hedònica, agradar (linking); en aquest últim participen de forma més important altres molècules a part de la dopamina, com els opiacis i els cannabinoides (Berridge, 2009). Un altre aspecte important a destacar és el que fa referència a la resposta de reforç en contraposició a la de càstig. En moltes ocasions aquests dos components s'han avaluat de forma conjunta donat que el mateix circuit del reforç participa en les dues respostes, tot i que en sentits oposats (Delgado et al., 2000; Rogers, 2011). No obstant, altres estructures, vinculades al dolor físic i emocional, com el ACC, s'han relacionat més específicament amb la resposta al càstig (Wrase et al., 2007).

De les idees expressades fins aquest punt destaquem algunes conclusions. Primer, sembla haver-hi una convergència en la participació de les àrees i les connexions frontoparietals en l'AN, així com del sistema límbic, i el sistema del reforç. Tot i que la implicació de diverses xarxes neuronals i àrees distants suggereix la possible alteració de les connexions estructurals entre aquestes regions (Fornito et al., 2012; Fornito and Bullmore, 2012), hi ha pocs estudis que hagin avaluat les connexions estructurals entre aquests circuïts. Segon, tot i que la resposta a -i la regulació envers- les relacions socials sembla una peça clau en l'AN, fins ara pocs estudis han avaluat les respostes cerebrals en contexts de tipus social. A més, entre els mecanismes que donen forma a les relacions socials, el sistema del reforç, o en un sentit més inclusiu i general, el sistema reforç-inhibició (Wierenga et al., 2014), està probablement implicat de manera molt significativa en les interaccions amb altres en l'AN, però les possibles alteracions en la resposta cerebral dels pacients no ha estat avaluada. Tercer, les alteracions en la percepció corporal molt probablement involucren alteracions en processos cognitius, relacionats amb la pròpia avaluació, possiblement en la pròpia identitat i també amb la interacció amb altres. El component cognitiu, però, no s'ha evaluat de forma separada al perceptiu o l'emocional.

Per poder resoldre aquestes qüestions, en aquesta tesi hem fet ús de diverses tècniques de neuroimatge (ressonància magnètica, RM), que explicarem breument. Per estudiar diferències en les connexions estructural (estructura dels tractes de substància blanca), hem utilitzat tècniques de difusió (DTI, per les sigles en anglès). Aquestes tècniques donen informació sobre l'organització, la coherència i la direcció dels tractes de substància blanca, que s'obté de forma indirecta gràcies a les propietats de moviment brownià de les molècules d'aigua i la identificació del tipus de moviment que tenen les molècules d'aigua que formen els tractes, restringit per la membrana axonal i la mielina, i per tant molt anisotròpic. Per evidenciar aquest moviment i poder inferir les característiques estructurals dels tractes de substància blanca, cal informació temporal (es realitza una adquisició ecoplanar, com en ressonància funcional) i l'aplicació de gradients magnètics en diferents direccions no col·lineals (normalment en un mínim de 6, però freqüentment més de 15). Aquesta mesura es pot quantificar vòxel a vòxel i dóna informació quantitativa en forma de mesures escalars, entre altres possibilitats. Pel que fa a aquestes mesures escalars, les més rellevants són la *fractional anistropy* (FA), que expressa la preferència de les molècules d'aigua per una difusió anisotròpica (al llarg del tracte), i la *mean diffusivity*, MD (~ADC) que codifica la quantitat de difusió de les molècules d'aigua sense tenir en compte la direcció. Aquestes dues mesures típicament estan correlacionades de forma negativa i en la majoria d'estudis en patologia de substància blanca la FA es troba disminuïda (i per tant la MD augmentada). Altres mesures complementàries que es deriven d'aquestes dues són l'*axial diffusivity* (AD) i la *radial diffusivity* (RD), que representen tant la mitjana de difusió en l'eix paral·lel (AD) com en el perpendicular (RD) de les fibres axonals. L'AD és sensible als canvis en la integritat de la substància blanca (degeneració axonal), mentre que RD és més sensible a canvis de la mielinització (Huettel et al., 2008; Jones et al., 2012). A més, aquesta informació sobre l'estructura dels tractes de substància blanca es pot complementar amb l'estudi de possibles canvis associats en el volum regional o global de substància grisa o blanca, mitjançant la tècnica de comparació basada en vòxels (Voxel-Based Morphometry, millorada amb l'ús de normalització DARTEL) de les imatges obtingudes de la seqüència de ressonància estructural (seqüència 3D-SPGR). Aquesta anàlisi, segueix els següents passos: segmentació de les imatges en els diferents teixits, normalització espacial de les imatges a un cervell tipus (es transformen les imatges originals per equiparar la posició i mida de les estructures a espai estereotàctic comú), modulació (es retorna a les imatges la informació del volum que tenien abans de la normalització) i suavitzat (homogeneïtza la informació de la intensitat entre un vòxel i els

contigus per millorar la relació senyal-soroll, ajudant, a més, a reduir l'efecte dels possibles errors de normalització)(Ashburner and Friston, 2000). Aquests passos permeten la comparació posterior entre grups en el valor de cada vòxel, el que ens dóna informació sobre canvis de volum entre grups.

Per aquest estudi també s'han utilitzat tècniques de ressonància magnètica funcional. Els passos de preprocessat incloïen, en aquest cas, el realineament de les imatges (corregir els moviments ocorreguts durant l'adquisició de les sèries temporals d'imatges de cada subjecte), normalització i suavitzat. En aquest cas, s'utilitza la detecció de la senyal BOLD (blood oxygen level dependent contrast) com una mesura indirecta del consum d'oxigen en les diferents regions cerebrals. Aquesta mesura es basa en les diferents propietats magnètiques de l'hemoglobina quan està proveïda i desproveïda d'oxigen (oxihemoglobina, amb propietats diamagnètiques, i desoxihemoglobina, amb propietats paramagnètiques, respectivament). Aquesta senyal permet avaluar les diferències en una funció cerebral concreta mitjançant la sostracció d'activacions: mesurem l'activitat cerebral BOLD davant una tasca d'interès i li restem l'activitat BOLD mentre es realitza una tasca control, que només difereixi de la nostra tasca experimental en l'activitat cerebral que volem mesurar. Altres tècniques una mica més complexes inclouen la possibilitat de mesurar no només quines regions presenten activacions diferents entre grups, sinó també possibles diferències entre la connexió funcional entre regions durant la tasca (per exemple amb tècniques de PPI -Psychophysiological Interactions-, o anàlisis d'interaccions psicofisiològiques). Altres tècniques, que no inclouen cap tasca, avaluen diferències en les activacions sincròniques entre regions duran l'estat de repòs, i permeten comparacions entre grups, per exemple en la connectivitat funcional en repòs entre regions. En aquest últim cas cal destacar la gran importància que ha tingut en els últims anys la DMN, un dels sistemes que ha demostrat una fluctuació sincrònica robusta de les seves àrees en situació de repòs i que es relaciona amb processos introspectius (Anticevic et al., 2012; Harrison et al., 2008).

Objectius:

Aquest treball té com a objectiu millorar el coneixement en les bases neurobiològiques de l'anorèxia nerviosa, subtipus restrictiu, en relació als components nuclears del trastorn com són la percepció de la imatge corporal, la implicació del sistema del reforç en el trastorn i els

possibles mecanismes implicats en la disfunció social que afecta els pacients. També pretenem estudiar com potencialment aquests símptomes i/o d'altres factors concomitants es traslladen a alteracions estructurals, principalment en els tractes de substància blanca. Amb aquests objectius, es va reclutar un grup de 20 pacients dones adultes, afectades d'AN de tipus restrictiu i sense comorbilitats. Van ser incloses de forma consecutiva a l'ingrés a l'Hospital de Dia de l'Hospital Universitari de Bellvitge. Es van reclutar també un grup de 20 dones sanes, aparellades amb el grup de pacients per gènere, dominància manual, mitjana d'edat i de nivell educatiu.

Els objectius principals van ser:

- Estudiar, en pacients amb AN comparades amb el grup control, les diferències d'anisotropia i difusió en els tractes de substància blanca cerebral mitjançant la comparació de mesures escalars (FA, MD, RD, AD) obtingudes amb tècniques de difusió amb resonància magnètica.

- Estudiar, en pacients amb AN comparades amb el grup control, les diferències en el patró de resposta cerebral en rebre una resposta d'acceptació o rebuig social manipulada experimentalment durant una sessió de ressonància magnètica funcional.

- Estudiar, en pacients amb AN comparades amb el grup control, les diferències en el patró de resposta de la xarxa neuronal per defecte durant de la visualització del propi cos o del cos d'una altra persona durant una sessió de ressonància magnètica funcional.

- Estudiar, en pacients amb AN comparades amb el grup control, les diferències en el patró de connectivitat funcional entre les àrees de la xarxa neuronal per defecte, davant de la presentació del propi cos i del cos d'una altra persona.

- Estudiar, en pacients amb AN comparades amb el grup control, les diferències en el patró de connectivitat funcional entre les àrees de la xarxa neuronal per defecte durant l'estat de repòs i en relació a les troballes en la tasca de percepció corporal.

- Estudiar, en pacients, les possibles associacions entre les troballes estructurals i funcionals i les diferents variables clíniques d'interès, com la severitat del trastorn.

Resultats:

Els resultats de les comparacions de les variables clíniques i neuropsicològiques van ser els següents:

- No es van trobar diferències entre grups en edat, dominància manual, o nivell educatiu.
- Les pacients presentaven un índex de massa corporal (IMC) inferior a les controls, així com una puntuació major en l'escala de severitat *Eating Disorders Inventory*, EDI-2) (Garner, 1991).
- Les pacients presentaven una major puntuació mitjana tant en l'escala de depressió (Hamilton, 1960) com en la d'ansietat (Hamilton, 1959).
- No es van trobar diferències entre grups en la variable de personalitat 'evitació del dany' inclosa en el qüestionari autoadministrat Temperament and Character Inventory (TCI-R) (Cloninger, 1999).
- Les pacients van presentar una major sensibilitat al càstig, mentre que no hi va haver diferències entre grups en la sensibilitat a la recompensa, mesurat amb l'escala Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001).
- Les pacients presentaven major puntuacions en símptomes d'ansietat social, mesurats amb l'escala Liebowitz Social Anxiety Scale (LSAS) (Heimberg et al., 1999).
- Es van trobar diferències significatives entre grups en la mesura de en la silueta corporal ideal, però no de la percebuda actual, del qüestionari Cross-cultural questionnaire (CCQ)(Penelo et al., 2011). Específicament, la silueta ideal en les pacients era més prima que en les controls.

Els resultats, per cadascun dels articles, van ser els següents:

ARTICLE 1.

- Es van trobar diferències entre pacients i controls al tracte Superior longitudinal esquerre. Les pacients presentaven una disminució de FA, acompanyada d'un increment de RD i MD.

- Es van trobar diferències entre pacients i controls al fòrnix i radiacions talàmiques bilaterals. Les pacients presentaven un increment de MD que es va acompanyar d'un increment de AD i RD i una disminució de FA.

-Variables de confusió com l'edat, símptomes ansiosos o depressius no van influir significativament en els resultats.

- No es van trobar associacions entre les mesures de FA/MD i les variables clíniques d'interès: edat, EDI-2, evitació del dany, durada de la malaltia, IMC i símptomes depressius i d'ansietat.

- No es van trobar diferències en els volums globals o regionals de substància gris o blanca, ni quan les anàlisis regionals es van dirigir específicament a les regions amb canvis significatius a nivell estructural.

ARTICLE 2.

- A nivell conductual, els dos grups van recordar millor les persones que les havien rebutjat que aquelles que les havien acceptat o que no havien donat resposta. Tots els subjectes van creure en la veracitat de l'avaluació social a la qual se les va sotmetre de forma experimental.

- En ser acceptades socialment, les pacients van mostrar una menor activitat en la part dorsomedial de l'escorça prefrontal (Broadmann àrees BA8 i BA9).

- En ser rebutjades socialment, les pacients van mostrar una major activació de l'escorça visual secundària (BA18).

- Interacció: Durant la resposta a l'acceptació, la sensibilitat al reforç es va associar, de forma diferencial entre els grups, amb l'activació de l'escorça insular bilateral-opèrcul frontal (correlació negativa en pacients) i amb el còrtex prefrontal, regions dorsomedial i dorsolateral (BA8, BA10) (correlació positiva en controls sans).

- Durant la resposta a la condició de rebuig, cap àrea es va associar de forma diferent entre els grups amb la sensitivitat al càstig.

- En les pacients, no es van trobar associacions entre l'activació cerebral durant la resposta d'acceptació i la severitat del trastorn, mesurada amb l'EDI-2.

- En les pacients, i en la condició de rebuig social, la severitat del trastorn (EDI-2) estava correlacionada amb l'activitat de l'estriat ventral (caudat), així com de les escorces prefrontal dorsomedial (BA8) i visual (BA17-BA18-BA19) (correlació positiva). També es va evidenciar una correlació negativa amb l'activació de l'escorça prefrontal dorsolateral.

- No es van trobar associacions entre els resultats i la duració de la malaltia o l'edat d'inici del trastorn.

- No es van trobar associacions significatives entre la resposta cerebral a qualsevol de les dues condicions (acceptació o rebuig) i les puntuacions en ansietat social mesurades amb l'escala LSAS.

ARTICLE 3.

- En les pacients, en mirar el seu propi cos en comparació amb el d'una altra persona, es va evidenciar una hiperactivitat de l'escorça parietal medial (precunya) i de les escorces ventral i dorsal de l'escorça cingulada posterior (vPCC i dPCC pels seus noms en anglès). Al nivell del dPCC, les pacients mostraven una major resposta al processament del seu propi cos, mentre que, a la precunya, la resposta en pacients no diferenciava entre la percepció del propi cos i el d'una altra persona, evidenciant, sobretot, una manca de resposta a la percepció de l'altre. Al nivell del vPCC es va trobar una resposta intermèdia entre la resposta del dPCC i la de la precunya.
- Les pacients van presentar un increment en la connectivitat funcional entre el dPCC i l'escorça cingulada anterior en resposta a la seva pròpia imatge.
- Les pacients van presentar un increment en la connectivitat funcional entre la precunya i la part posterior de l'escorça temporal mitja esquerra en resposta a la percepció del cos de l'altra persona.
- Durant l'estat de repòs les pacients van mostrar un increment en la connectivitat entre el dPCC i el gir angular esquerre.
- Es va trobar una associació entre la connectivitat de la precunya-àrea temporal mitja i la duració de la malaltia. Aquesta associació, però, no va sobreviure la correcció per comparacions múltiples.
- No es van trobar associacions entre els resultats i les variables clíniques d'interès [(edat d'inici, duració de la malaltia, motivació per estar prim (EDI-2), distorsió de la imatge corporal (EDI-2), consciència interoceptiva (EDI-2), evitació del dany (TCI-R), pròpia percepció de la forma corporal (CCQ) i forma corporal ideal (CCQ)].
- De forma complementària, les anàlisis a nivell de tot el cervell van mostrar que les pacients presentaven un augment en l'activitat de l'escorça parietal superior i de la zona de transició parieto-occipital durant la percepció del cos d'un mateix.

Discussió:

En la present tesi doctoral s'han avaluat alteracions neuroanatòmiques i neurofuncionals en un grup de 20 pacients amb anorèxia nerviosa, subtipus restrictiu. En el primer estudi, que va avaluar alteracions estructurals, es van trobar que les pacients presentaven canvis de la microestructura en la part parietal del tracte longitudinal superior esquerre i al fòrnix, sense alteracions de volum regional o global en la substància blanca o la substància grisa. En el segon estudi les respostes de les pacients durant les condicions de ser acceptades o rebutjades socialment es va interpretar en relació amb una alteració de les conductes motivades durant la interacció social en l'AN. Concretament, aquestes respostes alterades estaven relacionades amb la resposa de la xarxa neuronal vinculada a processos de cognició social i la modulació d'aquesta resposta per àrees del sistema del reforç. El tercer estudi va posar de manifest alteracions en àrees parietals medials en pacients amb AN durant l'avaluació de la pròpia imatge corporal i en relació a la imatge d'una altra persona. Aquestes alteracions es van acompanyar de diferències en el patró de connectivitat funcional entre les parts posteriors i anteriors de les àrees de la DMN i entre regions posteriors d'aquesta xarxa. Donat que les alteracions del component posterior estaven presents tant durant la tasca com en repòs, es va suggerir que l'alteració en aquestes regions era mantinguda i estable, podent-se interpretar com una alteració neurobiològica nuclear en l'AN. En relació a aquests resultats, suggerim la rellevància d'un circuït prefrontoparietal, així com dels sistemes del reforç (estriat ventral, ínsula) i motivacionals en contexts socials, en pacients amb AN. Aquests resultats, com serà exposat a continuació, suggereixen també la possible alteració d'aquests circuits en relació a la pròpia avaluació de l'aparença i l'enteniment de l'altre, críticament involucrats en les relacions socials.

Circuït prefrontoparietal

Les àrees parietals han estat àmpliament implicades en l'AN, en estudis estructurals i funcionals. Tant les regions medials com les laterals estan involucrades en funcions relacionades amb la integració de diversos elements necessaris per a la composició mental de la imatge corporal, en el sentit més ampli. A més, les regions medials, com s'ha comentat, estan relacionades amb funcions d'avaluació de tipus autoreferencial, també implicades en processos d'avaluació de la identitat pròpia durant tasques de percepció corporal. Dos dels estudis presentats per aquesta tesis donen suport a les alteracions d'aquest circuït. En l'Estudi 1, es va trobar una disminució de

la FA (i un increment de RD i MD) al tracte superior longitudinal (SLF), el més gran que connecta regions parietals i frontals. En concret, les alteracions es van localitzar als axons del SLF-II, que connecta àrees frontoparietals laterals. A l'Estudi 3 es van trobar alteracions en àrees parietals medials durant l'avaluació de la percepció corporal, pròpia i d'una altra persona. En relació a la percepció d'un mateix, els resultats van indicar que les pacients presentaven una hiperresposta de l'escorça cingulada posterior (PCC), conjuntament amb una major connectivitat funcional d'aquesta regió amb l'escorça cingulada anterior (ACC). Els resultats dels dos estudis (1 i 3) podrien estar relacionats amb diferents aspectes de les alteracions de la percepció de la pròpia imatge corporal en les pacients amb AN. En concret, mentre que les alteracions entre àrees parietals laterals i premotores (Estudi 1) semblen estar més involucrades en alteracions generals del processament de la pròpia imatge corporal possiblement més relacionades amb la integració de la informació sensorial (Hodzic et al., 2009a; Serino et al., 2013), la formació de la identitat corporal sembla estar més relacionada amb estructures medials (Estudi 3). Tot i que les regions medials (Estudi 3) es connecten preferentment mitjançant l'SLF-I, l'SLF-II (Estudi 1) integra les funcions de les porcions I i III de l'SLF de forma bidireccional, suggerint que les alteracions en AN es localitzarien en vies que sustenten un alt grau d'integració dels diferents processos necessaris per a dur a terme el processament de la imatge corporal.

Igualment, en aquests dos estudis també es va suggerir la implicació d'àrees parietals o del circuït prefrontoparietal en aspectes relacionats amb les interaccions socials o interpersonals. A l'Estudi 1 es va hipotetitzar una relació entre les alteracions observades a l'SLF amb els dèficits en *weak central coherence* observats en AN (hiperatenció al detall en detriment del processament global) (Lopez et al., 2009; Treasure, 2013). Aquest estil cognitiu s'ha associat amb dèficits en la identificació de les emocions facials, contribuint a una pitjor comprensió del context en àmbits socials, el que, evidentment, té unes implicacions en les habilitats i relacions socials (Happé and Frith, 2006). En AN, aquest estil sembla poder relacionar-se amb la hiperatenció al cos (Watson et al., 2010), així com amb la important disfunció social associada al trastorn (Treasure, 2013). A l'Estudi 3, vam suggerir de forma específica alteracions en l'associació entre la percepció del propi cos i la comprensió d'aspectes socials, derivats d'una manca d'activació de la precunya davant la visualització del cos d'un altre persona, així com l'augment, possiblement compensatori, de connectivitat funcional amb àrees temporals vinculades amb l'emmagatzemament de la informació biogràfica i del coneixement dels altres

(Andrews-Hanna et al., 2014a; Andrews-Hanna et al., 2014b). Aquests resultats posen de manifest el gran solapament entre l'avaluació del jo i dels altres en relació a la imatge corporal (van der Velde, 1985), i estan possiblement relacionats amb els problemes en la formació de l'esquema d'un mateix que s'observa en pacients amb AN (Stein and Corte, 2007).

No és possible, però, extreure conclusions sobre la direcció d'aquestes troballes. Per exemple, podria ser que els individus vulnerables a desenvolupar AN fossin aquells que tenen un estil cognitiu de *weak central coherence* i pobres habilitats socials, tot això associat a alteracions estructurals del SLF. Al contrari, també podria ser que, en aquests subjectes vulnerables, determinats canvis durant l'adolescència conduïssin a alteracions de les habilitats visuoespacials i dèficits d'integració social i emocional, així com amb una deficitària percepció d'un mateix i de la seva relació amb els altres que facilitessin el desenvolupament del trastorn (Alexander et al., 2007; Darki and Klingberg, 2015; Giorgio et al., 2010; Klingberg, 2006; Pfeifer and Peake, 2012). A més, també és possible que aquests canvis estructurals i funcionals estiguin associats a canvis nutricionals i a les pròpies distorsions cognitives del trastorn un cop desenvolupat. La preocupació per l'aparença física associada amb l'aprenentatge (motivacional) i l'entrenament d'un biaix envers parts del cos (focus atencional al detall) pot estar modulant aquestes alteracions en el context de plasticitat cerebral i canvis en la substància blanca durant els processos d'aprenentatge (Zatorre et al., 2012). Tot i que és possible que ambdós processos coexisteixin, diverses evidències donen pes a la presència d'alteracions- tret en el SLF, almenys, a nivell estructural. Per exemple, les variacions en canvis microestructurals de regions parietals i frontals semblen explicades fins un 75-90% per components genètics; a més, alteracions de la microestructura en aquest tracte s'han associat amb amb puntuacions altes en la escala de personalitat d'evitació del dany (Yau et al., 2013), i s'han trobat tant en pacients adolescents com en recuperades (Bischoff-Grethe et al., 2013; Frank et al., 2013b).

Sistema de reforç-inhibició i motivació social

Els resultats dels Estudis 1 i 2 van suggerir alteracions en les respostes de reforç (i càstig) en pacients amb AN associades a dos estímuls diferents vinculats a la patologia: el menjar i les relacions socials. A l'Estudi 1, es van trobar alteracions microestructurals (augment de MD, RD i AN, disminució de FA) al fòrnix, una estructura rellevantment vinculada a l'alimentació, l'emoció i el processament del reforç. Aquestes alteracions s'han vist replicades en estudis previs i

posteriors al nostre Estudi 1 (Frank et al., 2013b; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014) i en altres condicions relacionades amb l'alimentació (Mettler et al., 2013; Metzler-Baddeley et al., 2013). A l'Estudi 2, la resposta davant l'acceptació i el rebuig social va ser més complexa, implicant estructures involucrades en cognició social (disminució de l'activitat de l'escorça dorsomedial durant l'acceptació) i visuals (augment de l'activitat occipital durant el rebuig social), que es van interpretar com una traducció neurobiològica del biaix negatiu observat a nivell conductual. A més, àrees directament implicades en la resposta o avaluació del reforç es van trobar associades o bé amb la severitat del trastorn (estriat ventral) o amb la sensibilitat a la recompensa (ínsula anterior), estructures que probablement modulen de forma important la resposta social.

Aquests resultats encaixen amb la concepció actual de la implicació del sistema del reforç (i inhibició) en l'AN, segons la qual l'alteració d'aquest sistema s'ha relacionat a canvis associats a canvis en la dieta i la restricció alimentària, així com a processos de condicionament, relacionats, a nivell social, amb el biaix negatiu (Harrison et al., 2010b; Keating, 2010). És interessant mencionar que aquestes alteracions en estructures del reforç s'han relacionat també amb la formació d'hàbits de conducta, més associats a parts posteriors del nucli estriat que anteriors, que es consideren possiblement vinculars a l'elevada refractarietat del trastorn, sobretot en amb temps llargs d'evolució de la malaltia (Walsh, 2013). En el nostre Estudi 2 la part posterior de l'estriat no es va trobar afectada, però sí l'anterior; és possible que aquests mecanismes d'hàbit siguin més difícils d'establir en relació a les relacions socials, donat que són molt variables i poc predictibles (Adolphs, 2001). Amb l'evolució del trastorn, la combinació d'hàbits en altres aspectes conjuntament amb el manteniment de la resposta esbiaixada al reforç i/o rebuig social pot estar influint de manera significativa en la resistència a la milloria. El model tindria un paral·lelisme amb el que s'ha suggerit en els models d'addicions a substàncies tòxiques, on unes vulnerabilitats prèvies (que poden relacionar-se, per exemple, amb la densitat de receptors de dopamina) contribueixen a l'establiment de la conducta, contribuint els canvis posteriors del sistema del reforç a la resistència del trastorn (Everitt and Robbins, 2013; Jog et al., 1999; Walsh, 2013; Yin et al., 2004).

En relació al biaix atencional, els resultats de l'Estudi 2 suggereixen la implicació d'àrees de diversos sistemes que modulen la resposta davant d'inputs de tipus social, i que probablement interactuen directament amb les estructures del sistema del reforç, com s'ha vist en estudis

previs (Delgado et al., 2005). L'alta motivació de les pacients per la persistència en la restricció alimentària i els símptomes -vinculat a estímuls socials, i relacionat amb el valor donat a l'aparença física i el cos- és més important que la motivació envers les necessitats bàsiques com el menjar i que les propietats intrínsecament reforçadores de menjar (Goldstone et al., 2009; Maslow, 1943). La implicació, en el desenvolupament de la malaltia, de sistemes tant primitius i potents com el del reforç, i altres xarxes que en modulen la seva resposta, està possiblement implicat en el desenvolupament, i sobretot, la resistència del trastorn al tractament.

3. El cos, la percepció d'un mateix i de l'altre, el reforç i les relacions socials.

Tot i la importància reconeguda per l'AN de la rellevància del concepte d'un mateix (Brunch, 1973; Stein and Corte, 2003; Stein and Corte, 2007; Stein and Corte, 2008; Williams and Reid, 2012), aquest aspecte probablement no ha rebut l'atenció que es mereix, sobretot des del punt de vista neurobiològic. De fet, segons el nostre enteniment, és la primera vegada que a un nivell teòric neurobiològic es dóna suport a la vinculació entre la percepció corporal, l'avaluació del propi cos i d'un mateix, les relacions socials i l'associació d'aquestes amb les alteracions en el sistema del reforç i d'altres sistemes motivacionals. L'organització de l'esquema d'un mateix es realitza de forma important durant l'adolescència, però va canviant i actualitzant-se al llarg de la vida (Pfeifer and Peake, 2012). Les relacions socials, que, almenys en part, es van formant mitjançant mecanismes d'aprenentatge associatiu, li van donant forma. Aquests esquemes influencien processos inferencials que motiven i regulen el nostre comportament amb els altres (Kendzierski and Whitaker, 1997; Sheeran and Orbell, 2000; Stein and Corte, 2008), i que tenen a veure amb la pròpia percepció d'un mateix, la percepció de l'altre i la interacció entre aquests dos components (Markus et al., 1985; van der Velde, 1985). La correcta interrelació dels diferents esquemes que es tenen d'un mateix s'ha associat amb una millor capacitat adaptativa a nivell social i, en pacients amb AN, s'ha observat una menor correlació entre aquests esquemes personals identitaris (Stein and Corte, 2007). Tots aquests factors involucrats en la construcció del concepte d'un mateix podrien ser importants en l'emergència i la persistència de l'AN en individus vulnerables, tant durant l'adolescència com en l'edat adulta. És interessant remarcar, en aquest context de desenvolupament del propi concepte, i en el marc del sistema reforç-inhibició (Wierenga et al., 2014), la importància i implicació d'aspectes d'*inhibició* i

ansietat que no hem avaluat en aquest treball. En aquest sentit, tot i les similituds entre AN i els trastorns d'ansietat en termes d'estil cognitiu i trets de personalitat, un factor diferencial entre aquests ells podria relacionar-se amb l'afectació d'aquestes respostes *inhibitòries* al constructe d'un mateix i la pròpia identitat, i viceversa.

Un altre factor que, per la seva rellevància en aquests processos, hem d'esmentar és la contribució de la capacitat interoceptiva en la construcció del mapa corporal i del propi concepte d'un mateix. És un concepte que vincula el medi intern amb la percepció i la regulació de les emocions, i a la vegada, l'empatia social (Brugger and Lenggenhager, 2014). En aquest context, una estructura repetidament vinculada a aquests processos és l'ínsula (Craig, 2009), i alguns autors n'han destacat la seva importància per l'AN i la seva vinculació amb la distorsió de la imatge corporal (Frank, 2015). Tot i que en els resultats dels nostres estudis hem suggerit un paper més important per a les estructures parietals, manca per clarificar el flux jeràrquic entre aquestes estructures durant la integració de la informació associada a la percepció del propi cos, i, a partir d'aquí, amb el concepte d'un mateix i la relació amb els altres (Vogt and Laureys, 2005).

4. Integració dels resultats en models previs i nova contribució a aquests models. Consideracions globals

Els resultats d'aquests estudis s'adapten al models actuals d'AN. Posen de rellevància el component cognitiu relacionat amb la percepció de la imatge corporal en AN (Cash and Deagle, 1997; Fernández et al., 1994; Fisher and Cleveland, 1958; Gaudio and Quattrocchi, 2012; Skrzypek et al., 2001), donen suport a la implicació d'un biaix cognitiu involucrat en les relacions socials (Treasure and Schmidt, 2013a), i a la implicació de les estructures del reforç en el trastorn (Bergh and Södersten, 1996; Frank, 2013; Kaye et al., 2011; Keating et al., 2012). Els resultats, sobretot de l'Estudi 2 -com hem anat suggerint- també poden ser integrats en el model del desequilibri entre els sistemes del reforç-inhibició (Wierenga et al., 2014). Altres models que queden una mica més allunyats dels nostres resultats han suggerit, per exemple, que l'AN és un trastorn de la regulació emocional (Haynos et al., 2015a; Haynos et al., 2015b; Wildes et al., 2014), o que pot ser contextualitzat en un marc de proximitat amb els trastorns d'ansietat, potser inclús en un contínuum, emfatitzant els processos de condicionament de la por vinculats amb el trastorn (Strober, 2004). En el model que presentem incorporem la

rellevància, a nivell neuropsicològic i neurobiològic, de la construcció de l'esquema personal, la seva vinculació amb la percepció del cos i les relacions socials, i el seu manteniment (veure Figura 7). Suggerim la implicació de les alteracions en connexions frontoparietals en aquests processos, possiblement com a factor de vulnerabilitat, i en canvi, la participació dels sistemes de reforç i motivacionals durant el desenvolupament de la malaltia i que tenen a veure amb la resistència a la milloria del trastorn. Aquestes hipòtesis, però, hauran de ser específicament avaluades en nous estudis.

5. Futures investigacions

De tot el que s'ha comentat amb anterioritat neixen noves qüestions per a ser investigades. Per exemple, una tasca bàsica interoceptiva (comptar els batecs cardíacs), que està íntimament relacionada amb la percepció corporal d'un mateix podria mostrar canvis en els circuïts esmentats. A més, seria interessant avaluar les diferents fases de la resposta al reforç i al càstig (p.ex. anticipació, recepció) en un context social. A nivell estructural, noves tècniques amb major sensibilitat, així com l'estudi conjunt del significat de les alteracions neuroanatòmiques en models animals, probablement contribuiran, en el futur, a una major comprensió dels processos de vulnerabilitat i persistència associats amb el trastorn (Zatorre et al., 2012).

A nivell assistencial, i donat la importància que hem donat a la formació de l'esquema d'un mateix en relació al cos i a les relacions socials, així com els processos de manteniment de la malaltia associats amb aquests últims, seria interessant avaluar una teràpia centrada en aquests aspectes, possiblement ajudant als pacients a la seva identificació (Treasure et al., 2012). A nivell més general, és interessant la reflexió, en AN i també en la població general, sobre el possible impacte de projectes d'educació emocional (i cognitiva) en relació amb el constructe d'un mateix i en relació al marc social i cultural específic.

Conclusions:

1. Les pacients amb anorèxia nerviosa, subtipus restrictiu, van presentar alteracions estructurals i funcionals en un circuït prefrontoparietal, que suggerim involucrat en la distorsió de la imatge corporal
    a. A l'Estudi 1, les pacients amb AN en comparació amb les control sanes, van presentar alteracions en la microestructura de la substància blanca (disminució de FA) al tracte longitudinal superior esquerre.
    b. A l'Estudi 3, les pacients amb AN en comparació amb les control sanes, van presentar una resposta incrementada de l'escorça cingulada posterior, juntament amb un increment en seva connectivitat funcional amb l'escorça cingulada anterior, durant la visualització de la pròpia imatge corporal.
2. Les pacients amb anorèxia nerviosa, subtipus restrictiu, van presentar alteracions en la resposta cerebral durant la visualització de la percepció del cos d'un altre, que suggerim estar relacionades amb dèficits en la comprensió d'un mateix i els altres.
    a. A l'Estudi 3, les pacients amb AN en comparació amb les control sanes, van presentar, davant la visualització del cos d'una altra persona, un dèficit d'activació i d'activació diferencial entre condicions a la precunya
    b. A l'Estudi 3, les pacients amb AN en comparació amb les control sanes, van presentar un increment en la connectivitat funcional entre la precunya i l'escorça temporal mitja durant la visualització del cos d'una altra persona.
    c. A l'Estudi 1, les pacients amb AN en comparació amb els controls, van presentar alteracions (disminució de FA) al fascicle longitudinal superior esquerre que podrien relacionar-se amb un estil cognitiu específic que determinés el tipus de relacions socials.

3. Les pacients amb anorèxia nerviosa, subtipus restrictiu, van presentar alteracions estructurals i funcionals en estructures del sistema del reforç
    a. A l'Estudi 1, les pacients amb AN en comparació amb les control sanes, van presentar alteracions en la microestructura de la substància blanca al fòrnix (increment de MD).

b. A L'Estudi 2, les pacients amb AN en comparació amb les control sanes, van presentar una associació diferencial entre la sensibilitat a la recompensa i l'activació de les escorces insulars, de forma bilateral, durant la resposta d'acceptació.
c. A L'Estudi 2, les pacients amb AN van presentar una associació entre la severitat de la malaltia i l'activació de l'estriat ventral durant la resposta al rebuig.

4. Les pacients amb anorèxia nerviosa, subtipus restrictiu, van presentar alteracions funcionals en ser acceptades o rebutjades socialment. Suggerim que aquestes alteracions estan relacionades amb aspectes motivacionals alterats durant les relacions socials.
    a. A l'Estudi 2, les pacients amb AN en comparació amb les control sanes, van presentar una hipoactivació de l'escorça prefrontal dorsomedial durant la resposta d'acceptació.
    b. A l'Estudi 2, les pacients amb AN en comparació amb les control sanes, van presentar una hiperactivació de l'escorça visual durant la resposta de rebuig.

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bulimia nervosa: an fMRI study. J Psychiatry Neurosci 35:163–76.

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Wagner A, Barbarich-Marsteller NC, Frank GK, Bailer UF, Wonderlich SA, Crosby RD, Henry SE, Vogel V, Plotnicov K, McConaha C, Kaye WH (2006b): Personality traits after recovery from eating disorders: do subtypes differ? Int J Eat Disord 39:276–84.

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Appendices

List of publications

Publications:

Marta Cano, Narcís Cardoner, Mikel Urretavizcaya, Ignacio Martínez-Zalacaín, Ximena Goldberg, **Esther Via**, Oren Contreras-Rodríguez, Joan Camprodon, Aida de Arriba-Arnau, Rosa Hernández-Ribas, Jesús Pujol, Carles Soriano-Mas, José M. Menchón. Modulation of limbic-prefrontal connectivity by Electroconvulsive Therapy in treatment resistant Depression. Accepted in Brain Stimulation. IF: 4.40.

Via E, Soriano-Mas C, Sánchez I, Forcano L, Harrison BJ, Davey CG, Pujol J, Martínez-Zalacaín I, Menchón JM, Fernández-Aranda F, Cardoner N. Abnormal Social Reward Responses in Anorexia Nervosa: An fMRI Study. PLoS One. 2015;10(7):e0133539. IF: 3.23.

Goldberg X, Soriano-Mas C, Alonso P, Segalàs C, Real E, López-Solà C, Subirà M, **Via E**, Jiménez-Murcia S, Menchón JM, Cardoner N. Predictive value of familiality, stressful life events and gender on the course of obsessive-compulsive disorder. J Affect Disord. 2015;185:129-34. IF: 3.38.

Harrison BJ, Fullana MA, Soriano-Mas C, **Via E**, Pujol J, Martínez-Zalacaín I, Tinoco-Gonzalez D, Davey CG, López-Solà M, Pérez Sola V, Menchón JM, Cardoner N. A neural mediator of human anxiety sensitivity. Hum Brain Mapp. 2015. In press.

Fagundo AB, **Via E**, Sánchez I, Jiménez-Murcia S, Forcano L, Soriano-Mas C, Giner-Bartolomé C, Santamaría JJ, Ben-Moussa M, Konstantas D, Lam T, Lucas M, Nielsen J, Lems P, Cardoner N, Menchón JM, de la Torre R, Fernandez-Aranda F. Physiological and brain activity after a combined cognitive behavioral treatment plus video game therapy for emotional regulation in bulimia nervosa: a case report. J Med Internet Res. 2014;16(8):e183. Impact factor 2013: 4.67. CITATIONS: 2

Via E; Zalesky A; Sánchez I; Forcano L; Harrison BJ; Pujol J; Fernández-Aranda F; Menchón JM; Soriano-Mas C; Cardoner N; Fornito A. Disruption of brain white matter microstructure in females with anorexia nervosa. The Journal of Psychiatry and Neuroscience. 10;39(4):130135. Impact factor 2013: 7.49. CITATIONS: 8

Via E, Cardoner N, Pujol J, Alonso P, López-Solà M, Real E, Contreras-Rodríguez O, Deus J, Segalàs C, Menchón JM, Soriano-Mas C, Harrison BJ. Amygdala activation and symptom dimensions in obsessive-compulsive disorder. British Journal of Psychiatry. 2014(1):61-8. Impact Factor 2013: 7.34. CITATIONS: 14

Via E, Cardoner N, Pujol J, Martínez-Zalacaín I, Hernández-Ribas R, Urretavizacaya M, López-Solà M, Deus J, Menchón JM, Soriano-Mas C. Cerebrospinal fluid space alterations in melancholic depression. PLoS One. 2012;7(6):e38299. Epub 2012 Jun 28. Impact Factor 2013: 3.53. Cerebrospinal fluid space alterations in melancholic depression. CITATIONS: 2

Via E, Radua J, Cardoner N, Happé F, Mataix-Cols D. Meta-analysis of gray matter abnormalities in autism spectrum disorder: should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? Arch Gen Psychiatry, 2011 (4): 409-18. Impact Factor 2013: 13.75. CITATIONS: 100

Radua J, **Via E**, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. Psychol Med., 2011(7): 1539-50. Impact Factor 2011: 5.43. CITATIONS: 90.

Submitted articles:

Esther Via, Ximena Goldberg, Isabel Sánchez, Laura Forcano, Ben J Harrison, Christopher G. Davey, Jesús Pujol, Ignacio Martínez-Zalacaín, Fernando Fernández-Aranda, Carles Soriano-Mas, Narcís Cardoner, José M. Menchón. Default Mode Network alterations during self-other body perception and resting-state in anorexia nervosa. Social Cognitive and Affective Neuroscience Journal. In review. IF: 7.37.

Real E, Subirà M, Alonso P, Segalàs, Labad J, Orfila C, López-Solà C, Martínez-Zalacaín I, **Via E**, Cardoner N, Jiménez-Murcia S, Soriano-Mas C, Menchón JM. Brain structural correlates of Obsessive-Compulsive Disorder with and without preceding stressful life events. The World Journal of Biological Psychiatry. In review. IF: 4.23

R.M. Molina-Ruiz, T. García-Saiz, J.C.L. Looi, **E. Via**, M. Rincón, Helena Trebbau López, Saray Rodriguez Toledo, Miguel Yus, Jose Luis Carrasco Perera, Marina Díaz-Marsá. Emotion processing in eating disorders: a fMRI study. Submitted to European Archives of Psychiatry and Clinical Neuroscience. In review. IF: 3.53.

Curriculum vitae

Esther Via

MD, Psychiatrist.

Pre-doctoral researcher in Clinical Neurosciences (neuroimaging).

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∝ 29/09/1981

CAREER OVERVIEW

Medical doctor in Psychiatry, with experience in structural and functional neuroimaging research (magnetic resonance) in mental disorders. I am interested in both clinical and research work in mental health and I would like to use this knowledge in the future to develop further education strategies to empower mental health in society.

KEY STRENGHTS

- Experience in research in several mental disorders.
- Experience in the participation of all the stages of research in neuroimaging: from imaging acquisition to paper writing and basic supervising.
- Technical experience in different softwares of image processing and analysing.
- Experience in clinical psychiatry during the specific training.
- Translational perspective of research in neurosciences, given the training in neuroimaging research in different mental disorders and the clinical experience as a psychiatrist.

Positions

06/2015-10/2015: Research- PhD submission. Universitat de Barcelona, Barcelona Spain.

12/2014-06/2015: **Visiting researcher** at the Melbourne Neuropsychiatry Centre (**MNC**). The University of Melbourne, Australia. Funded by the Australian Education Department- **Endeavour Research Fellowship recipient** 2014-2015. Supervisor: A/Prof Ben J Harrison.

1/2014-12/2014: **Research contract** at the *Insitut d'Investigació Biomèdica de Bellvitge* (IDIBELL), *Hospital Universitari de Bellvitge*, Barcelona. Supervisors: Dr Soriano-Mas, Dr Cardoner.

1/2014-12/2014: **Research contract** at the *Insitut d'Investigació Biomèdica de Bellvitge* (IDIBELL), *Hospital Universitari de Bellvitge*, Barcelona. Supervisors: Dr Soriano-Mas, Dr Cardoner.

1/12/2013-31/12/2013: Awarded with a **grant** entitled "Ajudes per a la finalització de la tesis", a competitive grant which offers an **economical help to present the Doctoral Thesis** whitin 6months. Bellvitge School of Medicine- University of Barcelona, Barcelona.

09/2010-09/2013: Awarded with a **Research Scholarship** entitled "Beca en Formació Post-MIR". Pre-doctorate position in the Neurosciences-Psychiatry and Mental Health group in IDIBELL (Institute of Biomedical Research of Bellvitge), *Hospital Universitari de Bellvitge*, Barcelona (Spain). Supervisors: Dr Soriano-Mas, Dr Cardoner. **Includes collaborative projects** with the **Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, Australia.** Supervisors: A/Prof. BJ Harrison and A/Prof. A Fornito-Dr A Zalesky.

08/2010: **Psychiatrist Assistant** position at the Emergency Room-Psychiatry Department, *Centre Fòrum, Hospital del Mar*, Barcelona

2006-2010: **Training in Psychiatry** at the *Bellvitge University Hospital,* Barcelona, Spain**. Includes a research exchange at The Maudsley Institute of Psychiatry, King's College, London, United Kingdom.** Supervisor: Prof. Dr. Mataix-Cols.

Research details

Participation in personal and group projects:

- Personal:

06/2010: Pre-doctoral research project: Meta-analysis of structural neuroimaging studies of autistic patients compared to healthy controls. Supervisor: Dr. Cardoner, Dr Mataix-Cols. University of Barcelona, Barcelona.

2012-: Presentation and acceptance of the Doctoral Thesis project: "Neuroimaging of anorexia nervosa: alterations of the white matter and pattern of activations during social reward and the perception of the self-image". University of Barcelona. Supervisors: Dr. Cardoner, Dr. Soriano-Mas.

- Researcher included in the following grants:

- *Epigenetic and environemental factors bracing cognitive impairment and late-onset depression in elderly and early stages of Alzheimer disease LC_OF*. Founded by: Instituto de Salud Carlos III. Spanish Economy and Competitivity department. Start-end date: 01/01/2015 - 31/12/2017

- *Conectividad cortico-límbica en pacientes con alteración de la regulación emocional: factores moduladores y desarrollo de terapias personalizadas basadas en la neuroimagen funcional* (Cortico-limbic connectivy in patients with emotional regulation alteration: modulating factors and development of personalized therapies based on functional neuroimaging). Founded by: Instituto de Salud Carlos III. Spanish Economy and Competitivity department. Start-end date: 01/01/2014 - 31/12/2016.

- Neurocognición y regulación emocional en condiciones extremas de peso: Estudio de la actividad cerebral y cambios asociados a una intervención basada en video juego terapéutico (Neurocognition and emotional regulation in extreme weight conditions: study of the brain activity and changes associated with a video-game based intervention). Founded by: Instituto de Salud Carlos III- Spanish Economy and Competitivity department. Start-end date: 01/01/2014 - 31/12/2016.

- El recuerdo de la extinción del miedo como biomarcador y predictor de respuesta terapéutica en los trastornos de ansiedad: Estudio mediante resonancia magnética funcional. (Fear extinction recall as a biomarker and response predictor in anxeity disoders: an fMRI study). Founded by: Instituto de Salud Carlos III. Spanish Economy and Competitivity department. Start-end date: 01/01/2013 - 31/12/2015

Collaboration in current group projects:

09/2010-present: Participation in neuroimaging research projects: eating disorders, major depression, obsessive-compulsive disorder, generalized anxiety disorder.

Specific tasks:

- Recruitment of participants (patients and controls).
- Neuropsychological assessments (patients and controls).
- Assistance in the acquisition of magnetic resonance (MR) images.
- Processing and analysis of the MR images.
- Participation in the writing of peer-reviewed scientific papers.
- Diffusion of results (scientific congressess).
- Collaboration in student's supervision.

Technical knowledge in neuroimaging:

1. **Experience in different modalities of analysis:**

- Diffusion images (magnetic resonance) (**DTI**, **Diffusion Tensor Imaging**).
- **Structural images** (magnetic resonance), mainly with **VMB (Voxel Based Morphometry)** and in SPM software.

- **Functional images** (magnetic resonance).
- **Meta-analysis** in neuroimage, with SDM software.

2. Courses and related trainings:

- 09/2010: **National course of SPM**. Clínic Hospital of Barcelona. Barcelona.

-10/2011: **London fMRI SPM course**, the Welcome Trust Centre for Neuroimaging, UCL, London, UK.

- 02/2012-09/2012: Training in the analysis of **DTI using TBSS** (tract based spatial statistics) in FSL. During the research stage at The Melbourne Universitiy, Melbourne, Australia (Supervisors: A/Prof. A Fornito-Dr A Zalesky).

Peer-reviewed published papers:

Via E, Soriano-Mas C, Sánchez I, Forcano L, Harrison BJ, Davey CG, Pujol J, Martínez-Zalacaín I, Menchón JM, Fernández-Aranda F, Cardoner N. Abnormal Social Reward Responses in Anorexia Nervosa: An fMRI Study. PLoS One. 2015;10(7):e0133539. IF: 3.23.

Goldberg X, Soriano-Mas C, Alonso P, Segalàs C, Real E, López-Solà C, Subirà M, **Via E**, Jiménez-Murcia S, Menchón JM, Cardoner N. Predictive value of familiality, stressful life events and gender on the course of obsessive-compulsive disorder. J Affect Disord. 2015;185:129-34. IF: 3.38.

Harrison BJ, Fullana MA, Soriano-Mas C, **Via E**, Pujol J, Martínez-Zalacaín I, Tinoco-Gonzalez D, Davey CG, López-Solà M, Pérez Sola V, Menchón JM, Cardoner N. A neural mediator of human anxiety sensitivity. Hum Brain Mapp. 2015. In press.

Fagundo AB, **Via** E, Sánchez I, Jiménez-Murcia S, Forcano L, Soriano-Mas C, Giner-Bartolomé C, Santamaría JJ, Ben-Moussa M, Konstantas D, Lam T, Lucas M, Nielsen J, Lems P, Cardoner N, Menchón JM, de la Torre R, Fernandez-Aranda F. Physiological and brain activity after a combined cognitive behavioral treatment plus video game therapy for emotional regulation in bulimia nervosa: a case report. J Med Internet Res. 2014;16(8):e183. Impact factor 2013: 4.67

Via E; Zalesky A; Sánchez I; Forcano L; Harrison BJ; Pujol J; Fernández-Aranda F; Menchón JM; Soriano-Mas C; Cardoner N; Fornito A. Disruption of brain white matter microstructure in females with anorexia nervosa. The Journal of Psychiatry and Neuroscience. 10;39(4):130135. Impact factor 2013: 7.49

Via E, Cardoner N, Pujol J, Alonso P, López-Solà M, Real E, Contreras-Rodríguez O, Deus J, Segalàs C, Menchón JM, Soriano-Mas C, Harrison BJ. Amygdala activation and symptom dimensions in obsessive-compulsive disorder. British Journal of Psychiatry. 2014(1):61-8. Impact Factor 2013: 7.34

Via E, Cardoner N, Pujol J, Martínez-Zalacaín I, Hernández-Ribas R, Urretavizacaya M, López-Solà M, Deus J, Menchón JM, Soriano-Mas C. Cerebrospinal fluid space alterations in melancholic depression. PLoS One. 2012;7(6):e38299. Epub 2012 Jun 28. Impact Factor 2013: 3.53.

Via E, Radua J, Cardoner N, Happé F, Mataix-Cols D. Meta-analysis of gray matter abnormalities in **autism spectrum disorder**: should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? Arch Gen Psychiatry, 2011 (4): 409-18. Impact Factor 2013: 13.75.

Radua J, **Via E**, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-matter volume differences in **autism spectrum disorder** versus healthy controls. Psychol Med., 2011(7): 1539-50. Impact Factor 2011: 5.43.

Participation in books:

Gálvez, V, Toledano P, **Via E**, Crespo JM,. "Inclusion in a research project". Original title: "Incorporación a la línea de investigación". Chapter included in "Manual del residente en psiquiatría" (Manual of Psychiatry residents). Ed Sociedad Española de Psiquiatría, Asociación Española de Psiquiatría, Sociedad Española de Psiquiatría Biológica. GlaxoSmithKline, 2009.

Oral communications in conferences/congresses:

E. Via, J Raduà, N Cardoner, D Mataix-Cols. Meta-analysis in structural VBM autism. Human Brain Mapping, 16th Annual International Meeting. Barcelona, june 2010.

E.Via. "Brain basis of addictions and other psychopathological associated disorders". Original title: "¿Cerebros comórbidos? Bases cerebrales de la adicción y otros trastornos psicopatológicos asociados". One-day congress "New challenges in the treatment of cocaine and alcohol adictions". Original title: "Nuevos retos en el abordaje de las adicciones a cocaína y alcohol". Alicante, Spain, 25/11/2010. **AND** Madrid, Spain, 27/12/2010.

E.Via, P.Toledano, V. Gàlvez, MP Alonso, C Segalàs, A Pertusa, E Real, JM Menchón, J Vallejo. TOC y suicidio. Oral communication. National Meeting of Psychiatrists in training (VII edition). Sponsored by Wyeth. Palma de Mallorca, February 2009.

Abstracts and Posters (selection):

- **Esther Via**, MA Fullana, C Soriano-Mas, CG Davey, JM Menchón, B Straube, T Kircher, J Pujol, N Cardoner, BJ Harrison. Failed ventromedial prefrontal cortex safety signal processing in GAD. Australasian Social Neuroscience. Brisbane, Australia, 4-5 June 2015.

- **Via Virgili, E.**, Fullana, M., Soriano. -Mas, C., López-Solà, C., Goldberg, X., Pujol, J., Martínez-Zalacaín, I., Tinoco, D., Blasco, M., Davey, C., Menchón, J., Cardoner, N., Harrison, B. Generalized anxiety disorder is characterised by a non-discriminative response of the ventromedial prefrontal cortex during fear

learning. European College of Neuropsychopharmacology Congress (ECNP), Amsterdam, The Neteherlands, 29 August-1 September 2015. P. 1. i. 055.

Awaiting for publication in the European Neuropsychopharmacology journal.

- **Via**, N Cardoner, J Pujol, P Alonso, M López-Solà, E Real, O Contreras-Rodríguez, JM Menchón, C Soriano-Mas, B Harrison. Symptom dimensions modulate amygdala activity in obsessive–compulsive disorder. European College of Neuropsychopharmacology Congress (ECNP), Barcelona, October 2013. P. 4. b. 001.

Published in: European Neuropsychopharmacology, 23: S511-S512.

- Narcis Cardoner, Oren Contreras-Rodriguez, **Esther Via**, Didac Macia-Bros, Veronica Galvez, Rosa Hernandez-Ribas, Mikel Urretavizcaya, Benjamin J Harrison, Jose Manuel Menchon, Carles Soriano-Mas, Jesus Pujol. Anterior Cingulate Cortex Connectivity Changes After Treatment with Electroconvulsive Therapy.

Published in: BIOLOGICAL PSYCHIATRY; 73, 9: 180S-180S.

- E. **Via**, C. Soriano-Mas, I. Sánchez, R. Hernández-Ribas, I. Martínez-Zalacaín, S. Jiménez-Murcia, J. Pujol, J.M. Menchón, F. Fernández-Aranda, N. Cardoner.The effects of social judgment in Anorexia Nervosa: a functional magnetic resonance study. European College of Neuropsychopharmacology Congress (ECNP), Viena, October 2012. P.1.e.011.

Published in: European Neuropsychopharmacology 22: S198.

- **Via** E, Soriano-Mas C, Pujol J, Urretavizcaya M, Hernández-Ribas R, Deus J, Soria V, López-Solà M, Menchón JM, Cardoner N. Testing cerebrospinal fluid alterations in melancholic depression by using different methodological approaches. HUMAN BRAIN MAPPING, 17th Annual International Meeting. Canadà, June 2011.

- E. **Via**, J Raduà, N Cardoner, D Mataix-Cols. Meta-analysis in structural VBM autism. HUMAN BRAIN MAPPING, 16th Annual International Meeting. Barcelona, June 2010.

- E.**Via**, P.Toledano, V. Gàlvez, MP Alonso, C Segalàs, A Pertusa, E Real, JM Menchón, J Vallejo. OCD and TOC y suicidio. VII National Meeting of Psychiatry Residents -Wyeth-. Palma de Mallorca, February 2009.

- V Gàlvez, **E. Via**, P. Toledano, B. Benjamin, E. Martínez-Amorós, R. Hernández, N Cardoner. Influence of gender and menstrual phase in the emotional state and emotional processing in a universitary sample. Congress of the Catalan Society of Psychiatry. June 2009.

Grants and Awards:

1. Grants:

January 2016- January 2018: **Rio Hortega Fellowship**, a competitive fellowship awarded by the Spanish Government, Instituto de Salud Carlos III, Economía y Competitividad Department. To be developed at the Hospital Parc Taulí, Sabadell, Barcelona, Spain.

January 2015- January 2017: "**Fundació La Caixa" Fellowship**, awarded by 'Mas Casadevall' Autism Foundation, for the specific Autism Research Training Program ARTP en el UC Davis MIND Institute, Sacramento, California, USA (resigned).

December 2014- June 2015: **Endeavour Research Fellowship**, a competitive fellowship awarded by the Australian Government.

1/12/2013: Awarded with a **grant** entitled "Ajudes per a la finalització de la tesis", and economical support to the finalization of the doctoral Thesis (University of Barcelona)- Campus Bellvitge.

12/2013: Awarded with a **grant** entitled "Ajudes per a la finalització de la tesis". (University of Barcelona)- Campus Clínic (resigned).

09/2010-09/2013: **Pre-doctoral Research Scholarship** (IDIBELL, Institute of Biomedical Research of Bellvitge), *Hospital Universitari de Bellvitge*, Barcelona (Spain).

2. Awards/nominations:

- Poster Award: **Via**, N Cardoner, J Pujol, et al. Symptom dimensions modulate amygdala activity in obsessive–compulsive disorder. European College of Neuropsychopharmacology Congress (ECNP), Barcelona, October 2013. P. 4. b. 001.

- Selection of a poster for oral presentation: E. **Via**, J Raduà, N Cardoner, D Mataix-Cols. Meta-analysis in structural VBM autism. HUMAN BRAIN MAPPING, 16th Annual International Meeting. Barcelona, June 2010.

- Nominated for poster award: Via E, Cardoner N, Pujol J, et al. Amygdala activation is modulated by symptom dimensions in Obsessive-Compulsive Disorder. Society of Biological Psychiatry, st Francisco, May 2013.

- 2nd prize-Oral presentation of a research study. E.**Via**, P.Toledano, V. Gàlvez, et al. OCD and TOC y suicidio. VII National Meeting of Psychiatry Residents -Wyeth-. Palma de Mallorca, February 2009.

- 1st prize-Oral presentation of a research study. V Gàlvez, **E. Via**, P. Toledano, et al. Influence of gender and menstrual phase in the emotional state and emotional processing in a universitary sample. Congress of the Catalan Society of Psychiatry. June 2009.

Academic memberships:

- Catalan Society of Psychiatry ("Societat Catalana de Psiquiatria")- Part of the Organization Committee.
- European College of Neuropsichopharmacology (ECNP).
- Spanish Society of Psychiatry ("Sociedad Española de Psiquiatría").
- Spanish Society of Biological Psychiatry ("Sociedad Española de Psiquiatría Biológica").

Other scientific activities:

- Participation as a reviewer for the following journals: *The Journal of the American Academy of Child and Adolescent Psychiatry*, *PlosOne*, *Psiquiatría y Salud Mental*, *Frontiers in Neuropsychiatric Imaging and Stimulation, Social Neuroscience*.

Other clinical experciece:

- **Specific clinical certificates/trainings:**
- 12/2011: Training (and certificate) in **ADI-R** (*Autism Diagnostic Interview*-Reviewed), the Moller Centre, Churchill College, Cambridge (UK).
- 10/2010: Training in *Obsessive-Compulsive Psicometrical scales*. October 2010, Barcelona.
- 06/2010: Training course on *Psicometrical Scales*. Catalan Society of Psychiatry, Barcelona (Spain).
- 04/2008: VII National Course on *Child and Adolescent Psychiatry*. "**Autism Spectrum Disoder**". Madrid (Spain).
- 10/2008: Intensive Course on *ECT and other physical therapies*. Hospital Universitari de Bellvitge, Barcelona (Spain).
- 02/2009 and 10/2014: Motivational Interview- I and II. Hospital Universitari de Bellvitge, Barcelona (Spain).
- **Clinical stages abroad:**
- 08/2004 - Clinical exchange in Gynaecology. Universidad Autónoma de Nuevo León, Monterrey, México.
- 03/2004-07/2004 – Medical School Exchange (ERASMUS): Paris-XII- Université Paris-Est Créteil, Paris (France).

Teaching experience

Between 2007-2011: **University-based**: Training in psychiatric clinical cases: 4h. (Medicine and Odontology), Training in pharmacology: 2h. (Medicine and Odontology), Case-based and theoretical lessons in neurosciences (social cognition and motivational systems): 6h. (Medicine).

2014. Teacher at the **online master** for research in mental health "Máster Interuniversitario de Iniciación a la Investigación en Salud Mental". 'Experimental designs in neuroimgaing' & 'Softwares for the analyses of neuroimaging data'.

Education

1999 - 2005	M.D., Graduate in Medicine and General Surgery by Universitat Autònoma de Barcelona, Spain.
2006 - 2010	Medical specialization in Psychiatry. Bellvitge University Hospital. Barcelona, Spain.

Others

Languages:

- Catalan and Spanish: Native languages.
- English: Fluent written, spoken and reading.
- French: Fluent spoken and reading.

Services to the community/associations:

- 03/2015-06/2015: Volunteer involved in the SonRise method for early stimulation in **autism** (SonRise Foundation for Autism), home-based programme.
- 05/04/2014: Volunteer at 'Aprenem', an association for families and patients with **autism**.
- 10/2003-09/2004: Member of the **Medical Students'** Association AECS.
- 06/2006- 02/2007: Member of the **non-profit organization** "Medicaments Solidaris", which facilitates the access to pharmacological treatment to East European countries.
- 09/2011-12/2011: **Psychiatrist volunteering** at the non-profit organization ACFAMES, Catalan Association for the relatives and patients affected by Schizophrenia (Associació Catalana de Familiars i Malalts d'Esquizofrènia).

Barcelona, September 2015