Developing and testing a novel neuroscience hypothesis of anorexia nervosa.

Submitted by Ian James Frampton to the University of Exeter
as a thesis for the degree of
Doctor of Philosophy in Psychology
In September 2013

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: …………………………………………………………..

Abstract

Eating disorders are difficult to treat: there is still no NICE-approved first-line treatment for anorexia nervosa. In part this could be due to a lack of a compelling theoretical model to account for the development and dogged persistence of the illness. Sociocultural factors implicating western preoccupation with thinness and attractiveness are likely to play a contributory role, but cannot be by themselves causal in societies where such ideals are dominant. Recent theoretical models in neuroscience predict that predisposing neurobiological factors in early brain development may render some young people more vulnerable than others to universal psychosocial pressures, especially during adolescence.

This dissertation reviews the existing evidence for abnormal neurobiological functioning in eating disorders, acknowledging that it is difficult to distinguish between the acute effects of starvation on the brain and possibly pre-existing underlying factors. Nevertheless, such empirical studies do support the development of a novel hypothesis implicating abnormal functioning of a neural network centred on the insula cortex in anorexia nervosa.

The *insula hypothesis* is tested in a series of functional imaging studies using Single Positron Emission Computed Tomography (SPECT) indicating focal abnormalities in the temporal region that persist following weight restoration treatment and correlate with neuropsychological deficits. A subsequent study using higher resolution functional Magnetic Resonance Imaging (fMRI) lends further partial support to the insula hypothesis (in three out of four tasks) and also implicates additional brain structures in the basal ganglia.

These findings, if replicated, could contribute to the development of novel therapeutic approaches to the treatment of anorexia nervosa, including real-time fMRI and mindfulness-based approaches, both of which have been shown to modulate insula activation. The studies presented here could hopefully also help to reduce the stigma and shame so often associated with eating disorders, for the benefit of sufferers and their families.

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List of abbreviations

ACC	Anterior Cingulate Cortex
AN	Anorexia Nervosa
AVS	Anterior Ventral Striatum
BMI	Body Mass Index
BN	Bulimia Nervosa
BSQ	Body Shape Questionnaire
CDI	Child Depression Inventory
ChEDE	Childrens' Eating Disorder Examination
ChOCI	Childrens' Obsessive Compulsive Inventory
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DA	Dopamine
DM	Diabetes Mellitus Type I
EDE	Eating Disorders Examination
EOAN	Early Onset Anorexia Nervosa
ERP	Event Related Potentials
fMRI	Functional Magnetic Resonance Imaging
GWAS	Genome Wide Association Studies
HAF	Hippocampal Amygdala Formation
HMPAO	99mTc-hexamethylpropyleneamineoxime
HPA	Hypothalamic- Pituitary-Adrenal Axis
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NIMH	National Institute of Mental Health
OCD	Obsessive Compulsive Disorder
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
RDoC	Research Domain Criteria
rtfMRI	Real Time Functional Magnetic Imaging
SIPN	Social Information Processing Network
SPECT	Single Positron Emission Computed Tomography
VBR	Ventricular Brain Ratio
5-HT	Serotonin

Acknowledgements

Chapter 1: Introduction

Foreword

Why is it that (fortunately) only a small percentage of young people develop an eating disorder, when the social pressures on thinness and attractiveness are by definition universal? This question began to interest me when working as a nursing assistant on the Eating Disorders ward at Gt. Ormond St. Hospital during my clinical training. I had a powerful sense that if we could understand what was going on in these children's brains, it might help us to understand more about their struggles with their eating disorder, and to understand what made *this* child more vulnerable than another to all the sociocultural pressures.

These initial questions contributed to my decision to train clinically in Paediatric Neuropsychology as a specialist in neuropsychiatry and neurodevelopmental disorders. I was therefore delighted when invited to return to the Eating Disorders Research Team at Gt. Ormond St. as visiting Consultant Neuropsychologist. At this time the team were publishing a series of neuroimaging studies inspired by Professor Isky Gordon using SPECT (Single Positron Emission Computed Tomography) showing that a significant and consistent proportion of their child patients had a localized unilateral reduction in cerebral blood flow in (predominantly) the temporal region of the brain. Interestingly, these localized reductions in blood flow (indexing altered neural activity) did not typically remit with weight gain at short-term follow up.

The team wondered whether this enduring alteration in neural activity could therefore be a marker of an underlying neurobiological basis for the disorder, or at least a 'scarring' effect of the illness that is slow to recover. They wondered what I could add to the picture neuropsychologically. Coming from a neuropsychiatric perspective, I was very keen to explore the relationship between eating disorder psychopathology and potentially relevant neuropsychological functions such as inhibition, on the basis that anorexia nervosa seems to be a perfect model of behavioural inhibition (in self-

starvation) accompanied by cognitive disinhibition (in the overwhelming thoughts and fears about fatness and loss of control).

Whilst I was busy helping the team design experimental research to explore these constructs, our collaborator from New South Wales, Professor Ken Nunn, offered to review the SPECT images. "It's the insula" was his terse opinion, sending me scurrying for my neuroanatomy textbooks. Ken explained that in his view a rate-limiting disconnection of a neural network involving the insula cortex could parsimoniously account for the symptoms of anorexia nervosa including drive for thinness, altered reward value of food and body image disturbance.

I remained focused on how such a neurobiological abnormality might be revealed in neuropsychological processing deficits; and thus two potentially competing hypotheses were established: Ken championing his 'DisKENnection' theory and my advocacy of an Inhibition in Anorexia Nervosa (IAN) model. With the generous support of our Norwegian partners at Oslo University Hospital, a series of workshops was established in Edinburgh, Oslo and Sydney to develop these theories and produce a testable model. After a great deal of lively debate we developed two lines of enquiry: firstly an exploration of the neuropsychological profile of anorexia nervosa (which was to become the doctoral work of my colleagues Dr. Kristin Stedal in Oslo and soon-to-be-Dr. Mark Rose in London); and secondly, a testable basis for the insula hypothesis. I managed to secure a generous PhD studentship from Oslo University Hospital, registered my studies under the skilled supervision of Professors Huw Williams and Tim Hodgson at the University of Exeter, together with my field supervisor Professor Bryan Lask; and this story begins:

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Ian Frampton

Exeter, September 2013

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(a) Aims, objectives and results[1]

Aim:

The aim of this research project is to develop and test a novel neuroscience hypothesis of anorexia nervosa.

Objectives:

1. To review the current state of the neuroscience of eating disorders;

2. To review the neuroimaging literature in anorexia nervosa, with particular reference to studies exploring the potential role of the insula cortex;

3. To develop a novel neuroscience hypothesis based on existing knowledge of the potential role of the insula in eating disorders and the current neuroscience;

4. To validate a Norwegian version of the Children's Eating Disorder Examination to enable the research to be conducted in the Realm;

5. To explore whether the previously identified altered regional cerebral blood flow (rCBF) in the temporal region (encompassing the insula cortex) persists in children with anorexia nervosa and is associated with neuropsychological functioning deficits following weight restoration treatment, potentially indexing an underlying neurodevelopmental risk factor;

6. To use high resolution fMRI techniques to test the hypothesis that rate-limiting dysfunction of a bilateral temporal region neural network centred on the insula cortex will be observed in patients with current anorexia nervosa compared with age-matched control participants;

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[1] Note: Headings in this Chapter are those required by Section 2.2.6 of the University of Exeter Teaching Quality Assurance Manual for the presentation of a thesis/dissertation including published papers.

7. To explore the theoretical and clinical implications of the findings and make recommendations for future research priorities.

Results

The current state of the neuroscience of eating disorders (Chapter 2 and the neuroimaging literature with particular reference to the role of the insula cortex (Chapter 3) are reviewed. A novel neuroscience hypothesis of rate-limiting dysfunction of a neural network centred on the insula cortex is proposed (Chapter 4) and refined (Chapter 5). A Norwegian validation of the Children's Eating Disorder Examination is conducted (Chapter 6), exploring the cognitive and behavioural elements of the overall model. A small-scale follow up study of weight-restored children identifies persisting abnormalities of regional cerebral blood flow in the temporal region (Chapter 7), which predicts neuropsychological dysfunction (Chapter 8) suggesting a localized underlying neurodevelopmental impairment and explores the neuropsychological element of the overall model. A study using functional magnetic resonance imaging in a sample of 21 patients with a current diagnosis of anorexia nervosa identifies functional abnormalities in neural networks including bilateral insula in response to a range of experimental tasks, lending partial support to the hypothesis (Chapter 9). The theoretical implications and future priorities for research and clinical practice are explored (Chapter 10).

(b) Research methodology

Chapter 6 explores the psychometric properties of a verified translation (Reas, Rø, Kapstad, & Lask, 2010) of the Children's Eating Disorder Examination into the Norwegian language (Bokmål) using a matched groups design. Chapter 7 evaluates regional cerebral blood flow using single positron emission computed tomography (SPECT) in a sample of nine participants who had previously undergone a scan at the start of their treatment, using a cross sectional design. Chapter 8 repeats the SPECT methodology described in the previous study to compare the nine who had abnormal regional cerebral blood flow with six who had normal scan results. In addition, the participants

were evaluated using neuropsychological tests derived from the Ravello Profile, a global standard neuropsychological assessment battery for anorexia nervosa (Stedal, Frampton, Landrø, & Lask, 2012; 2012; Rose, Davis, Frampton, & Lask, 2011). Chapter 9 uses functional neuroimaging techniques to test the hypothesis that 21 participants with anorexia nervosa will evidence specific impairment of neural networks incorporating bilateral insula cortex, when compared with healthy control participants in a matched group design.

(c) The contribution made by the papers in the context of the approved field of study

Chapter 2: Frampton, I., & Rose, M. (2013). Eating disorders and the brain. in B.Lask & R.Bryant-Waugh (Eds.), *Eating disorders in childhood and adolescence* (pp.125-147). London: Wiley.

This chapter presents an overview of the current state of knowledge about the role of the brain in eating disorders. It emphasizes how restricting food intake has a significant effect on brain structure and function. The paper suggests that novel neuroimaging techniques allow us to understand more about the acute and long-term effects of eating disorders on the brain.

This chapter briefly reviews a range of recent neuroscience theories that propose a potential role for brain factors in making some people more vulnerable than others to developing an eating disorder. These conceptual models (explored in more detail in Rose and Frampton, 2011), predict a range of neurodevelopmental factors that are relevant in the predisposition to, the onset and maintenance of eating disorders. Rose and Frampton (2011) argue that the US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) Project (http://www.nimh.nih.gov/research-funding/rdoc.shtml) provides a useful framework to evaluate and compare models.

It is encouraging that different authors are positing distinct features at each level of the RDoC framework (such as different key neurotransmitters or neural circuits), which should help in designing experimental tests to decide

between them. For example, Kaye, Fudge, and Paulus (2009) focus on aberrant serotonin and dopamine pathways, whereas Hatch et al (2010) offer an integrated model linking eating disorders to other neurodevelopmental conditions such as OCD. It may be that this is a good stage of the neuroscience for researchers to focus their activity on designing tests to falsify existing models, rather than creating more novel ones. Experimental tests of the predictions arising from the existing models will enhance our understanding of eating disorder neuroscience more than the creation of new models. The Insula hypothesis is chosen as the focus for the present study as at the time it was the only model including a recommendation for how to test it. Rose and Frampton (2011) present a detailed review of all the published eating disorder neuroscience models including a description of their characteristics, evidence base, clinical applicability and testability.

The chapter also introduces a fundamental neurodevelopmental model predicting the relationship between neurobiological functioning, neuropsychological functioning and cognitive-emotional-behavioural functioning. The model is reproduced in Figure 1 below:
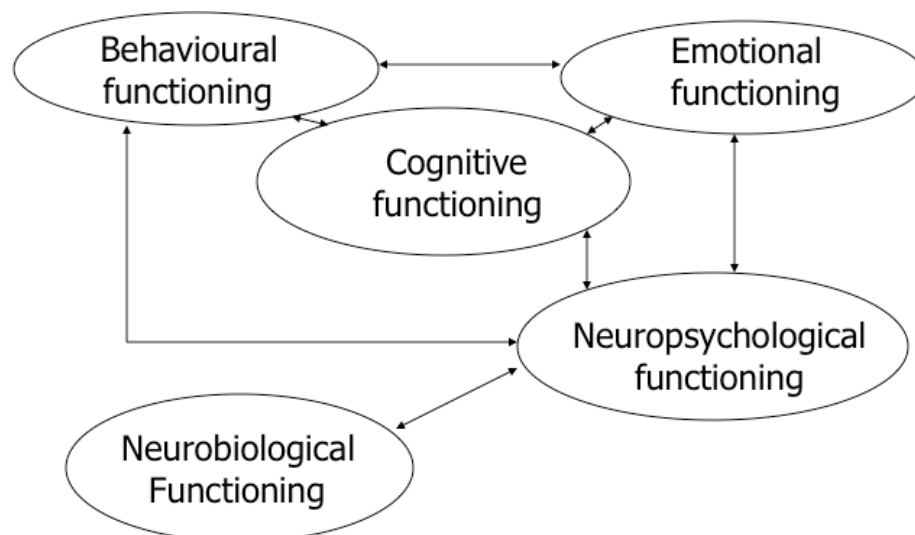
Figure 1: conceptual relationship between neurobiological, neuropsychological and psychological functioning (based on Frampton & Rose, 2013).

Chapter 3: Fuglset, T., & Frampton, I. (2011). Neuroimaging. in B.Lask & I.Frampton (Eds). *Eating disorders and the brain* (pp. 56-105). London: Wiley.

This chapter reviews the range of techniques used to obtain brain images. The various imaging techniques are outlined, along with a summary review of findings from eating disorders research using each of these techniques. The clinical and theoretical implications are discussed.

Chapter 4: Nunn, K.P., Frampton, I., Gordon, I., & Lask, B. (2008). The fault is not in her parents but in her insula – a neurobiological hypothesis of anorexia nervosa. *European Eating Disorders Review*, *16*, 355–360.

This chapter contains the first theoretical paper exploring how the reported abnormalities of brain function in anorexia nervosa (AN) include impairment of neural circuits involving cortical (orbito-frontal, somatosensory and parietal) and sub-cortical (amygdala, hippocampus, thalamus, hypothalamus and striatum) structures. The insula cortex serves an integrative function for all the structures relevant to the features of AN and as such may be central to this impairment. The hypothesis that a rate limiting dysfunction of neural circuitry integrated by the insula can account for the clinical phenomena of AN is proposed. It is argued that such dysfunction could account for the known psychopathology, neuroimaging abnormalities and neuropsychological deficits. Proposals to test this hypothesis are made.

Chapter 5: Nunn, K., Frampton, I., Fuglset, T., Törzsök-Sonnevend, M., & Lask, B. (2011). Anorexia nervosa and the insula. *Medical Hypotheses*. 76. 353-357

This chapter extends the hypothesis that underlying rate-limiting dysfunction of insula cortex is a predisposing risk factor for the development of anorexia nervosa. Supporting evidence for this hypothesis is presented from anatomical and clinical research of insula cortex damage in humans and neuroscientific studies of relevant clinical features including taste, pain perception and reward processing. It is argued that this hypothesis, if

sustainable, would be the first fully to explain the disorder and predicts promising novel treatment possibilities including Cognitive Remediation and Motivation Enhancement Therapies. It is argued that the knowledge that the challenging behaviours so characteristic of AN are the result of underlying cerebral dysfunction, rather than being purely volitional, could help to reduce the stigma patients experience and improve the therapeutic alliance in this poorly understood and difficult to treat disorder.

Chapter 6: Frampton. I., Wisting, L., Øverås, M., Midstund, M., & Lask, B. (2011). Reliability and validity of the Norwegian translation of the Child Eating Disorder Examination (ChEDE). *Scandinavian Journal of Psychology*, *52*, 196-9

This chapter contains the first study of the thesis and explores the psychological (cognitive and behavioural) elements of the model shown in Figure 1. In order to explore eating disorder psychopathology in Norwegian patients, it was first necessary to establish the psychometric properties of a Norwegian translation of the Children's Eating Disorder Examination (ChEDE). The Norwegian version of the ChEDE 12.0 was administered to 15 Norwegian children with anorexia nervosa (AN), 15 children with diabetes mellitus type 1 (DM) and two groups of 15 age-matched controls. The groups were compared using a matched groups design. The subscale scores of the AN group were significantly higher than those of the other groups, and the DM comparison group did not differ from its control group. Inter-rater reliability was generally high (r= 0.91 to 1.00), although there were significant differences between raters on specific items for individual participants. Alpha coefficients for each of the ChEDE subscales indicated a high degree of internal consistency. It is concluded that the Norwegian version of the ChEDE 12 has adequate psychometric properties and can be recommended for clinical and research use with young people with eating disorders in Norway.

Chapter 7: Frampton I., Watkins E., Gordon I., & Lask B. (2011). Do abnormalities in regional cerebral blood flow in anorexia nervosa resolve after weight restoration? *European Eating Disorders Review*, *19*. 55-58

This chapter contains the second study of the thesis and explores the neurobiological element of the overall model shown in Figure 1. Previous research has identified localised abnormalities of cerebral blood flow in anorexia nervosa, suggesting reduction of cerebral activity and function in specific regions. There has been a debate as to whether such findings are secondary to starvation or indicative of a primary abnormality predating the illness, representing an underlying biological substrate. This small study, the first in early onset anorexia nervosa, reports findings of regional cerebral blood flow (rCBF) at both baseline and follow up. Nine participants who had previously undergone rCBF studies indicating abnormal regional blood flow at the start of treatment had a repeat scan at an average of 4.2 years later. Seven out of the nine had persisting reduced cerebral blood flow in one area of the brain, predominantly the medial temporal region. These data suggest that in the majority of cases rCBF does not return to normal following weight restoration, indicating that an abnormality in temporal region brain function may predate the onset of the illness and thus indicate a predisposing risk factor. The implications for future research are explored.

Chapter 8: Frampton, I., Hutchinson, A., Watkins, E., & Lask, B. (2012). Neurobiological status at initial presentation predicts neuropsychological functioning in early onset anorexia nervosa at four-year follow-up. *Developmental Neuropsychology*, 37, 1–8.

This third study in the thesis explores whether neurobiological status (indexed by regional cerebral blood flow) at initial presentation predicts neuropsychological status at four-year follow up in a sample of children with early onset anorexia nervosa and tests the relationship between these elements in Figure 1. Neuropsychological assessment was conducted on 15 females four years after their initial treatment, and matched controls. At follow up there were significant differences between subgroups (based on neurobiological status at initial presentation) and matched controls in long-term visual memory and cognitive inhibition. This study offers preliminary evidence that neurobiological abnormalities at initial presentation predict

neuropsychological status at follow up, suggesting a distinct neurodevelopmental subtype of early onset anorexia nervosa.

Chapter 9: This chapter presents data from the final study in the thesis exploring functional brain activation in current patients and healthy control participants. The aim of this study is to explore whether patients currently diagnosed with AN will evidence significantly different patterns of neural activation compared to healthy control participants in networks incorporating bilateral insula, across four functional tasks. Two tasks were chosen that have been used in previous functional imaging studies in eating disorders (Body Task and Food/Shape Word Stroop Task). Two additional tasks were chosen to assess neuropsychological domains that have been shown in 'offline' studies to differentiate between patients with anorexia nervosa and healthy controls: Mental Rotation and Switch task, reflecting studies identifying impaired visual spatial functioning (Rose, Frampton, & Lask, 2013) and switching ability (Jonsson, Rose, Harvey, & Lask, 2013) in AN respectively. It is hypothesised that patients would exhibit significantly altered patterns of neural activation of networks incorporating the insula across all four tasks, when compared with healthy control participants.

Using these probes, these studies demonstrated that activation of bilateral insula, bilateral putamen, precuneous and associated gyri was significantly different between patient and comparison participants. Conjunction analysis did not reveal any single overlapping area that differentiated between groups for all tasks, and this was confirmed using a region of interest mask of bilateral insula with small volume correction.

These findings lend partial support to the insula hypothesis of anorexia nervosa. The original hypothesis was based on a robust prediction that insula activation differences alone would distinguish between patient and comparison participants in all tasks; in the event, three out of four tasks showed activation differences in this region as envisioned in the original model described by Nunn et al (2008).

A paper based on this chapter is currently under review in the journal *Neuroimage*: *Clinical.*

Chapter 10: Frampton, I., & Lask, B. (2011). Future directions. In B.Lask & I.Frampton (Eds.), *Eating disorders and the brain* (pp.208-218). London: Wiley.

This chapter explores how novel neuroimaging technologies and increased understanding about the neurobiological bases of psychological processes give us a unique opportunity to construct a more complete neuroscientific account of eating disorders. It is argued that this description should be able to tell us something about the underlying cause, assessment and diagnosis, treatment, prevention and future research priorities for eating disorders. Future priorities for research into the genetic, molecular, cellular, neurocircuitry, behavioural and phenomenological aspects of eating disorders are proposed. It is argued that clear differences between theoretical models will facilitate direct head-to-head comparisons in experimental trials that only one of the models can survive. By collaborating in the design and implementation of such studies, we will be able to develop and refine eating-disorder neuroscience. As well as helping us to understand more about the factors that cause and maintain eating disorders, ultimately these endeavors will help to develop novel treatment approaches for the benefit of patients.

Chapter 11: Conclusions

This chapter contextualizes the findings of the empirical studies in the broader neuroscience and eating disorder literature. It reviews the extent to which the Insula hypothesis could be applicable to adult-onset anorexia nervosa and related conditions such as bulimia nervosa and binge eating disorder. It also addresses whether neuroscience-based accounts of psychiatric disorders can be proven as causal, and identifies some potential future research strategies. Finally, the positives and negatives of neuroscience-based models of anorexia nervosa for patients and their families are explored.

(d) Statement of the candidate's contribution to co-authored papers

A Vancouver Declaration is appended to each co-authored chapter and paper to clarify the contribution of other authors. My contribution is as follows:

Chapter 2: I wrote all the sections of this chapter apart from the review of the neuropsychology, which was contributed by my co-author. I coordinated the submission of the chapter and led on revisions in response to editorial comments.

Chapter 3: I established the template for the table summarizing results of neuroimaging studies, which was then populated by my co-author. I wrote the accompanying text, submitted the chapter and led on revisions in response to editorial comments.

Chapter 4: I contributed to discussions and debates leading to the collaborative writing of this paper based on the original hypothesis of the first author, Professor Nunn. I coordinated the writing of drafts, submitted the paper and led on revisions in response to editorial comments.

Chapter 5: I contributed to discussions and debates leading to the collaborative writing of this paper based on the original hypothesis of the first author, Professor Nunn. I coordinated the writing of drafts, submitted the paper and led on revisions in response to editorial comments.

Chapter 6: I designed and coordinated this study, leading on data analysis and interpretation. I coordinated the writing of drafts, submitted the paper and led on revisions in response to editorial comments.

Chapter 7: Based on SPECT data provided by Professor Gordon, I coordinated the writing of drafts, submitted the paper and led on revisions in the light of editorial comments.

Chapter 8: I designed the neuropsychological component of this study, leading on data analysis and interpretation. I coordinated the writing of drafts, submitted the paper and led on revisions in the light of editorial comments.

Chapter 9: I designed this study and led the international team of co-authors under the supervision of Professor Huw Williams and my field supervisor Professor Lask. I supervised data collection by Norwegian-speaking research assistants and liaised with the imaging centre. I was responsible for image preprocessing under the supervision of Dr. Jensen and conducted image analysis under the supervision of Professor Hodgson. I wrote the first draft of the paper and revisions based on feedback from my supervisors and co-authors.

Chapter 10: I wrote the first draft of this chapter and contributed to amendments based on feedback from my co-author.

Chapter 11: I wrote this chapter.

(e) Literature review

An introductory overview of eating disorders neuroscience is reported in Chapter 2. Chapter 3 contains a review of the neuroimaging literature. Chapters 4 and 5 summarise neuroanatomical and neuroscientific studies of the clinical features of eating disorders and insula function in order to develop a novel hypothesis.

Chapter 2: Eating Disorders and the Brain

Frampton, I, & Rose, M. (2013*). Eating disorders and the brain. in B.Lask & R.Bryant-Waugh (Eds.), *Eating disorders in childhood and adolescence* (pp.125-147). London: Wiley.

This chapter presents an overview of the current state of knowledge about the role of the brain in eating disorders. It emphasizes how restricting food intake has a significant effect on brain structure and function. The paper suggests that novel neuroimaging techniques allow us to understand more about the acute and long-term effects of eating disorders on the brain. Recent neuroscience theories also propose a potential role for brain factors in making some people more vulnerable than others to developing an eating disorder. These insights could have profound implications for the way we understand and treat eating disorders.

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Using these probes, these studies demonstrated that activation of bilateral insula, bilateral putamen, precuneous and associated gyri was significantly different between patient and comparison participants. Conjunction analysis did not reveal any single overlapping area that differentiated between groups for all tasks, and this was confirmed using a region of interest mask of bilateral insula with small volume correction.

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A paper based on this chapter is currently under review in the journal *Neuroimage*: Clinical.

Title: Testing the Insula Hypothesis - an fMRI study of adolescents with anorexia nervosa.

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Testing the insula hypothesis – an fMRI study of adolescents with anorexia nervosa.

Abstract

Introduction: Anorexia nervosa is a poorly understood and difficult to treat disorder. It has been suggested that neurobiological risk factors may make some young people more vulnerable than others to universal social and media pressures. The aim of this study is to test the hypothesis that underlying rate-limiting disconnection of a neural network centred on insula cortex could parsimoniously account for the clinical features of the disorder.

Method: Twenty-one adolescent patients with a current clinical diagnosis of anorexia nervosa participated in four functional imaging studies (exploring responses to body image, mental rotation, task switching and inhibition); activation responses were contrasted with 14 healthy control participants.

Results: For three out of the four tasks, significant differences in contrast activation patterns were observed between groups in bilateral insula, controlling for depression, trait anxiety and obsessive-compulsive features. Additional differences were observed in bilateral putamen and left precuneus. Conjunction analyses identified no common overlapping activation differences across all four tasks.

Discussion: The results of this study, the first fMRI investigation of adolescents with anorexia nervosa, do not allow us fully to refute the insula hypothesis. It is unlikely that focal and predicted differences in neural activation are the result of the generalized effect of starvation on the brain. Future prospective and longitudinal neuroimaging studies will help to explicate the effects of starvation and weight recovery on neural functioning. These results implicate potential novel treatments including neurobiofeedback and mindfulness training, both of which have been shown to have an effect on insula function and structure.

Testing the insula hypothesis– an fMRI study of adolescents with anorexia nervosa

Introduction

Anorexia Nervosa (AN) is a serious illness, characterised by an inability to maintain a minimum normal body weight, intense fear of gaining weight, distortion in perception of body weight or shape, and an undue importance of body weight or shape on self-evaluation (American Psychiatric Association, 2000). Patients with AN may also engage in compensatory behaviours such as laxative and diuretic misuse, excessive exercising and self-induced vomiting. Additionally, patients often suffer from low self-esteem, high levels of anxiety, guilt and self-disgust, and often deny or are unaware of the seriousness of their illness (anosognosia).

The prognosis of AN is poor. In a meta-analysis of 119 studies, Steinhausen (2002) reported that 46.9% of patients recovered fully, 33.5% had an intermediate outcome, and 20.8% developed a chronic course. The same author reported a mean crude mortality rate of 5%, and the presence of other psychiatric illnesses at follow-up was common. There is currently no empirically established first-line treatment for AN (National Institute of Clinical Excellence, 2004), and treatment is complicated by the fact that many patients resist or refuse treatment. Frequent and often life-threatening medical sequelae of AN include those due to low-weight and compensatory behaviours (such as self-induced vomiting), and can lead to cardiovascular, gastrointestinal, renal, haematological, skeletal, endocrine, metabolic and dermatological complications (Sharp & Freeman, 1993).

Historically, psychosocial theorists have attempted to account for eating disorders as a consequence of societal pressures for thinness and attractiveness (especially for adolescent females); however, such approaches fail to explain why fortunately only a small percentage of the population at risk develop a serious illness, despite the universal nature of the media and cultural messages.

The possibility that AN might be a neurodevelopmental disorder, such that factors in early brain development render some individuals especially vulnerable to the environmental risk factors, was first proposed by Braun and Chouinard (1992). Subsequently, several models have been developed to explore the relationship between eating disorder psychopathology and underlying neural and neuropsychological functioning. For example, the Connan, Campbell, Katzman, Lightman and Treasure (2003) model focuses on pre- and peri-natal factors and childhood stages of development and propose that there is an interaction between genes, early life experience, and psychosocial environment at puberty, which may make an individual susceptible to developing anorexia nervosa via alteration of appetite and emotional regulation systems. Alternatively, Marsh Maia and Peterson (2009) suggest that self-regulation encompasses cognitive and inhibitory control, the ability to organize thoughts, emotions and behaviour to attain goals.

In this way, the theoretical neuroscience models have attempted to make direct connections between eating disorder psychopathology (such as extreme dietary restriction and intrusive thoughts about weight and shape), neuropsychological functioning (such as impaired cognitive inhibition) and potential underlying neural substrates. For example, according to March et al (2009), anatomical and functional disturbance of frontal-striatal circuits may contribute to a failure of inhibitory cognitive control, leading to the intrusive thoughts about weight or shape. These thoughts elicit compensatory or maladaptive behaviours to reduce the associated anxiety, manifesting in a variety of ways such as compulsions, rigid and ritualistic behaviour and purging.

Kaye, Fudge and Paulus (2009) suggest that a core precipitating risk factor for AN is disturbed appetite and reduced food intake. Since appetite is a drive governed by a complex interaction of psychobiological factors, including the reward properties of food, homeostatic needs and flexible approaches to eating, they suggest that numerous structures are involved, including taste receptors in the tongue, the medulla and nucleus of the tractus solitarius (NTS) of the brainstem, the thalamus, anterior insula and gustatory cortex, amygdala, frontal and parietal cortex. As a result, numerous neuropsychological processes are

implicated, including interoceptive awareness, affective relevance, conflict-monitoring, flexibility, working memory, planning and reward-processing.

Alongside the development of these theoretical neuroscience models, empirical studies have explored brain functioning in currently unwell patients and those who have recovered from AN. Early studies by Ellison, Foong, Howard, Bullmore, Williams et al. (1998) showed a series of pictures of high-calorie foods to six adult patients and six controls while collecting functional MR images. They confirmed the hypothesis that patients experiencing 'calorie fear' would show a neural response similar to that in patients with simple phobias when confronting their feared object, involving increased activation of anterior cingulate and left insula regions. They also found that calorie fear in people with AN was associated with increased activation of the left hippocampal-amygdalar formation, which may therefore mediate conditioned fear to high-calorie foods.

Uher, Murphy, Brammer, Dalgleish, Phillips, Ng et al. (2004) assessed nine women who had long-term recovered from restricting AN with a group of eight chronically ill adult patients with restricting AN and a healthy control group of nine participants, showing them pictures of food and non-food items in the scanner. They found that compared to the chronically ill patients, the recovered women had increased activation of a range of brain regions, including the right lateral prefrontal, apical prefrontal and anterior cingulate cortices (ACCs). Compared to the controls, the recovered women also had increased medial, prefrontal and anterior cingulate activation, as well as reduced activation of the parietal lobe.

 Santel, Baving, Krauel, Munte and Rotte (2006) invited 13 adult patients with AN and 10 control participants to rate visual food and nonfood stimuli for pleasantness during fMRI in both a hungry and a satiated state. AN patients rated the food stimuli less pleasant than controls. When satiated, AN patients showed decreased activation in left inferior parietal cortex relative to controls. When hungry, AN patients showed decreased activation of the right visual occipital cortex compared to the healthy control group, suggesting that patients with AN may experience decreased food-related somatosensory processing when satiated

and attentional processing biases when hungry, which might in combination facilitate restricted eating in AN.

Wagner et al. (2008) used fMRI to test whether adult patients with eating disorders process taste stimuli differently than healthy participants, using a region of interest (ROI) approach to test neural activation in primary and secondary taste cortical regions after sucrose and water administration. The results showed that 13 patients, recovered from AN, had significantly lower activation in the insula (including the primary cortical taste region) and ventral and dorsal striatum in response to both sucrose and water, compared to 13 age-matched control participants, suggesting that recovered AN patients may process taste stimuli differently than controls, based on differences in neural activation patterns.

Sachdev, Mondraty, Wen and Gulliford (2008) explored body image disturbance in 10 adult patients with AN compared with 10 controls using fMRI and showed that when processing self versus non-self images, control participants had greater activation than patients in the middle frontal gyri, insula, precuneus and occipital regions, while the patients did not have greater activation in any region. They concluded that such discrepant emotional and perceptual processing may underlie the distortion of self-images by patients with AN.

Redgrave et al. (2008) aimed to measure brain activation in six adult patients with AN and six control participants performing a novel emotional Stroop task using fat, thin and neutral words and a control stimulus. Reaction times increased in the patient group in thin and fat conditions. In the thin vs non-word contrast, patients showed greater activation than controls at the junction of left insula, frontal and temporal lobes and in left middle and medial frontal gyri. In the fat vs non-word contrast, controls showed greater activation in left dorsolateral prefrontal cortex and right prefrontal areas. The authors conclude that mechanisms underlying attentional bias in AN likely differ under conditions of positive and negative valence. They suggest that this paradigm is a promising tool to examine neural mediation of emotional response in AN.

Given such a wide variety of studies implicating a vast range of neural systems, it may be parsimonious to explore whether there could be an underlying dysfunction in a common core system that could alone account for the wide range of observed neural and clinical features of AN. Nunn, Frampton, Fuglset, Törzsök-Sonnevend and Lask (2011) propose that dysfunction within a single brain region can account for the aetiology and maintenance of AN. They suggest that the clinical phenomena of AN may be explained by rate-limiting dysfunction in a single structure - the insula - which reduces its capacity to integrate information from cognitive, affective and physiological systems. This underlying risk factor may interact with socio-cultural pressures, gender, life events including puberty and psychosocial stressors, to precipitate the illness during adolescence, thus accounting for the aetiology of AN (Nunn et al, 2011).

This hypothesis suggests that the insula is unable to perform its functions to integrate information from cognitive, affective and physiological systems. These functions include:

• Regulation of the autonomic nervous system;
• Regulation of appetite and eating;
• Monitoring of the body state;
• Perception and integration of disgust;
• Reception, perception and integration of taste;
• Monitoring and evaluation of digestive-system status;
• Integration of thoughts and feelings;
• Investment of emotion in language;
• Regulation of the experience of pain.

In this way, the insula hypothesis can be distinguished from previous empirical studies and theoretical models that have implicated a very wide range of alternative neural systems. Rose and Frampton (2011) suggest that the neuroscience of eating disorders has now reached the stage where opposing theoretical models can be directly compared against each other, in order to advance the neuroscience. The aim of this study is therefore to explore whether adolescent patients currently diagnosed with AN will evidence significantly different patterns of neural activation compared to healthy control participants

in networks incorporating bilateral insula, across four functional tasks. This study aimed for the first time to invite adolescents with adolescent onset anorexia nervosa in current inpatient treatment to participate, and so to distinguish acute (and potentially underlying) neurobiological correlates of the illness from the long term effects of chronic and enduring starvation in the previous studies of adults.

Two tasks were chosen that have been used in previous functional imaging studies in eating disorders (Body Task and Food/Shape Word Stroop Task). Two additional tasks were chosen to assess neuropsychological domains that have been shown in 'offline' studies to differentiate between patients with AN and healthy controls: Mental Rotation and Switch task, reflecting studies identifying impaired visual spatial functioning (Rose, Frampton, & Lask, 2013) and switching ability (Jonsson, Rose, Harvey, & Lask, 2013) in AN respectively. Thus there were three bases for task selection: a) those associated with AN generally; b) those differentiating AN from control participants; and c) those addressing specific functions relating to AN.

We hypothesised that adolescent patients with a current clinical diagnosis would exhibit significantly altered patterns of neural activation of networks incorporating the insula across all four tasks, when compared with healthy control participants.

Methods

Participants

Twenty one right handed female patients aged between 13 and 19 with a current clinical diagnosis of anorexia nervosa participated in the study. The patients were undergoing inpatient treatment at a specialist adolescent eating disorders centre at Oslo University Hospital and their medical fitness to participate was confirmed by their co-ordinating doctor. All participants gave informed consent to participate and additional assent was provided by parents of children under the age of sixteen. The study was approved and overseen by the Research Ethics Committee of Oslo University Hospital. A control group of fourteen age-matched right-handed females with no current or previous history of psychiatric illness was recruited from local schools and colleges in the Oslo area.

Psychometric assessment

All participants were assessed using validated adult or child versions of Norwegian translations of the Eating Disorder Examination (Frampton, Øverås, M. Midtsund, M., & Lask (2011), Beck Depression Inventory (Chioqueta, & Stiles 2004), State-Trait Anxiety Inventory (Spielberger, Diaz-Guerrero, & Strelau, 1990) and a Norwegian version of the Children's Obsessive Compulsive Disorder Inventory (ChOCI, Shafran et al, 2003).

Tasks and procedures

Four functional tasks were selected on the basis that they had been shown in differentiate between patients with AN and control participants in previous functioning imaging (Body Shape and Food/Body Stroop Tasks) or 'offline' neuropsychological (Switch and Mental Rotation Tasks) studies. Tasks were presented on a video projector screen within the MRI scanner and verbal or button-press response data were recorded. All subjects were trained using a standardized shorter version of each task before entering the scanner to confirm that they understood the basic requirements.

Switch task: A modified version of the Meiran switch task was used (Woolley et al, 2008) requiring cognitive switching between two spatial dimensions. A target dot appeared in one of four corners of a grid with an arrow in the middle of the grid (see Figure 1a). If the central arrow was horizontal, the participant had to indicate whether the target was on the left or right side of the grid (left or right button); if the central arrow was vertical, participants had to indicate whether the target was in the lower or upper half of the grid (up or down button). Each target was visible for one second with a mean inter-trial interval of 2.4 seconds. During switch trials (n = 32, 21%) the central arrow changed position, which occurred after every 4-6 repeat trials (n = 120, 79%). The event-related analysis contrasted activation associated with repeat trials from activation associated with switch trials (switch minus repeat). For further details see Rubia et al (2006); Figure 1 Panel A.

Body Shape Task: Three sets of black-and-white line drawings of female bodies in swimming costumes were used to represent underweight (BMI < 17.5), normal-weight (20 < BMI < 25), and overweight (BMI > 27.5) female bodies in similar positions. The drawings were matched to silhouette scales and photographs of women with known BMI to fit the selected weight categories (see Figure 1b). The control stimuli were line drawings of houses of varied sizes and styles. Each image was shown for 2.5 sec, followed by a blank screen for 0.5 sec. Ten body pictures in a 30-sec block ("on" condition) were followed by 10 control pictures ("off" condition). This sequence was repeated five times for each type of stimuli. For further details see Uher et al (2005); Figure 1 Panel B.

Mental Rotation Task: Drawings of 3D cube-based structures made up of a series of ten cubes with right-angled 'elbows' developed by Ecker, Brammer, David and Williams (2006) were presented on the video projector screen in pairs (see Figure 1c). The 3D objects in each pair were either the same (same pair) or mirror images (different pair). In the same pair presentation, the two objects could be rotated into congruence with each other. In the presentation of a different pair, the two objects differed by a reflection, as well as a rotation in either x or z dimension and could not be rotated into congruence. A total of 99 trials of five seconds duration (plus inter-trial interval of one second) were presented in random order with respect to the identical/mirror image condition

and the angular. Forty percent of the trials per condition were the same pair, and 60% of the trials were a different pair. Once the object pair appeared on the screen, subjects were asked to decide whether the objects were the same or mirror images. Subjects were instructed to respond as quickly as possible while keeping errors to a minimum. As soon as a decision was reached, the subjects indicated their choice by pressing one of the two buttons on a keypad. The nature of the response ('same' or 'different') and reaction time was recorded. For further details see Ecker et al (2006); Figure 1 Panel C.

Stroop Task: Based on the methods described by Green and McKenna (1993), participants viewed neutral or food/shape related words translated into Norwegian and printed in one of four colours (red, yellow, blue or green) and instructed to report the colour of the ink the word was written in. Words were presented in ten blocks of eight for two seconds during which time the scanner was off to enable audio recording of response accuracy and latency via in-scanner microphone connected to a recording laptop; Figure 1, Panel D.

Please insert Figure 1 about here

Image Acquisition

Participants were imaged on a GE Signa 1.5T Horizon LX System (General; Electric, Milwaukee, WI, USA) at the Curato Røentgen Imaging Centre in Oslo, Norway. A quadrature birdcage headcoil was used for RF transmission and reception.

Structural MRI acquisition: Two conventional MRI datasets were acquired for subsequent morphometric analysis and coregistration of functional images: 1) Coronal 3D spoiled grass (SPGR) dataset, TR = 21ms, TE = 5ms, flip angle = 35°, 256x256x200 matrix, 1.7mm slice thickness; 2) High Resolution Gradient Echo dataset, TR = 3000 ms, TE = 40m, 3mm slice thickness.

Functional MRI acquisition: Gradient-echo echoplanar MR imaging (EPI) data were acquired in each of 28 non-contiguous planes parallel to the anterior-posterior commissure, T2-weighted MR images depicting BOLD (Blood Oxygen Level Dependent) contrast covering the whole brain were acquired with TE =

40ms, TR = 2000ms flip angle = 80°, in-plane resolution = 3.1mm, slice thickness = 4mm, slice-skip = 0.5mm. The Stroop task used a gradient-echo sequence (TE = 40ms TR 4000ms; 70° flip angle) with each acquisition compressed into the first 2000ms of the repetition time, leaving 2000ms when the scanner was silent. The stimulus was presented at the start of each silent period, allowing each trial to be performed in the absence of scanner noise.

Image Processing

Data were analysed using SPM8 software (www.fil.ion.ucl.ac.uk/spm). Images for each participant were realigned to the first volume (Friston, Frith, Frackowiak, & Turner, 1995a) and the anatomical image was coregistered to the mean functional image to ensure that they were aligned. The images were spatially normalized (Friston et al., 1995b) to a standard EPI template (Evans et al., 1993), resampled at 3x3x3 mm, and smoothed using a 6mm full-width half-maximum (FWHM) isotropic kernel. Data were high-pass-filtered using a cutoff value of 128 seconds.

For each functional task two regressors of interest were modeled together with six 'nuisance' movement regressors that were of no interest. In each case, a resulting contrast image was moved to a second level random effects two-samples t-test (thresholded at p < 0.001, uncorrected, minimum cluster size n = 10) using BDI raw score, STAI trait anxiety and ChOCI raw score as covariates. The contrasts entered into the second level model were as follows: Switch task: Switch minus Repeat; Body shape task: Body minus House; Mental rotation task: Switch minus Repeat; Stroop task: Food minus Neutral.

To protect against the probability of type 1 error, we employed an extent voxel threshold cut-off of 10. This combination of intensity and extent thresholds produces a per voxel false positive probability of < 0.000001 (Forman et al., 1995). The X,Y,Z coordinates of all activation clusters were transformed from normalized MNI space (i.e. SPM coordinates) to Talairach space (www.talairach.org) in order to ascertain the site of activation relative to the atlas of Talairach and Tournoux, (1988).

Results

Participant characteristics

Table 1 shows the participant characteristics. The patient and control participant groups were matched for age. The patient group scored significantly higher than the control group on assessment of eating disorder psychopathology, depression, anxiety and obsessive-compulsive features. They also had a significantly lower group mean BMI centile.

Please insert table 1 about here

Behavioural data

There were no significant between group differences on behavioural performance (error rates) for the Switch, Rotation and Body Tasks. Due to recording technical problems, it was not possible to evaluate between-group mean reaction time differences for the Stroop Task.

Functional imaging data

Between group independent samples T-tests were performed for each of the key within task/subject contrasts, as determined by inspection of the maximum activation differences between groups (Table 2 column 1 identifies the key contrasts for each task). Column 2 in Table 2 shows the number of participants in each study. For the Stroop Task, two patient participants did not contribute data as Norwegian was not their first language and data from one control participant were excluded due to scanner technical problems. For the Body Task, data from three patients and one control participant did not complete this task due to scanner technical problems. For the Rotation Task, data from two control participants were excluded due to scanner technical problems. All participants completed the Switch Task.

Functional data analysis

Movement parameters were entered for individual participants as nuisance covariates and BDI total raw score, Trait Anxiety T Score and ChOCI raw score entered into the 2nd level group level contrasts as co-variates of interest. (see Table 2).

Please insert Table 2 about here

The results showed significant activation differences in a range of regions between patient and control participants. For the Stroop task, there were significant differences in the left middle occipital gyrus, left and right insula and right postcentral gyrus (shown in Figure 2a); for the Body task, there were significant differences in the right insula and left precuneus (shown in Figure 2b); for the Mental Rotation task, there were significant differences in the right putamen (shown in Figure 2c); and for the switch task there were significant differences in the left putamen and right insula (shown in Figure 2d). None of these activation differences survived statistical thresholding when BMI centile was entered into the 2nd level model as a co-variate.

Please insert Figure 2 about here

A conjunction model was fitted to the primary task contrast data (within subjects factor) by patient or control group (between subjects factor) to explore whether all four tasks shared a common activation difference between groups. The results revealed no significant differences in activation of voxels between patient and control participants that overlapped for all tasks. Given the a-priori hypotheses about the role of the insula, a Region of Interest (ROI) Mask of bilateral insula cortex with small volume correction was applied (using the WFU_Pickaltas toolbox, Maldjian, Laurienti, Burdette, & Kraft, 2003) to the Conjunction Analysis. Again there were no common areas of activation that overlapped for all tasks.

Discussion

These studies aimed to test the hypothesis that neural networks centred on the insula cortex are selectively impaired in young people with anorexia nervosa. Using a range of experimental probes, we demonstrated that activation of bilateral insula, bilateral putamen, precuneus and associated gyri was significantly different between patient and comparison participants (though these differences disappeared by controlling for BMI-centile). Conjunction analysis did not reveal any single overlapping area that differentiated between groups for all tasks, and this was confirmed using a region of interest mask of bilateral insula with small volume correction.

These findings lend partial support to the insula hypothesis of anorexia nervosa. The original hypothesis was based on a robust prediction that insula activation differences alone would distinguish between patient and comparison participants in all tasks; in the event, three out of four tasks showed activation differences in this region as envisioned in the original model described by Nunn et al (2008). Figure 3 shows the original schematic network model overlaid with the structures (in red) showing differences in activation during the experimental studies.

Please insert Figure 3 about here

The finding that bilateral insula activation differentiates between the groups is consistent with recent findings in eating disorder neuroscience of altered insula functioning in processing of pain (Bär, Berger, Schwier, Wutzler, & Beissner, 2012), food images (Holsen et al, 2012), disgust (Joos et al, 2011) and reward (Cowdrey, Park, Harmer, & McCabe, 2011). It is also consistent with the review by Nunn et al (2011) into the role of insula cortex in a range of disorder-relevant features such as regulation of appetite, taste, monitoring of the body state and the experience of disgust, all of which are core elements of anorexia nervosa.

The observed differences in brain activation in the cognitive tasks between patient and control participants in this study can be related to the abnormalities

in neuropsychological processing that have been identified in AN (in body image processing, inhibitory control and switching, for example), and how these could contribute to the development and maintenance of the disorder (through distorted body image, failure to inhibit morbid preoccupation with weight and shape and impaired cognitive flexibility, for example).

It has been suggested that the insula is 'the Central Station of the brain' due to its rich connectivity and linkage of higher cortical structures with emotion processing networks. This proposed function is both a strength and a weakness of the current hypothesis, since it could be argued that given its role in so many aspects of mental life, it would be extraordinary if the insula were not implicated in some way in a range of psychiatric disorders. For example, Shepherd, Matheson, Laurens, Carr and Green (2012) have recently shown bilateral reduction of insula volume in patients with schizophrenia.

Nevertheless, the relative specificity of the differential activation pattern across such diverse tasks is striking; and arguably analogous to the range of functions – both generic to many disorders and specific to individual disorders - ascribed to the frontal lobes in other neuroscientific traditions. Future studies may be able to derive more 'finely-tuned' analyses of insula sub-structures (at least in distinguishing between anterior and posterior regions) with the benefit of enhanced image resolution. On the basis of the current results, it could be suggested that there is a more nuanced role for the insula in AN, given its interconnectivity with such a wide range of other brain regions and its varied cytoarchitectonic features.

There are several important constraints in the design of the current studies. Not least, as cross-sectional snapshots of insula functioning during the acute phase of the eating disorder, it is not possible to ascertain whether the observed activation patterns are a correlate of low weight or index underlying functioning differences predating starvation. All the significant differences in activation patterns between patient and control participants disappeared when controlling for BMI centile. However, this is an inevitable artifact of fMRI analytic models, where a very subtle difference between groups (in BOLD contrasts of two experimental conditions) is obliterated by controlling for a very large difference

between them (in BMI centile). Additionally, there is a tautological risk in controlling for the independent variable (weight status) that defines our two experimental groups (low weight patients with anorexia nervosa verses normal weight control participants). In any case, it could be argued that general starvation-related effects on the brain are more likely to be global rather than focal and localized to specific predicted networks. Prospective and longitudinal studies are required to explore these issues: though the former raise ethical and logistical concerns in recruiting large samples for scanning before disorder onset; and the latter face the challenge of maintaining contact with participants after their intensive treatment.

The studies reported here also have some strengths in being hypothesis-driven, using a range of disorder-specific (body shape and food words) and neutral (switch task and mental rotation) stimulus material. The analyses partialed out the effect of relevant emotional factors including anxiety, depression and obsessive-compulsive features to maximise the signal associated with core eating disorder related differences in activation between groups.

These findings, if replicated, may have important treatment as well as theoretical implications. Recent studies in healthy participants using real-time fMRI (rtfMRI) by Caria et al (2007) has shown that it is possible to use 'neurobiofeedback' to train participants to modulate insula activation using live feedback in the scanner. This study investigated whether healthy participants could voluntarily gain control over right anterior insula activity. Participants were provided with continuously updated information of the target ROI's level of activation by visual feedback in the scanner. All participants were able to successfully regulate BOLD-magnitude in their right anterior insular cortex within three sessions of four minutes each. Training resulted in a significantly increased activation cluster in the anterior portion of the right insula across sessions. This group study investigating the volitional control of emotionally relevant brain regions by using rtfMRI training confirms that self-regulation of local brain activity with rtfMRI is possible. It may be that the development of similar techniques for patients with AN could prove valuable. Alternatively, mindfulness meditation techniques that have demonstrable structural effects on the insula cortex (Hölzel et al, 2007) could also help to ameliorate a potentially core processing deficit.

More generally, the findings suggest that facilitating functional changes in neural networks centred on the insula cortex may offer a novel way of developing effective treatments. For example, Case, Wilson and Ramachandran (2012) suggest that a dysfunction in interactions between inferior parietal lobule (concerned with body image), insula, and hypothalamus may underlie AN. They speculate that methods to correct visuo-proprioceptive integration in constructing body image may help rehabilitate patients' judgments of size and weight regarding their own bodies. The theoretically-based development of such novel and creative therapies could help to establish effective treatments for this poorly understood and difficult to treat disorder.
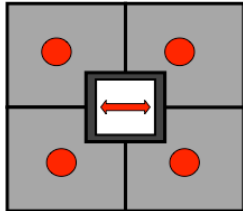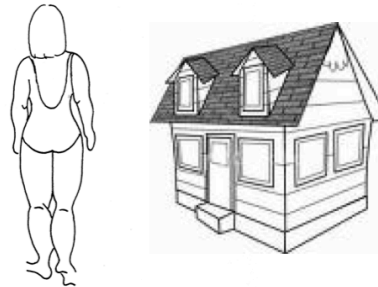
Panel A: Switch task   Panel B: Body task
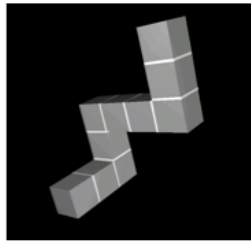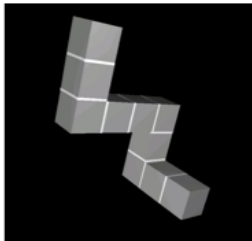
Panel C: Mental rotation task   Panel D: Stroop task

Figure 1: Examples of functional task items.

The Switch Task (Panel A) was to indicate on a four-button response box whether the illuminated circle in each trial was on the left or right hand side of the array if the arrow pointed left-to-right, or on the top and bottom of the array if the arrow pointed up-and-down. Every three to six trials the orientation of the arrow switched.

The Body Task (Panel B) was to indicate on a two-button response box whether the image on screen was a person or a house.

The Mental Rotation Task (Panel C) was to indicate on a two-button response box whether the two images were the same (even if rotated) or different.

The Stroop Task (Panel D) was to report the colour of text for food/shape and neutral words presented in Norwegian (Bokmål).

	Patients (n = 21)		Controls (n = 14)		Significance	
	Mean	StDev	Mean	StDev	T Score	P
Age (Years)	17.0	2.2	16.1	1.2	1.56	ns
BMI centile	13.3	7.5	63.7	32.7	6.15	<0.001
EDE global score	3.8	1.1	1.3	0.8	7.03	<0.001
BDI total	32.4	9.7	8.6	6.8	7.95	<0.001
STAI state t-score	68.6	9.5	53.1	10.3	4.57	<0.001
STAI trait t-score	69.0	8.3	56.3	8.1	4.47	<0.001
ChOCI total raw score	16.3	6.4	7.6	6.1	5.43	<0.001

Table 1: Participant characteristics. (EDE = Eating Disorders Examination; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; ChOCI = Children's Obsessive Compulsive Inventory).

Task	n	X	Y	Z	Voxels	T-value	Z-value	Neuroanatomical location
Stroop Task (food - neutral words)	19/13	-36	-72	-10	103	3.92	3.48	L Middle occipital gyrus, BA 19
		42	-26	-12	229	3.45	3.13	R Insula, BA 13
		38	-40	58	95	3.42	3.11	R Postcentral gyrus, BA 40
		-44	-12	10	160	3.36	3.06	L Insula, BA 13
		34	56	0	86	3.23	2.96	R Middle Frontal Gyrus, BA 10
		64	-28	8	87	3.09	2.85	R Superior Temporal Gyrus, BA 42
Body Task (body - house images)	18/13	46	-30	16	1384	5.03	4.21	R Insula, BA 13
		-54	-10	6	923	5.87	4.69	L Superior Temporal Gyrus, BA 22
		-50	-36	14	124	4.54	3.89	L Superior Temporal Gyrus, BA 41
		-22	-76	22	36	4.41	3.81	L Precuneus, BA 31
		-22	-42	-24	40	3.92	3.47	L Cerebellum, Anterior lobe
Mental Rotation Task (different - same)	21/12	-22	-82	34	306	3.69	3.53	L Occipital lobe, BA 7
		44	-12	52	131	3.19	2.94	R Precentral Gyrus, BA 7
		22	18	0	73	3.15	2.91	R Putamen
Switch Task (switch - repeat)	21/14	-32	-8	0	141	5.80	4.76	L Putamen
		42	22	-18	77	4.45	3.90	R Inferior Frontal Gyrus, BA 47
		44	16	2	36	4.13	3.67	R Insula, BA 13

Table 2: Significant activation differences between participant groups controlling for anxiety (STAI = State-Trait Anxiety Inventory Trait T Score), depression (BDI = Beck Depression Inventory raw score) and obsessive-compulsive features (ChOCI = Child Obsessive Compulsive Inventory Total Severity raw score): independent sample t-tests, voxel cluster threshold 10, p<0.001, uncorrected. n = number of patients/controls included in each analysis; BA = Brodmann Area of neuroanatomical location, as determined by Talairach Client software from www.talairach.org
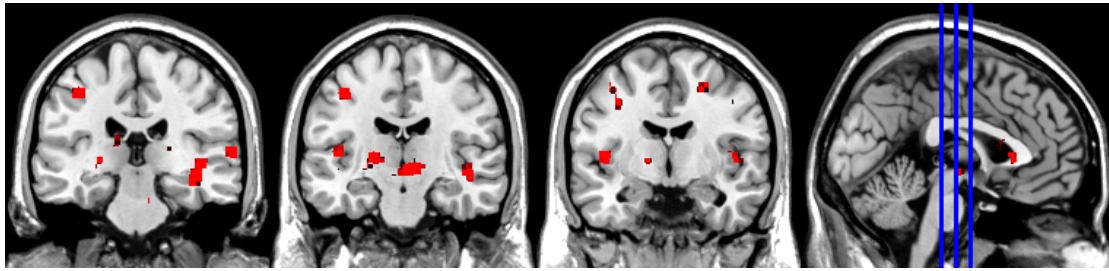
Panel A: Stroop Task (Food – neutral words, patients > controls)
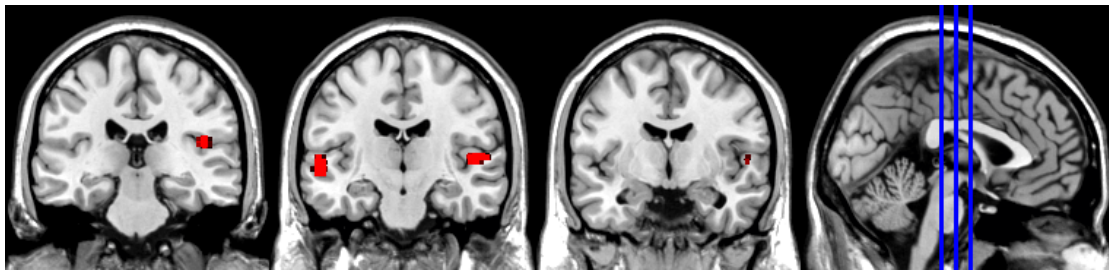
Panel B: Body Task (Body – house images, patients < controls)
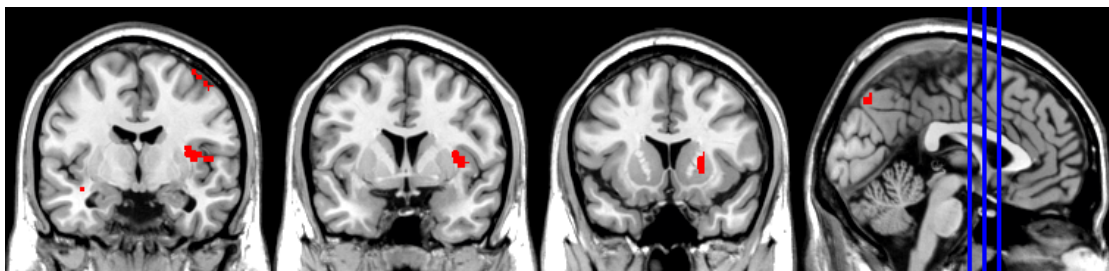
Panel C: Mental Rotation Task (Different – same, patients < controls)
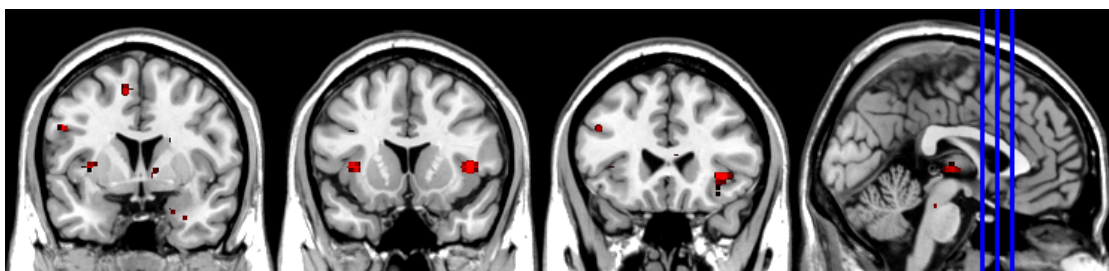
Panel D: Switch Task (switch – repeat, patients < controls)

Figure 2: Significant activation differences between groups on functional tasks. Red areas indicate 'T-score' maps of clusters of voxels (cluster threshold = 10) differing significantly between groups, p < 0.001 uncorrected.
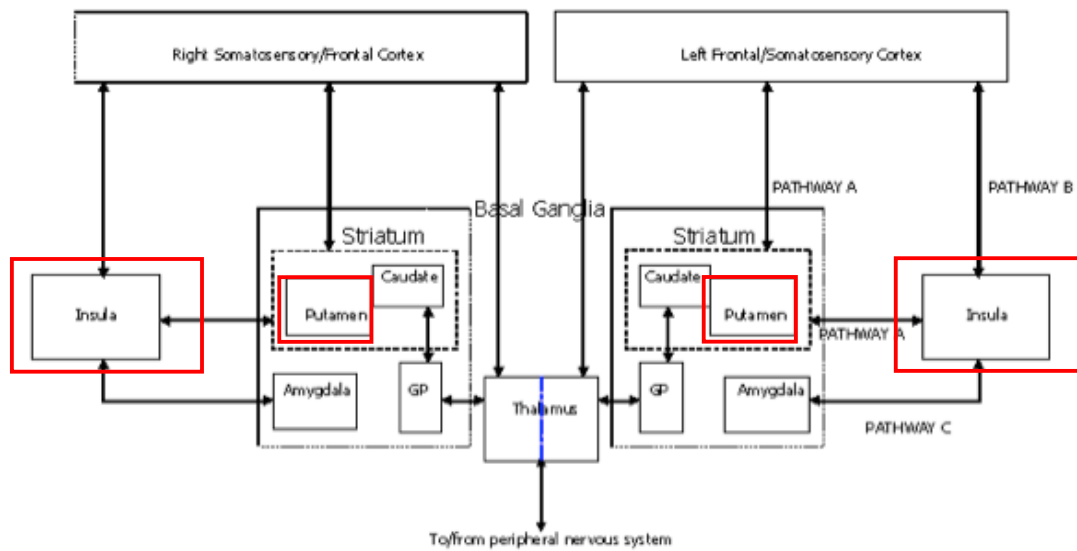
Figure 4: Schematic bilateral coronal section illustrating functional insula networks that regulate direct corticalu   subcortical pathways: (The proposed pathways are labeled on one side only for visual simplicity) Pathway A – Insula via Striatum to Frontal Cortex, Pathway B – Insula to Somatosensory Cortex, Pathway C - Insula to Amygdala. GP = Globus Pallidus (Nunn, Frampton et al. 2008). Red boxes indicate significant between group differences observed in the present study.

Chapter 10: Frampton, I., & Lask, B. (2011). Future Directions. in B.Lask & I.Frampton (Eds). *Eating Disorders and the Brain*. (pp. 208-218). London: Wiley.

This chapter explores how novel neuroimaging technologies and increased understanding about the neurobiological bases of psychological processes give us a unique opportunity to construct a more complete neuroscientific account of eating disorders. It is argued that this description should be able to tell us something about the underlying cause, assessment and diagnosis, treatment, prevention and future research priorities for eating disorders. Future priorities for research into the genetic, molecular, cellular, neurocircuitry, behavioural and phenomenological aspects of eating disorders are proposed. It is argued that clear differences between theoretical models will facilitate direct head-to-head comparisons in experimental trials that only one of the models can survive. By collaborating in the design and implementation of such studies, we will be able to develop and refine eating-disorder neuroscience. As well as helping us to understand more about the factors that cause and maintain eating disorders, ultimately these endeavors will help to develop novel treatment approaches for the benefit of patients.

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Chapter 11: Conclusions

Introduction

The studies reported in this thesis are taken together to argue that it is not possible to refute the Insula hypothesis of anorexia nervosa on the basis of the obtained data. However, the hypothesis itself relies on several assumptions that beg further scrutiny:

The role of early environmental factors on brain function

The Insula hypothesis is predicated on an assumption that environmental factors influence early brain development. This assumption is derived from neurobiological theory and research. For example, Hebbian theory predicts that repeated exposure to external stimuli will: "… induce lasting cellular changes that add to its stability. When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." (Hebb, 1961). Or, to put it more succinctly, cells that fire together, wire together…

The concept of additive (genetically determined) factors specifying the overall neural structure, which is then 'pruned' through subtractive (environmentally determined) experience has been described by Goodman (1989). This mechanism predicts that early environmental factors (such as prenatal exposure to alcohol or other teratogens *in utero*) can cause a range of psychiatric conditions including, potentially, eating disorders.

Early environmental factors implicated specifically in the pathogenesis of anorexia nervosa include obstetric complications (Favaro, Tenconi, & Santonastaso, 2006) and a spring season of birth bias (Winje, Willoughby, & Lask, 2008), possibly explained by exposure to ultra-violet sunlight radiation during early pregnancy contributing to abnormal neurodevelopment (Davis & Lowell, 2006).

Specificity of the insula hypothesis for early onset anorexia nervosa

It is implicit in the empirical studies reported in the thesis that the hypothesis applies to early onset anorexia nervosa, since all the participants came from paediatric treatment settings and were clinical diagnosed with anorexia nervosa. This begs the question of whether the hypothesis can be applied to later adolescent or adult onset anorexia nervosa, or indeed to related disorders such as bulimia nervosa or binge eating disorder.

Future studies will be needed of participants with adult onset anorexia nervosa and bulimia nervosa in order to determine the specificity of the hypothesis for early onset anorexia nervosa. However, from a theoretical perspective, Chapter 2 emphasises that early onset anorexia nervosa should be distinguished from adult onset forms of the disorder, on the basis that children and adolescents are experiencing rapid brain development and so may be acutely sensitive to the neurological effects of starvation. Equally, it is argued that developmental theory suggests the possibility that behavioural features (refusal to eat) may precede the classical cognitive features (overvalued ideas of weight and shape), for children rather than adults with anorexia nervosa.

Specificity of the causal role of the insula in development of eating disorders

As Chapter 5 indicates, one of the weaknesses of the hypothesis is that the insula is such a highly connected structure involved in so many aspects of mental life, that it is impossible to determine that it has a unique role in eating disorders. As Chapter 9 describes, abnormal insula function has been observed in other psychiatric disorders such as Schizophrenia. Nevertheless, as argued in Chapter 5, the known functions of insula cortex, derived from a range of human and animal studies not related to eating disorders, do map closely onto the core clinical characteristics of regulation of appetite, taste, monitoring of the body state, experience of pain, disgust and empathy.

Even more difficult to sustain is the argument that the insula cortex has a causal role in the genesis of the disorder. All the empirical studies reported in the thesis are based on participants who are already (or who have previously been) diagnosed with anorexia nervosa, and thus it is not possible to determine that they were experiencing abnormal functioning of insula networks prior to the onset of their disorder. It is equally possible that the observed abnormalities are a 'scar' of the disorder that are slow to recover, or that may never fully recover.

As Chapter 10 suggests, prospective and longitudinal studies are required to explore these issues: though the former raise ethical and logistical concerns in recruiting large samples for scanning before disorder onset; and the latter face the challenge of maintaining contact with participants after their intensive treatment. The SPECT data reported in Chapters 7 and 8 suggest that a subset of patient with early onset anorexia nervosa do experience persistent unilateral hypoperfusion, primarily in the temporal region, independent of weight restoration status.

The insula cortex is a vast neural territory with distinct cytoarchitectural regions having different connectivity patterns with other regions of the brain. Future refinement of the theory should specify which parts of insula cortex are predicted to relate to specific symptom patterns or clusters in individual patients. For example, It has been suggested that the anterior insula cortex (AIC) contains interoceptive representations that provide the basis for all subjective feelings from the body and perhaps emotional awareness (Craig, 2009). The insula hypothesis predicts that patients with impaired subjective bodily feelings and reduced emotional awareness should evidence functional (and perhaps also subtle micro-structural) abnormalities in AIC that precede the manifest onset of their disorder.

Large-scale 'premorbid' imaging studies of the micro-structural and functional integrity of insula cortex in thousands of children prior to onset of eating disorder in a few is not logistically (or arguably ethically) possible. However,

the overall model presented in Chapter 1 does predict that screening neuropsychological assessments could be developed to 'index' underlying neurobiological abnormalities that confer an increased underlying predisposition to developing anorexia nervosa, given subsequent socio-cultural and contextual precipitating factors (BBC TV, 2011). The Ravello profile collaboration (Stedal, Frampton, Landrø, & Lask, 2012) is an attempt to specify a minimum dataset of neuropsychological assessment tasks that could be used in large-scale population-based studies to identify and follow up 'high-risk' individuals; potentially scanning studies could be offered at this 'prodromal' stage experimentally to explore whether there are any signs of structural and functional abnormality confined to discrete insula regions, and whether these individuals are at an increased risk of the later development of anorexia nervosa.

An alternative research design to explore the potential causal role of insula dysfunction in anorexia nervosa could be to explore its structural and functional integrity in parents and siblings of patients. The search for such 'endophenotypes' is based on the assumption that shared genetic characteristics between patients and first-degree relatives should be observed in shared structural and functional phenotypes (provided that the basis for the disorder is at least partly genetic, of course. Nunn, Frampton and Lask (2012) review the evidence for a genetic basis for the Insula hypothesis).

Such structural and/or functional neuroendophenotypes have recently been reported in relatives of patients with OCD (Chamberlain et al., 2008), with stimulant drug addiction (Ersche et al., 2012) and with ADHD (Piront et al., 2013). To date, no similar neuroimaging studies have been conducted in relatives of patients with eating disorders. However, studies of neuropsychological functioning in first-degree relatives have identified a cognitive endophenotype of impaired set shifting for anorexia nervosa (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005), suggesting that this could be a valuable research strategy to explore in neuroimaging studies.

Treatment implications of the Insula hypothesis

As Chapters 9 and 10 suggest, the Insula hypothesis does suggest specific treatment approaches. Given the hypothesis that (some forms of) anorexia nervosa are the result of dysregulation of a neural network centred on the insula cortex, effective interventions should aim to modify its structure and function. For example, body-focused meditation has been shown to change the structure of the right anterior insula of meditation practitioners who incorporate the practice into their daily routine over many years (Lazar et al., 2005; Hölzel, Ott, & Gard, 2008). However, these studies also showed increased volume in other brain areas including the left inferior temporal gyrus and right hippocampus, suggesting that the effects are not limited to the insula.

Nevertheless, a recent review of mindfulness meditation practice in eating disorders (Rodríguez, Cowdrey & Park, 2013) concludes that evidence is emerging that mindfulness-based interventions may be able to target some aspects of the underlying psychopathology in anorexia nervosa, eliciting changes in eating behaviour as well as cognitive-affective processing. This suggests that future integrated research designs exploring the neural, behaviour and cognitive correlates of mindfulness approaches in eating disorders could be valuable.

Alternative treatment approaches have been proposed by Case, Wilson and Ramachandran (2012) who suggest that a dysfunction in interactions between inferior parietal lobule (concerned with body image), insula, and hypothalamus may underlie anorexia nervosa. They speculate that methods to correct visuo-proprioceptive integration in constructing body image may help rehabilitate patients' judgments of size and weight regarding their own bodies.

Cognitive Remediation Therapy (CRT) has also recently been proposed as a potential treatment for early onset anorexia nervosa (Lindvall & Lask, 2011). Although CRT is not explicitly linked to alteration in insula function, it has been developed to address cognitive functioning deficits that persist after weight

restoration in anorexia nervosa, including set shifting difficulties, weak central coherence, visuo-spatial deficits and impaired decision-making. Parallel imaging studies have revealed abnormal activation of insula cortex in fMRI studies of these same deficits in set shifting, central coherence, visual-spatial processing and decision-making, suggesting that a number of the cognitive deficits in anorexia nervosa can be linked to insula dysfunction. Future research studies could explore structural and functional changes in insula cortex associated with effective CRT treatment.

Finally, Caria et al. (2007) have shown that it is possible to use real-time fMRI neurofeedback to train participants to modulate insula activation using live feedback in the scanner. This study investigated whether healthy participants could voluntarily gain control over right anterior insula activity. Participants were provided with continuously updated information of the target ROI's level of activation by visual feedback in the scanner. All participants were able to successfully regulate BOLD-magnitude in their right anterior insula cortex within three sessions of four minutes each. Training resulted in a significantly increased activation cluster in the anterior portion of the right insula across sessions. This approach could be tested in patients with anorexia nervosa to explore whether increased ability to modulate activation of insula networks leads to any changes in symptoms.

Turning to more conventional psychological therapies, a specific form of cognitive behavioural therapy (CBT) has been approved by the UK National Institute for Health and Care Excellence (NICE, 2004) for the treatment of bulimia nervosa; however there is no NICE-recommended evidence-based CBT treatment for anorexia nervosa at the current time. Updated guidance is due in January 2014 and several treatment trials are ongoing. Despite this lack of research evidence for anorexia nervosa, studies have shown that effective CBT can alter brain function in other neurodevelopmental disorders such as OCD, so the effect of future CBT treatments on insula function could be explored.

Limitations of neurobiological accounts of eating disorders

There is a risk that tentative hypotheses implicating causal underlying neurobiological mechanisms for psychiatric disorders 'leak out' into clinical and public domains and become established as fact. The Insula hypothesis has received substantial attention in print and broadcast media (see Appendix II for example of Press coverage), suggesting that there is considerable interest in new ways of understanding psychiatric disorders.

However, as Singh and Wengaard (2011) caution, there is a great risk inherent in such 'neuro-essentialist' accounts. They suggest that research involving 'neurotechnology' such as fMRI and genetic tools such as gene sequencing, candidate gene searches, and animal models are used increasingly to explore the biological bases of complex disorders such as anorexia nervosa. Although the knowledge produced by such methods is valuable, the impact of neurobiological models of anorexia nervosa generated by these technologies on how patients conceptualize their illness in relation to personal identity is still largely unknown.

Some of the concerns about neuroimaging are shared by neuroscientists, social scientists and ethicists who have raised questions about the interpretation of neuroimaging data, particularly in relation to the translation of raw statistical data into significant findings. Analysis of neuroimaging is no less immune to statistical manipulation than any other science. Vul, Harris, Winkielman and Pashler (2009) have outlined the ways in which the choice of statistical method used to interpret brain imaging data influences whether a statistically significant effect is found in identifying a specific brain structure as being implicated in a cognitive or psychological process.

However, the great majority of the lay public are unaware that fMRI technology is based on computational physics, and that the colourful pictures generated are a result of complex statistical data processing. Therefore fMRI images are highly susceptible to misrepresentation. For example, coloured images of localised functions in the brain have the potential of being

interpreted by the public to mean that complex psychological processes occur in one specific region of the brain (McCabe, & Castel, 2008). The media often encourage this interpretation, which could be characterized as a new form of phrenology, 'with the lumps on the inside'. Of course, the brain is not a static structure and the phenomenon of localised functions should not be taken out of the context of the complex dynamism that is involved in brain structures and processes.

The media, and therefore the general public, have a tendency to attribute more credibility to explanations for behaviour or psychological processes when a brain image is attached (Weisberg, Goldstein, Rawson, & Gray, 2008). This response could be due to a range of factors, such as a tendency to favour reductionist models of complex psychological processes; as well as the visual elegance of brain images.

For patients with anorexia nervosa, distinctive clinical features such as anosognosia (denial of illness) may moderate outcomes of participation in fMRI research in the context of perceptions of the relationship of the self to the illness. The persuasive power of fMRI is, therefore, likely to be moderated by the phenomenology of the presenting condition, and empirical research is urgently needed to explore such nuances.

There may be a clinical benefit to exposure to fMRI and/or a brain-based explanation of anorexia nervosa. The fusion of personal identity and the illness is a therapeutic challenge in treating people with low weight eating disorders. A biological model, presented by a neurobiological hypothesis and reinforced by participation in fMRI research studies, may over time assist in a separation between the person and their illness, with positive implications for treatment acceptability and (possibly) treatment outcomes. There is some evidence that feedback from neuropsychological testing has a positive effect on patients with anorexia nervosa (Lopez, Roberts, Tchanturia, & Treasure, 2009).

A neurobiological model of anorexia nervosa might relieve the guilt and blame that families and patients frequently report. For us as researchers and clinicians, it is therefore imperative that we strike a balance between adopting a cautious and appropriately skeptical experimental approach to trying to falsify our hypotheses, whilst sharing the neuroscience sensitively and appropriately with patients and families who are struggling to find a way to cope with such a serious and difficult to treat disorder.

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Appendices

Vancouver Declaration

Name: Anna Hutchinson

Frampton, I., Hutchinson, A.,Watkins, E. & Lask, B. (2012). Neurobiological status at initial presentation predicts neuropsychological functioning in early onset anorexia nervosa at four-year follow-up. *Developmental Neuropsychology.* 37(1), 1–8.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I was responsible for conducting and scoring neuropsychological assessment appointments under the supervision of the first author. I contributed to the analysis and interpretation of data.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to drafts of the article.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: ____29/05/2013____

Vancouver Declaration

Name: Beth Watkins

Frampton I., Watkins E., Gordon I., and Lask B. (2011). Do abnormalities in regional cerebral blood flow in anorexia nervosa resolve after weight restoration? *European Eating Disorders Review*, 19 (1). 55-58

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I was responsible for the logistical organization of the study, making contact with participants and arranging scanning appointments.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to drafts of the article.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _Beth Watkins_

Date: _23/05/13_

Vancouver Declaration

Name: Beth Watkins

Frampton, I., Hutchinson, A.,Watkins, E. & Lask, B. (2012). Neurobiological status at initial presentation predicts neuropsychological functioning in early onset anorexia nervosa at four-year follow-up. *Developmental Neuropsychology.* 37(1), 1–8.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I was responsible for the logistical organization of the study, making contact with participants and arranging scanning and neuropsychological assessment appointments.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to drafts of the article.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

Signed: *Beth Watkins*

Date: 23/05/13

Vancouver Declaration

Name: Mark Rose

Frampton, I and Rose, M. (2013). Eating Disorders and the Brain. in B.Lask and R.Bryant-Waugh (eds). *Eating Disorders in Childhood and Adolescence*. London: Wiley. 125 – 147

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I reviewed the neuropsychological literature in eating disorders.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I wrote the section of the paper reviewing the neuropsychological literature and reviewed a draft of the whole chapter.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: ___24/05/13___

Vancouver Declaration

Name: Bryan Lask

Chapter 11: Frampton, I and Lask, B. (2011). Future Directions. in B.Lask and I.Frampton (eds). *Eating Disorders and the Brain*. London: Wiley. 208 – 218.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the content plan for this chapter.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I reviewed a draft prepared by my co-author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _Bryan Lask_

Date: _24 – 05 – 13_

Vancouver Declaration

Name: Bryan Lask

Nunn, K.P., Frampton, I., Gordon, I. and Lask, B. (2008). The fault is not in her parents but in her insula – a neurobiological hypothesis of anorexia nervosa. *European Eating Disorders Review*, 16, 355–360.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the theoretical model of the role of the insula cortex in anorexia nervosa. I contributed to the review of the literature.

2. My contribution to drafting the article or revising it critically for important intellectual content:
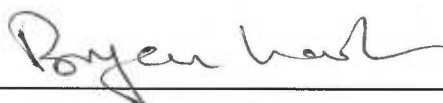
I contributed to initial drafts of the article and submitted critical reviews to the second author.

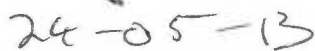3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: _____ 24-05-13

Vancouver Declaration

Name: Bryan Lask

Frampton I., Watkins E., Gordon I., and Lask B. (2011). Do abnormalities in regional cerebral blood flow in anorexia nervosa resolve after weight restoration? *European Eating Disorders Review*, 19 (1). 55-58

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

As Principal Investigator I oversaw the logistical organization of the study.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to drafts of the article.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: _____

Vancouver Declaration

Name: Bryan Lask

Frampton, I., Hutchinson, A.,Watkins, E. & Lask, B. (2012). Neurobiological status at initial presentation predicts neuropsychological functioning in early onset anorexia nervosa at four-year follow-up. *Developmental Neuropsychology*. 37(1), 1–8.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

As Principal Investigator I oversaw the logistical organization of the study.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to drafts of the article.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: _____24-05-13_____

Vancouver Declaration

Name: Bryan Lask

Nunn, K., Frampton, I., Fuglset, T., Törzsök-Sonnevend, M. & Lask, B. (2011). Anorexia Nervosa and the insula. *Medical Hypotheses*. 76(3):353-7

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I oversaw the review of the neuroscience literature concerning the role of the Insula.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the second author.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

Signed: _____

Date: _____24 - 05 - 13_____

Vancouver Declaration

Name: Kenneth Nunn

Nunn, K., Frampton, I., Fuglset, T., Törzsök-Sonnevend, M. & Lask, B. (2011). Anorexia Nervosa and the insula. *Medical Hypotheses.* 76(3):353-7

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I originated the theoretical model of the role of the insula cortex in anorexia nervosa. I contributed to the review of the neuroscience literature.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the second author.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

What a privilege to be part of it all.

Signed: Confirmed by email_____

Date: 24th September 2013_____

Vancouver Declaration

Name: Kenneth Nunn

Nunn, K.P., Frampton, I., Gordon, I. and Lask, B. (2008). The fault is not in her parents but in her insula – a neurobiological hypothesis of anorexia nervosa. *European Eating Disorders Review*, 16, 355–360.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I originated the theoretical model of the role of the insula cortex in anorexia nervosa. I contributed to the review of the literature.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the second author.

3.   Approval of the version published:

I approved the version that is published.

Any comments:

What a privilege to be part of it all.

Signed: Confirmed by email_____

Date: 24th September 2013

Vancouver Declaration

Name: Tone Fuglset

Nunn, K., Frampton, I., Fuglset, T., Törzsök-Sonnevend, M. & Lask, B. (2011). Anorexia Nervosa and the insula. *Medical Hypotheses.* 76(3):353-7

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

 I contributed to the review of the neuroscience literature concerning the role of the Insula.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I reviewed a draft of the article.

3. Approval of the version published:

I approved the version that is published.

Any comments:

I agree the Vancouver Declaration in the two attached files.

Signed: confirmed by email _____

Date: 4th July 2013_____

Vancouver Declaration

Name: Tone Fuglset

Fuglset, T. and Frampton, I. (2011). Neuroimaging. in B.Lask and I.Frampton (eds). Eating Disorders and the Brain. London: Wiley. 56 – 105.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I summarized the research literature in eating disorders neuroimaging and produced Table 1 in the chapter and contributed to the first draft of the chapter.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I reviewed a draft of the chapter prior to publication.

3. Approval of the version published:

I approved the version that is published.

Any comments:

I agree the Vancouver Declaration in the two attached files.

Signed: confirmed by email_____

Date: 4th July 2013_____

Appendix II: Knowledge Transfer

Media Presentations

1. BBC TV Inside Out – Tx 30/11/2009

http://www.bbc.co.uk/programmes/b00p7kjy

2. BBC Radio Four Woman's Hour – Tx 01/04/2009

http://www.bbc.co.uk/radio4/womanshour/03/2009_13_wed.shtml

3. Canadian Broadcasting Company – The Point – Tx 15/04/2009

http://www.cbc.ca/thepoint/MT/2009/04/

Print Presentations

1. The Daily Express (2009). *Anorexia linked to brain problem, offering new hope it can be treated.* Monday 30th March

2. The Daily Mail (2009). *How some girls are born to be anorexic: Eating disorder may be linked to brain abnormality.* Monday 30th March

3. The Observer (2009). *Anorexia risk 'could be predicted.* Sunday 29th March.

Anorexia linked to brain problem, offering new hope it can be treated

A MEDICAL breakthrough that indicates mental illnesses are caused by a brain abnormality is challenging long-held beliefs about psychological disorders.

Pretty Frances Good, 19, a recovering anorexic, suffered food and body image problems []

The pioneering research, carried out on anorexics as young as eight and using powerful new brain-imaging techniques, could lead to different treatments.

The British-led international study also suggests the brain abnormality is a cause of anorexia and not a result of it.

Psychologist Dr Ian Frampton of Exeter University, one of two researchers leading the study, said: "We believe subtle problems in early brain development make patients susceptible to anorexia. We need to re-examine other mental health problems."

The work was led by Professor Brian Lask of Great Ormond Street Children's Hospital, a leading expert on the potentially deadly eating disorder.

He and his team used novel scanning techniques to reveal that the brains of anorexics were malfunctioning in the insula, a key area that controls eating, anxiety and body image. This persists after weight recovery, suggesting the problem exists before the onset of the illness.

> **We believe subtle problems in early brain development make patients susceptible to anorexia**
> Psychologist Dr Ian Frampton

Up to a third of sufferers are affected by the brain abnormality which is highlighted only by the sophisticated tests. The team believes other biological causes in the brain affect the remaining two-thirds of sufferers, which is why so many patients relapse.

Dr Frampton explained: "They are predisposed to fail because the fault is there in their brains. You cannot easily cure people if there is an active defect."

The findings, published in the journal Medical Hypothesis, could help settle the debate that parents and size zero models cause anorexia due to unhealthy attitudes towards food and body image. It will also open up the debate about causes of other mental illnesses such as depression and bipolar disorder.

Dr Frampton added: "The discovery of differences in the insula begins to explain why anorexics behave the way they do. Not all adolescents are susceptible to excessive dieting. It is only those who have this biological defect."

He believes new therapies might help to control anorexia where up to 40 per cent of sufferers relapse within a year.

Frances Good, 19, a recovering anorexic, suffered food and body image problems, unlike her twin sister.

She said: "I remember feeling fat next to my sister aged eight and in secondary school I worried about my weight."

Problems began when Frances, from London, developed a chronic stomach condition at 14. She added: "I believe this is a biological condition. Images of skinny models can make things worse but there was something in me that feels on edge."

Frances, who is studying for a psychology degree, said: "It will always be there, but I may not always express it through food."

Anorexia is defined as a body weight at least 15 per cent below that expected. Mary George, of the eating disorder website Beat, insisted: "While there may be a genetic component to it, we believe the pressures for young people to look ideal are factors."

Mail Online

How some girls are born to be anorexic: Eating disorder may be linked to brain abnormality

By **Daniel Martin**
UPDATED: 01:17, 30 March 2009

Spice Girl Geri Halliwell has admitted suffering from anorexia for many years

Thousands of girls may be born at risk of suffering anorexia, according to a study that could revolutionise treatment of the eating disorder.

Most sufferers are predisposed to the condition because of the way their brains developed in the womb, it is claimed.

The research threatens to overturn decades of scientific orthodoxy holding that anorexia is primarily caused by social factors, such as the pressure to lose weight to emulate size zero models.

Charities say the findings raise the prospect of drugs being developed to treat anorexia.

Alternatively, doctors could screen girls at the age of eight to assess risk and treat accordingly.

The study, led by Dr Ian Frampton, consultant in paediatric psychology at London's Great Ormond Street hospital, will be unveiled at a conference at the Institute of Education in the capital this week.

Dr Frampton said: 'Our research shows that certain kids' brains develop in such a way that makes them more vulnerable to commonly-known risk factors for eating disorders - such as the size zero debate, media representations of very skinny women and bad parents.'

Dr Frampton's team tested more than 200 anorexia sufferers from Britain, the U.S. and Norway. Most were females aged between 12 and 25 being treated in private hospitals in Edinburgh and Maidenhead.

The researchers found around 70 per cent had suffered damage to neurotransmitters - which help brain cells communicate - or had undergone other subtle changes in the structure of their brains.

One in every few hundred girls may be affected in this way, according to Dr Frampton.

© Getty Images

Tragic: Both singer Karen Carpenter and Brazilian model Ana Carolina Reston died of complications arising from anorexia

He said the condition is caused by random conditions, not poor maternal diet or environmental.

The 'imperfect wiring' of the brain is similar to that seen in people with dyslexia, depression or hyperactivity.

Dr Frampton said: 'These findings could help us to understand a disease we don't know how to treat.

'Arguments that social factors, such as girls feeling under pressure to lose weight to look like high-profile women in the media, contain logical flaws because almost everyone is exposed to them, yet only a small percentage of young people get anorexia.

'Those things are important but there must be other factors, involving genetics and science, that make some young people much more vulnerable than others.'

Around 1.1million people are estimated to have an eating disorder in Britain, most commonly anorexia and bulimia.

Susan Ringwood, chief executive of Beat, the eating disorders charity, said: 'It could pave the way for the first drugs to be developed to treat eating disorders, similar to the way that anti-depressants help rebalance the brain of people with depression.

'And it will help parents understand they aren't to blame.

'Parents always blame themselves when their child develops an eating disorder.

'But what we are learning more and more from research in this area is that some people are very vulnerable to anorexia.

'That is down to genetic factors and brain chemistry, and not them trying to look like celebrity models or suffering a major traumatic event early in their lives.'

She added: 'This research is a key missing part of the jigsaw of our understanding of anorexia.'

Find this story at www.dailymail.co.uk/health/article-1165628/How-girls-born-anorexic-Eating-disorder-linked-brain-abnormality.html

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Anorexia risk 'could be predicted'

Study suggests that subtle differences in brain development in womb can increase vulnerability

Denis Campbell, health correspondent
The Observer, Sunday 29 March 2009

Thousands of girls are predisposed to develop anorexia because of the way their brains developed in the womb, says a major new study.

The report's authors say children could be screened at the age of eight to identify the signs that make them more vulnerable to risk factors such as the size zero fad and the cult of the super-thin celebrity. Eating disorder charities said the findings, which will be revealed at a conference at the Institute of Education in London this week, could revolutionise the treatment of anorexia.

"Our research shows that certain kids' brains develop in such a way that makes them more vulnerable to the more commonly-known risk factors for eating disorders, such as the size-zero debate, media representations of very skinny women and bad parents," said Ian Frampton, one of the authors, who is an honorary consultant in paediatric psychology at London's Great Ormond Street hospital.

Frampton and his colleagues conducted in-depth neuropsychological testing on more than 200 people in the UK, America and Norway who suffer from the condition. Almost all of those who took part in the study were girls and young women aged between 12 and 25 who were being treated for anorexia at private hospitals in Edinburgh and Maidenhead that are part of the Huntercombe medical group.

They found that about 70% of the patients had suffered damage to their neurotransmitters, which help brain cells communicate with each other, had undergone subtle changes in the structure of their brains, or both.

One in every few hundred girls may be affected in this way, according to Frampton, who said the condition was random and not the result of poor maternal diet or environmental factors, such as widespread use of chemicals. Imperfect wiring in the brain's insular cortex that may lead to dyslexia, ADHD or depression in other children produces what he calls "an underlying vulnerability" among some young people that makes them more likely to develop anorexia.

Previously, scientists believed that being chronically underweight caused changes in a person's brain. This new research is significant because it suggests that the opposite process explains the origins of anorexia. "These findings could help us to understand this beguiling disease that we don't know how to treat," added Frampton.

"Arguments that social factors such as girls feeling under pressure to lose weight in order to look like high-profile women in the media contain logical flaws because almost everyone is exposed to them, yet only a small percentage of young people get anorexia.

"Those things are important but there must be other factors, involving genetics and science, that make some young people much more vulnerable than others."

Between 2 and 3% of children and young adults develop an eating disorder. Anorexia is the rarest of them. About four women in every thousand develop it. Cases among men are rare but not unknown. It can lead to serious health problems and prove fatal. Karen Carpenter, the 1970s pop star, died in 1983 at the age of 32 from a heart attack brought

on by the condition.

In recent years, the fashion industry has come under pressure to protect the health of its models following widespread anger about the size-zero trend and the deaths of two models. On the eve of a photographic shoot in November 2006, Brazilian model Ana Carolina Reston died from complications arising from anorexia. It was reported that she had been living on a diet of apples and tomatoes. It followed the death that summer of Uruguayan model, Luisel Ramos, who died of heart failure at the age of 22 after not eating for several days in an attempt to stay thin.

Susan Ringwood, chief executive of the leading eating disorders' charity, Beat, welcomed the latest research.

"It could pave the way for the first drugs to be developed to treat eating disorders, similar to the way that anti-depressants help rebalance the brain of people with depression," she said.

"And it will help parents understand that they aren't to blame. Parents always blame themselves when their child develops an eating disorder. But what we are learning more and more from research in this area is that some people are very vulnerable to anorexia and that is down to genetic factors and brain chemistry, and not them trying to look like celebrity models or suffering a major traumatic event early in their lives.

"This research is a key missing part of the jigsaw of our understanding of anorexia."

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