# Eating disorders and compulsivity: neural, computational, and psychopharmacological approaches

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# BRIEF ABSTRACT

This DPhil thesis takes the transdiagnostic construct of compulsivity as a basis for investigation into eating disorders, which are severe psychiatric disorders with high mortality rates.

This thesis includes three experimental studies (discussed in Chapters 3 to 5), which investigate different aspects of eating disorders and compulsivity.

The first experimental study (Chapter 3) is a multimodal magnetic resonance imaging study, in which the neural basis of compulsivity was investigated in participants who had recovered from anorexia nervosa and control participants. We used a task with functional magnetic resonance imaging which incorporated key elements of compulsivity, performed a resting-state analysis with frontostriatal seeds, and analysed glutamate levels using magnetic resonance spectroscopy. We neither found evidence of the hypothesised frontostriatal differences, nor of a difference in glutamate levels in participants, but did find parietal differences in both the resting-state and task-based analyses.

The next study, discussed in Chapter 4, aimed to investigate adaptive learning in eating disorders. We predicted that participants in two clinically-relevant groups (those who had recovered from anorexia nervosa, and those who had elevated eating disorder symptoms) would show diminished adaptation of their learning rates in a task which manipulated environmental volatility, and that this would correspond to a reduction in pupil dilation to volatile outcomes in these groups compared to control participants. However, we found elevated adaptation of learning rates in those who had recovered from anorexia nervosa, which may be attributed to heightened learning rates in this group in particular in the first block.

The final experimental study is discussed in Chapter 5, and investigated whether a dietary supplement, N-acetylcysteine, would improve performance of those with elevated eating disorder symptoms on tasks which measure compulsive and impulsive responding. However, this did not seem to be the case, though N-acetylcysteine was well-tolerated.

# FULL ABSTRACT

Eating disorders are psychiatric disorders characterised by impaired eating habits or weight control behaviours, often accompanied by overvaluation of the importance of shape or weight, or control of eating. These disorders have substantially elevated mortality, and patients often experience a chronic course of illness. Further understanding of the neurobiology of eating disorders might allow progress in treatment. The work described in this thesis uses a transdiagnostic factor, compulsivity, which has previously been implicated in eating disordered behaviour, as a basis for further investigation into the neurobiology of eating disorders.

The three experimental studies presented in the thesis apply a number of methodologies including multimodal magnetic resonance imaging (voxel-based morphometry, resting-state functional connectivity, task-based functional magnetic resonance imaging and magnetic resonance spectroscopy), computational modelling of behaviour, and psychopharmacology. The studies presented herein are all cross-sectional studies, with participant groups selected to minimise confounds from the physical effects of active eating disorders.

The first study presented is a magnetic resonance imaging investigation, which assessed the neural underpinnings of compulsive behaviour in participants recovered from anorexia nervosa compared to controls, using a psychological task which probes set-shifting and reversal learning, a resting-state analysis using seed regions implicated in compulsive behaviour, and an analysis of glutamate, a neurochemical which has also been implicated in compulsive behaviour. We predicted that we would find reduced OFC activation to reversal learning, decreased dorso-striatal-frontal connectivity and increased ventro-striatal-frontal connectivity, and reduced levels of glutamate in the participants who had recovered from anorexia nervosa compared to controls. The main differences observed for both the task based and resting analyses were in the parietal cortex, indicating that parietal regions may be involved in compulsive behaviour in eating disorders. There was no difference in glutamate levels in those who had recovered from anorexia nervosa compared to control participants.

The second study applied computational methods to investigate the ability of participants from two eating disorder risk groups to adjust their learning rates adaptively in response to changes in environmental volatility. Measures of pupil dilation, which is thought to reflect central noradrenergic activity, were also collected, as noradrenaline is thought to play an important role in mediating cognitive flexibility. We predicted that those in the two eating disorder risk groups would show reduced learning rate adaptation, compared to control participants, and that this would be more prevalent for negative outcomes. We also predicted a reduced pupil dilation response to volatility in the risk groups compared to the control group. Participants who had recovered from anorexia nervosa adjusted their learning rates more than the two other experimental groups, potentially due to heightened learning rates in the initial block of the task; and participants with high levels of eating disorder symptoms had reduced pupil dilation responses to non-volatile rewarding outcomes. Both of these findings were unexpected, and are discussed within Chapter 4.

The third study examined whether N-acetylcysteine, a glutathione precursor, might alter compulsive or impulsive responding on a battery of psychological tasks in a group with elevated eating disorder symptoms. N-acetylcysteine was administered in a randomised, double-blind, placebo-controlled design using a dosing regimen previously shown to be effective in certain compulsive disorders. We predicted that N-acetylcysteine would improve performance on tasks which measure compulsive and impulsive responding, and in particular that it would reduce perseverative errors on the Wisconsin Card Sorting Task. However, relative to placebo, no effect was found of N-acetylcysteine on measures of compulsivity or impulsivity.

Overall, the first study discussed provides evidence for altered parietal activity in tasks probing compulsivity in participants who have recovered from anorexia nervosa, which suggests that the parietal cortex is related to compulsive responding in this disorder rather than frontostriatal differences as expected, and gives more weight to suggestions that the parietal cortex should be investigated as an additional component in the network of regions thought to be responsible for compulsive responding. In the second study, we found that those who have recovered from anorexia nervosa display increased learning rate adjustment in the face of environmental 'volatility', which might either suggest that they over-respond to environmental change, or may be due to heightened learning rates in the initial block of the task. Heightened learning rates in the initial block of the task might suggest that performing a novel task leads to heightened uncertainty in these participants, which could be maladaptive over prolonged periods of time. The final study discussed suggests that NAC may not work by reducing compulsive or impulsive responding, and thus other investigations may be necessary to discover its mechanism of action in compulsive disorders. Due to the limited side effects experienced by participants taking NAC, it could be a safe adjunct to trial in ED treatment. These findings could be extended in future work, hopefully leading to a better understanding and more specific treatment of the compulsive element of eating disorders as well as other psychiatric disorders where compulsivity plays a significant psychopathological role.

# DEDICATION

*To all those who said 'you can'*

*when I said 'I can't'*

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# GLOSSARY

| | |
|---|---|
| 3T | 3 Tesla |
| 7T | 7 Tesla |
| ACC | anterior cingulate cortex |
| ADHD | attention deficit hyperactivity disorder |
| AFNI | Analysis of Functional NeuroImages (software) |
| AGN | Affective Go/No-go Task |
| AIC | Akaike information criterion |
| AN | anorexia nervosa |
| AN-BP | anorexia nervosa (binge/purge type) |
| ANOVA | analysis of variance |
| AN-R | anorexia nervosa (restricting type) |
| ARFID | avoidant/restrictive food intake disorder |
| AST | Attention Switching Task |
| BBR | boundary-based registration |
| BDD | body dysmorphic disorder |
| BDI-II | Beck Depression Inventory-II |
| BED | binge eating disorder |
| BET | FMRIB's Brain Extraction Tool |
| BIO | Bayesian ideal observer model |
| BMI | body mass index |
| BN | bulimia nervosa |
| BOLD | blood-oxygen-level dependent |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CBT | cognitive behavioural therapy |
| CBT-E | enhanced cognitive therapy |
| CGT | Cambridge Gambling Task |
| CIA | Clinical Impairment Assessment questionnaire |
| CN | non-switch when the target is known |
| CRLB | Cramér-Rao lower bound |
| CSF | cerebrospinal fluid |
| CUREC | Central University Research Ethics Committee |
| DCd | dorsal caudate |
| DDT | delay discounting task |
| DMN | default mode network |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ edition |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ edition |
| EA | participant group who have high scores on the Eating Attitudes Test |
| EAT-26 | Eating Attitudes Test – 26 item version |
| EAT-40 | Eating Attitudes Test – 40 item version |
| ED | eating disorder |
| EDE | Eating Disorder Examination |
| EDE-Q | Eating Disorder Examination – Questionnaire version |
| EDNOS | eating disorder not otherwise specified |
| EDS | extra-dimensional shift |

| | |
|---|---|
| EDTA | ethylenediaminetetraacetic acid |
| EPI | echo-planar imaging |
| EPQ | Eysenck Personality Questionnaire |
| FD | framewise displacement |
| FEAT | FMRI Expert Analysis Tool (toolbox) |
| FILM | FMRIB's Improved Linear Model |
| FLIRT | FMRIB's Linear Image Registration Tool |
| fMRI | functional magnetic resonance imaging |
| FMRIB | Oxford Centre for Functional Magnetic Resonance Imaging of the Brain |
| FNIRT | FMRIB's Non-Linear Image Registration Tool |
| FOV | field of view |
| FPN | frontoparietal network |
| FSL | FMRIB Software Library (software) |
| FSL-VBM | FSL's Voxel-Based Morphometry toolbox |
| FWE | family-wise error |
| FWHM | full width at half maximum |
| GABA | γ-aminobutyric acid |
| GLM | general linear model |
| Glx | glutamate + glutamine (composite metabolite) |
| GM | grey matter |
| GRAPPA | generalised autocalibrating partialyl parallel acquisition |
| HADS | Hospital Anxiety and Depression Scale |
| HAM-D | Hamilton Depression Rating Scale |
| HC | healthy control participants |
| HFBA | heptafluorobutyric acid |
| HIV | human immunodeficiency virus |
| ICA | independent component analysis |
| IDED task | intra-dimensional extra-dimensional task |
| IDS | intra-dimensional shift |
| IPL | inferior parietal lobule |
| IQ | intelligence quotient |
| k | cluster size |
| LC | liquid chromatography |
| LC-MS/MS | liquid chromatography–tandem mass spectrometry |
| LPI | 'Left-Right, Posterior-Anterior, Inferior-Superior' coordinate order |
| MCFLIRT | Motion Correction using FMRIB's Linear Image Registration Tool |
| ME-ICA | multi-echo independent component analysis (toolbox) |
| MNI | Montreal Neurological Institute |
| MPRAGE | magnetization-prepared rapid-acquisition gradient echo |
| MR | magnetic resonance |
| MRI | magnetic resonance imaging |
| MRS | magnetic resonance spectroscopy |
| NA | noradrenaline |
| NAC | N-acetylcysteine |
| NAc | nucleus accumbens |
| NART | National Adult Reading Test |
| NICE | National Institute for Health and Care Excellence |
| OCC | occipital cortex |

| | |
|---|---|
| OCD | obsessive-compulsive disorder |
| OCI-R | Obsessive Compulsive Inventory – Revised |
| OCPD | obsessive-compulsive personality disorder |
| OCRD | obsessive-compulsive and related disorders |
| OFC | orbitofrontal cortex |
| OSFED | other specified feeding or eating disorder |
| PAT | parallel acquisition techniques |
| PCC | posterior cingulate cortex |
| PET | positron emission tomography |
| PUT | putamen |
| QA | quality assurance |
| RA | participant group who have recovered from anorexia nervosa |
| RDoC | Research Domain Criteria |
| RF | radio frequency |
| ROI | region of interest |
| RSFC | resting-state functional connectivity |
| RT | reaction time |
| RV | reversal learning event |
| SCID | Structured Clinical Interview for the DSM |
| SCID-5-RV | Structured Clinical Interview for the DSM-5, Research Version |
| SCID-IV | Structured Clinical Interview for the DSM-IV |
| SD | standard deviation |
| SEM | standard error of the mean |
| semi-LASER | semiadiabatic localization by adiabatic selective refocusing |
| SH | set change event |
| SNR | signal-to-noise ratio |
| SPECT | single-photon emission computed tomography |
| SPM | Statistical Parametric Mapping (software) |
| SSRI | selective serotonin reuptake inhibitor |
| SSRT | stop-signal reaction time |
| SSS | Self-Starvation Scale |
| STAI | Spielberger State-Trait Anxiety Inventory |
| STAI-S | Spielberger State-Trait Anxiety Inventory – State items |
| STAI-T | Spielberger State-Trait Anxiety Inventory – Trait items |
| TE | echo time |
| TFCE | threshold-free cluster enhancement |
| TI | inversion time |
| TR | repetition time |
| UFED | unspecified feeding or eating disorder |
| UK | United Kingdom |
| VAPOR | variable power and optimized relaxation delays |
| VBM | voxel-based morphometry |
| VGA | video graphics array |
| WCST | Wisconsin Card Sorting Task |
| WM | white matter |
| YBC-EDS-SRQ | Yale-Brown-Cornell Eating Disorder Scale Self-Report Questionnaire |
| YBOCS | Yale-Brown Obsessive Compulsive Scale |

# 1 INTRODUCTION

## 1.1 OVERVIEW

This research aims to better characterise the transdiagnostic concept of compulsivity in eating disorder psychopathologies, using a range of methods: magnetic resonance imaging (MRI), computational modelling, and psychopharmacology. It is hoped that this might lead towards the development of novel treatment strategies in the future.

Eating disorders (EDs), specifically anorexia nervosa (AN) and bulimia nervosa (BN), are important sources of morbidity and mortality in young individuals. AN in particular has one of the highest mortality rates of all psychiatric disorders (Arcelus et al., 2011; Chesney et al., 2014); moreover, there is a lack of effective treatments (Balestrieri et al., 2013; Wilson et al., 2007), and recovery rates remain low (Berkman et al., 2007).

One important reason for the inefficacy of treatments is the difficulty in elucidating the neurobiological underpinnings of psychiatric disorders. Identifying these underpinnings is hampered by the current classification systems, such as that represented by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013). Currently, classification of psychiatric disorders is based on symptom clusters. In practice, however, there is much within-disorder heterogeneity, and between-disorder homogeneity (Hyman, 2007).

One possible solution to this problem is to search for transdiagnostic neuropsychological traits which a) have a neurobiological basis and b) are central to some (but not all) psychiatric disorders (Gillan et al., 2017; Insel et al., 2010; Robbins et al., 2012). The requirement for transdiagnostic traits to have a neurobiological basis should ensure that

translational research has a principled basis for developing further treatments. Additionally, the transdiagnostic and cross-category nature of these traits can allow ideas or knowledge from research in one disorder to be applied to other disorders in which the same domain is affected.

One suggested transdiagnostic trait is compulsivity (Robbins et al., 2012), which is the tendency to carry out the same behaviour repeatedly even though its consequences may be harmful (Figee et al., 2015; Gillan et al., 2016, 2017; Voon et al., 2015). Compulsivity has been hypothesised to play a key role in EDs (Godier & Park, 2014). This body of work takes the link between EDs and compulsivity as a basis for further research into EDs.

The research described in this thesis focuses on answering three main questions, each with a separate experimental study. These studies use varying methodologies, including behavioural tasks, task-based functional MRI (fMRI), resting state MRI, and computational modelling.

Firstly, is there neural evidence for trait abnormalities in compulsivity in patients with AN? To answer this question, we performed a study with two key objectives: to see whether a task which probes compulsivity elicits differences in brain activation in those who have recovered from AN compared to healthy controls, and whether these groups show a difference in functional brain connectivity at rest in brain regions and circuits which are involved in compulsive behaviours. Additionally, in this study we investigated whether there are underlying differences in levels of glutamate between these groups using magnetic resonance spectroscopy (MRS), because glutamate activity has been linked to compulsivity (Grados et al., 2015; Pittenger et al., 2011).

Secondly, is cognitive inflexibility (which is a sub-domain of compulsivity) related to an inability to use relevant changes in the environment to alter learning and behaviour? This

study used a reinforcement-learning task to derive estimates of the extent to which individuals in 'at risk' groups for EDs adapt their learning in a 'volatile' environment. A finding of reduced adjustment in learning between volatile and stable blocks in the ED groups would imply that compulsivity in people at risk of EDs is based on a problem in adaptive learning; this could account for perseveration in unhelpful behaviours and cognitive inflexibility. Moreover, this kind of difference in learning is potentially remediable by suitable computerised training programmes, offering a new potential for psychological treatment in a field where there is much unmet need. Measures of pupil dilation, which is thought to reflect central noradrenergic activity, were also collected, as noradrenaline is thought to play an important role in mediating cognitive flexibility. We predicted that we would observe a reduced difference in pupil dilation between volatile and stable blocks in the ED groups.

Thirdly, is it possible to modify neuropsychological measures of compulsivity in patients with subclinical eating disorder symptoms using a dietary supplement (N-acetylcysteine; NAC) known to be effective in other disorders in the compulsivity spectrum (Deepmala et al., 2015)? If so, this might not only help elucidate the neuropsychological mechanism of action of NAC, but might also justify further research with this supplement in EDs.

In the next section, a definition of EDs is given, and the current state of the psychiatric options available to individuals who suffer from EDs is discussed.

## 1.2 EATING DISORDERS

### 1.2.1 Definitions and Diagnostic Criteria

An ED is a psychological disorder characterised by a definite disturbance in eating habits or weight control behaviours. There may also be the presence of overvaluation of the

importance of shape and weight, or the control of eating. For a diagnosis of an ED, symptoms should not be secondary to any general medical or other psychiatric condition (Fairburn & Harrison, 2003).

There are a number of putatively distinct types of eating disorder, including AN, BN, Binge eating disorder (BED), and avoidant/restrictive food intake disorder (ARFID), amongst others (American Psychiatric Association, 2013). EDs are associated with a range of symptoms, including physical symptoms (such as low weight/weight loss, amenorrhea in some, lanugo), cognitive symptoms (such as the overvaluation of weight and shape, an ego-syntonic attitude towards the disorder), behavioural symptoms (such as restriction of nutritional intake, compulsive exercising and/or other compensatory behaviours) and social symptoms (such as withdrawal from the outside world) (Fairburn & Harrison, 2003). For an eating disorder to be diagnosed, the behaviours must not simply be present, but also cause a functional impairment (including the risk to health of being underweight) or clinical levels of distress (American Psychiatric Association, 2013). The key diagnostic criteria for the main DSM-5 EDs are presented in Table 1 and described below.

*Table 1: Diagnostic Criteria for some of the main EDs within the Feeding and Eating Disorders section of the DSM-5*

| **Anorexia nervosa (AN)** | **Bulimia nervosa (BN)** | **Binge eating disorder (BED)** | **Other specified feeding or eating disorder (OSFED)** |
|---|---|---|---|
| Restriction of energy intake relative to requirements leading to significantly low body weight (given context) – which is below minimally normal or expected | Recurrent episodes of binge eating, characterised BOTH by eating within a discrete amount of time an amount of food which is definitely larger than what most individuals would eat in a similar period of time under similar circumstances, AND by a sense of lack of control over eating during that episode | Recurrent episodes of binge eating, described as in Bulimia Nervosa | Symptoms characteristic of a feeding and eating disorder that cause clinically significant distress or impairment in social, occupational or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the feeding and eating disorders diagnostic class |
| Intense fear of gaining weight or becoming fat OR persistent behaviour that interferes with weight gain | Recurrent inappropriate compensatory behaviours in order to prevent weight gain, such as self-induced vomiting or misuse of laxatives or diuretics | The binge-eating episodes are associated with three (or more) of the following: eating much more rapidly than normal; eating until uncomfortably full; eating large amounts of food when not feeling physically hungry; eating alone because of feeling embarrassed by how much one is eating; feeling disgusted with oneself, depressed or very guilty after the binge | |
| Disturbance in the way in which one's body weight or shape is experienced, OR undue influence of body weight or shape on self-evaluation, OR persistent lack of recognition of the seriousness of the current low body weight | The binge eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 months | Marked distress regarding binge eating is present | |
| | Self-evaluation is unduly influenced by body shape and weight | The binge eating occurs, on average, at least once a week for 3 months | |
| | The disturbance does not occur exclusively during episodes of AN | Binge eating is not associated with the regular use of inappropriate compensatory behaviour, and does not occur exclusively during AN or BN | |

A diagnosis of AN is made when individuals meet three specific criteria, outlined in Table 1 (American Psychiatric Association, 2013). There are two sub-types of AN. The restricting type (AN-R) is characterised by restriction of energy intake and the *absence* of binging (overeating over a discrete period of time, accompanied by loss of control) and purging (compensatory behaviours which may include vomiting or laxative/diuretic abuse) (American Psychiatric Association, 2013). This sub-type describes those who have typically achieved weight-loss through dieting, fasting or exercise. The binge-eating/purging type (AN-BP) is diagnosed when during the last three months the individual has engaged in recurrent episodes of binge eating or purging behaviour. These sub-types are identical other than these criteria relating to the presence of binging and purging behaviour. Amenorrhea has been removed as a necessary criterion for the diagnosis of AN between the DSM-IV and the DSM-5, partly because there appear to be few clinical or psychological differences between those who suffer from AN with and without amenorrhea, along with evidence suggesting that there is not a consistent relationship between a level of body fat and amenorrhea (Attia & Roberto, 2009).

BN is diagnosed based on the presence of binges along with compensatory behaviours aimed at avoiding weight gain (see Table 1). If these behaviours occur in an individual exclusively during episodes of AN, this suggests a diagnosis of AN-BP. Notably, AN and BN share an important possible diagnostic criterion, which is that self-evaluation is excessively influenced by body shape or weight (American Psychiatric Association, 2013).

In contrast, BED is a disorder which is characterised by a pattern of binges accompanied by distress, but without the overvaluation of control of eating, shape and weight that is seen in AN and BN. Binges in BED are defined as in BN, and several additional features are present (see Table 1). BED is a new inclusion in the DSM-5, and was not presented in the DSM-IV (except as an example of an eating disorder not otherwise specified

(EDNOS)); as such, there have been correspondingly fewer studies about its prevalence, incidence and course (Smink et al., 2012).

There are several other EDs defined in the DSM-5, such as rumination disorder, pica and ARFID. In brief, rumination disorder includes repeated regurgitation of food (such as re-chewing, re-swallowing, or spitting out), Pica involves the consumption of non-nutritive substances (e.g. paper), and ARFID is defined as a failure to meet appropriate nutritional needs associated with either weight loss, nutritional deficiency, dependence on enteral feeding or oral nutritional supplements, or interference with psychosocial functioning (American Psychiatric Association, 2013).

Feeding or eating behaviours which cause clinically significant distress but do not meet the full criteria for any of the above disorders are classified as having an 'other specified feeding or eating disorder' (OSFED) (see Table 1). This is a residual category typically diagnosed when an individual meets some of the criteria for a disorder, but not sufficient for the diagnosis to be made – for example, the behaviours may occur at a lower frequency, or weight may not be significantly low (American Psychiatric Association, 2013). Clinicians also have the option to diagnose an 'unspecified feeding or eating disorder' (UFED) when they do not chose to specify why criteria are not met, or they have not had sufficient detail about the patient to make a more specific diagnosis (American Psychiatric Association, 2013). This residual category (which includes both OSFED and UFED) was formerly known as 'eating disorder not otherwise specified' (EDNOS) in the DSM-IV (American Psychiatric Association, 2013).

### 1.2.2 Prevalence

EDs have a relatively high prevalence among the general population, with an elevated prevalence in women. Based on DSM-5 criteria, lifetime prevalence of AN among women

may be as high as 4%, with BN being around 2% (Smink et al., 2013). Notably, one of the aims when determining the DSM-5 criteria for EDs was to reduce the number of individuals in the residual category, which had previously been the most prevalent (Call et al., 2013). This led to the removal and clarification of criteria within the definition of AN and BN, such that prevalence estimates which pre-date the DSM-5 criteria overestimate the residual category and underestimate AN and BN (viz. Hoek, 2006; Smink et al., 2012). The residual category of EDNOS, or OSFED/UFED in the DSM-5, formerly had a prevalence in women estimated at over 2%; typically, estimates of AN were below 1%, and estimates of BN were between 1 and 2% (Fairburn et al., 2007; Machado et al., 2007; Smink et al., 2012). Estimates of prevalence in men for any ED are generally below 1% (Mitchison & Mond, 2015; Raevuori et al., 2014). Overall lifetime prevalence by the age of 80 across genders in the US in the early 2000s was estimated at 0.6% for AN, 1.1% for BN and 3.9% for BED (Hudson et al., 2007).

In general, EDs onset during the teenage years, with one large study in the United Kingdom (UK) reporting that AN onsets between 10 and 14 years of age, whereas BN onsets between 15 and 19 years of age (Micali et al., 2013).

### 1.2.3 Comorbidity

EDs have a high level of comorbidity with other disorders. A large study (n = 2436), which included only female inpatients who were treated for a primary diagnosis of AN, BN or EDNOS, found that EDs were highly comorbid with certain other classes of psychiatric disorder. They reported that 94% of their sample evidenced comorbid mood disorders, 56% evidenced anxiety disorders, and 22% evidenced substance use disorders (though this was more likely in BN than in AN). They also found that there was a higher prevalence of obsessive-compulsive disorder (OCD) in AN (Blinder et al., 2006). A similar set of comorbidities was found in a recent review of European studies, with >50% of patients

experiencing comorbid anxiety disorders, >40% experiencing mood disorders, >20% experiencing self-harm, and >10% experiencing substance use (Keski-Rahkonen & Mustelin, 2016). Relatedly, a study in those with AN and BN found that 41% of their sample had comorbid lifetime OCD (Kaye et al., 2004).

In adolescence, the picture is similar – with elevated rates of mood and anxiety disorders observed in those with full or partial EDs (Lewinsohn et al., 2000). Moreover, dysthymia and obsessive-compulsive personality disorder (OCPD) positively predicted the presence of an ED in adolescence (Zaider et al., 2000).

### 1.2.4 Prognosis and outcomes

Despite the presence of some effective treatments, EDs are recognised as being among the psychiatric disorders with the highest risk of mortality. All EDs have an increased mortality rate, and, along with substance abuse disorders, are considered the psychiatric disorders with the highest mortality rates (Arcelus et al., 2011; Chesney et al., 2014; Hoang et al., 2014). However, this is especially notable for AN, which has a standardised mortality ratio of 5.86, compared to 1.93 and 1.92 for BN and EDNOS respectively (Arcelus et al., 2011). Indeed, a meta-analysis of excess mortality in psychiatric disorders from 1998 indicated that EDs and substance abuse carried the highest all-cause mortality risks, with a mortality rate for EDs of five times that expected (Harris & Barraclough, 1998). Many factors lead to this increased risk of mortality. Notably, the risk of suicide in those with AN is heightened, such that one in five deaths of those with AN can be attributed to suicide (Arcelus et al., 2011). BN also conveys a heightened risk of suicide, such that together, those with EDs have a 4.8 times higher risk of death by suicide (Hoang et al., 2014; Suokas et al., 2014). The leading cause of death in patients with EDs in a UK study was pneumonia, along with deaths from physical causes resulting from the ED, respiratory or cardiovascular problems (Hoang et al., 2014).

Furthermore, EDs often have a protracted course, often including relapse or failure to achieve full remission. The recovery rate for AN is particularly low. In a cohort of Finnish twins, the 5-year clinical recovery rate was 66.8% (Keski-Rahkonen et al., 2007). Other studies have found a lower recovery rate – one study found a recovery rate of 33% after 7.5 years of follow-up (Herzog et al., 1999), with another finding the recovery rate was typically below 50% (Steinhausen, 2002). One reason for this difference in prevalence rate is that Keski-Rahkonen et al. studied individuals in the community (of whom only about 50% had received a diagnosis or support from a health-care professional) (Keski-Rahkonen et al., 2007). It is possible to assume that those who did not receive support from a health-care professional may have experienced less severe AN; resulting in a correspondingly higher recovery rate. BN has a higher recovery rate than AN, with one study finding 74% achieved full remission by 7.5 years (Herzog et al., 1999), though a more recent review of 79 studies found a full recovery rate of 45% (Steinhausen & Weber, 2009). As BED has previously not been a separate diagnostic category in the DSM, there is little known about recovery rates or course, especially in individuals with BED who are not overweight or obese (Smink et al., 2012). It is worth noting that there is evidence to demonstrate that treatments are less effective in those with a longer course of ED (Treasure & Russell, 2011), partly driven by the fact that a longer duration of illness predicts a worse prognosis, for AN at least (Errichiello et al., 2016; Zipfel et al., 2000).

There is also a large global disease burden for EDs. Whilst there is high variance in the disability-adjusted life years (DALYs) for these disorders, EDs account for approximately 1.2% of the DALYs attributable to mental and substance abuse disorders (Whiteford et al., 2013). This is higher in regions such as Western Europe (Whiteford et al., 2013).

### 1.2.5 Treatment

There are a number of treatments for EDs recommended by the National Institute for Health and Care Excellence (NICE). NICE recommends a number of different psychological therapies for adults with AN, such as individual eating-disorder-focused 'enhanced cognitive therapy' (CBT-E) (Fairburn et al., 2003), the Maudsley Anorexia Nervosa Treatment for Adults (Schmidt & Treasure, 2014), and specialist supportive clinical management (McIntosh et al., 2006; National Institute for Health and Care Excellence, 2017). For children and young people, AN-focused family therapy for children and young people should be considered (National Institute for Health and Care Excellence, 2017). The guidelines recommend that medication is not offered as the sole treatment for AN (National Institute for Health and Care Excellence, 2017), which corresponds to research indicating that whilst selective serotonin reuptake inhibitors (SSRIs) and antipsychotics are often prescribed, there are few psychoactive medications which show benefit in AN (Balestrieri et al., 2013). The NICE guidelines recommend that BN in children and young adults is treated using Family Therapy for Bulimia Nervosa, and self-help or CBT-E for adults with BN. Medication is not recommended as the sole treatment for BN. For BED, guided self-help or group CBT-E are recommended; again, medication is not recommended as the sole treatment for BED (National Institute for Health and Care Excellence, 2017).

It is clear, however, that there is still a requirement for novel, effective treatment options. This is evidenced by the research detailing increased mortality rate and a protracted course for many individuals, along with a noticeable global burden of health (see Section 1.2.4). A recent movement in psychiatric research towards searching for transdiagnostic factors might allow further understanding of many psychiatric disorders (including EDs), with the potential for delivering more, and better, treatment options in the future (Insel et al., 2010).

## 1.3 THE TRANSDIAGNOSTIC APPROACH

The transdiagnostic approach arises from the acknowledgment that the traditional diagnostic criteria for psychiatric disorders are constructed from perceived clusters of symptoms, and may lack value for pathophysiological scientific research (Haro et al., 2014; Insel et al., 2010). This is because specific diagnostic labels might not reflect the underlying biological or psychosocial causes of a disorder; rather, they reflect the symptoms an individual is currently experiencing (Insel et al., 2010). Whilst there is likely to be a relationship between symptoms and underlying causal factors, this relationship might not be sufficiently close for further progress to be made in the understanding and treatment of psychiatric disorders.

Transdiagnostic factors are putative underlying biological and psychological constructs which can cut across different psychiatric disorders, as is evidenced for example in the Research Domain Criteria (RDoC) project (Insel, 2014; Insel et al., 2010). Above and beyond this definition, for these factors to have potential use, they should have a relationship with the underlying pathophysiology of the disorder. This would often be expected to take the form of a psychobiological variable, perhaps based on a neural understanding of the pathology. This psychobiological underpinning is necessary as it is this which would lead to advances in psychiatry: not only could it be expected that the divisions between categories of disorder might be less arbitrary and more meaningful if the disorders are related to the quantifiable functioning of separate biological or cognitive mechanisms; but also these underlying mechanisms might provide potential treatment targets, along with biomarkers for prediction of treatment response. Conversely, when a classification system does not rely on psychobiological underpinnings, different underlying mechanisms might be causal in different cases of the same ‘disorder’, leading to heterogeneity in presentation, course, and in treatment response (Hyman, 2007; Insel et al., 2010; Robbins et al., 2012). Furthermore, a

non-biological classification system might lead to anomalies such as homogeneity observed with patients with different diagnoses, or a pattern of heightened incidence of various putatively separate disorders within one family, which might be better explained by transdiagnostic factors reflecting shared underlying (heritable) biological risk factors or cognitive mechanisms of action (Fineberg et al., 2017).

## 1.4 COMPULSIVITY

### 1.4.1 Definition

Compulsivity may be defined as the tendency to rigidly repeat actions or behaviours which are neither beneficial or associated with reward (conversely, they may be associated with adverse consequences) (Robbins et al., 2012). The performance of these actions or behaviours may be accompanied by a feeling of loss of control (Fineberg et al., 2017). Compulsive phenomena are typically seen in OCD and are usually viewed as a response to problematic intrusive thoughts (obsessions), precipitating heightened anxiety; which can be neutralised by performing compulsive rituals. It has been argued that many of the compulsive behaviours of other psychiatric disorders are also aimed at avoiding negative experiences, though often in a non-rational way (Chamberlain et al., 2009). However, recent research indicates that compulsive behaviours might alternatively arise from excessive habit formation (Gillan, Robbins, et al., 2015), and/or lack of behavioural inhibition and deficits in reversal learning (Fineberg et al., 2017).

Compulsivity might be considered a transdiagnostic factor, as it appears to be an inherent part of a number of different disorders. Compulsivity may not be a unitary construct, but may instead be underpinned by separable cognitive processes (Fineberg et al., 2014, 2017; Robbins et al., 2012) such as cognitive flexibility, attentional disengagement, habit learning and lack of behavioural inhibition (Fineberg et al., 2014, 2017). Furthermore,

compulsive behaviour has a putative neurobiological basis in the corticostriatal system (Alexander, 1986; Cummings, 1993; Groenewegen & Uylings, 2000; Robbins et al., 2012; van den Heuvel et al., 2016).

### 1.4.2 Compulsive disorders

#### *1.4.2.1 Obsessive-compulsive disorder*

Traditionally, there are a number of disorders which have been strongly associated with the concept of 'compulsivity'. One of these is OCD. This disorder is characterised by intrusive thoughts and compulsive rituals, which cause clinically significant distress or impairment in everyday functioning, or are present for over 1 hour per day (American Psychiatric Association, 2013). Common compulsive behaviours are hand-washing or cleaning rituals, along with checking rituals. These ritualistic behaviours seem perhaps to be related to excessive habit formation (Gillan, Robbins, et al., 2015), but associations have also been found with diminished cognitive flexibility in both patients and their first degree relatives (Chamberlain et al., 2005, 2008).

#### *1.4.2.2 Obsessive-compulsive personality disorder*

OCPD is a personality disorder - personality disorders are defined as impairments in personality functioning and the presence of certain pathological personality traits. For a diagnosis of OCPD, an individual should display impairments in self-functioning: for example, they may be excessively devoted to work and productivity, to the exclusion of leisure or social activities. They may also have difficulty completing tasks due to rigidity and inflexible internal standards. Individuals with OCPD should also display impairments in interpersonal functioning, with difficulties in either empathy or intimacy; and should show pathological personality traits, either in relation to compulsive rigid perfectionism or perseveration. These impairments should be stable and consistent across time and situations

and not normative for the context (American Psychiatric Association, 2013). The compulsive aspect of this disorder is apparent in the rigid perfectionism, and the perseveration and inflexible internal standards.

#### *1.4.2.3 Obsessive-compulsive and related disorders*

From 2013, the DSM-5 has included a category known as 'Obsessive-Compulsive and Related Disorders' (OCRDs), (American Psychiatric Association, 2013). This includes disorders which are considered to include compulsive behaviour or cognitions as primary features. One of these disorders is trichotillomania (also known as hair-pulling disorder), in which the patient repeatedly pulls out their own hair and has made unsuccessful attempts to terminate this behaviour. The 'compulsive' aspect of this disorder is apparent: the patient often wishes to cease the behaviour, and is aware that it may lead to negative consequences such as bald patches or negative interpersonal consequences, but attempts to stop are unsuccessful. Excoriation (skin-picking disorder) is another OCRD, which is similar to trichotillomania in that it is characterised by a repetitive behaviour which can lead to damage to the physical appearance and causes distress but persists nevertheless.

Body dysmorphic disorder (BDD) is within the OCRD category (American Psychiatric Association, 2013). BDD is defined by a preoccupation (sometimes occupying over an hour a day or otherwise causing significant impairment in daily life or distress) with a perceived deficit in appearance, accompanied by repetitive behaviours (such as grooming, body checking, or comparing) (American Psychiatric Association, 2013). Here, the compulsive aspect is less obvious, but the repetitive behaviours are thought to be compulsive in that they may cause negative emotions, individuals feel driven to perform them and find them hard to curtail, and they do not lead to beneficial outcomes (Phillips et al., 2010). It is thought that almost all (>99%) of those with BDD present with compulsive symptoms over their lifetime (Phillips et al., 2005, 2010), which indicates that these compulsive symptoms are highly

prevalent within those who have a BDD diagnosis. Additionally, the features of BDD compulsive behaviours seem to support the view that compulsive actions are not performed purely to reduce the anxiety caused by preoccupations; for example, there was reported to be no reduction in distress during compulsive mirror-gazing (Veale & Riley, 2001).

#### *1.4.2.4 Addictions*

Compulsivity is also a recognised feature of addictive disorders, whereby the initially hedonic, rewarding effects of addictive substances lead to repeated use, which over time becomes compulsive (Lubman et al., 2004). When compulsive, there might be strong negative consequences to drug taking (e.g. interpersonal conflict, conflict with the law, health issues), but these negative consequences are unable to override the compulsive need to take the substance (Everitt & Robbins, 2005). This form of compulsivity has also been related to habit formation, but in this case the habit is likely to be linked to the dependency-inducing effects of the substance consumed.

## 1.5 ARE EDS COMPULSIVE DISORDERS?

### 1.5.1 EDs and compulsive behaviours or rituals

EDs can also be understood from a perspective of compulsive behaviour (Godier & Park, 2014; Rothenberg, 1986; Steinglass & Walsh, 2006), a view which has been espoused since at least the 1930s (Palmer & Jones, 1939). Many of the behaviours which are performed in EDs are performed rigidly and repeatedly (e.g. exercising, calorie counting, body checking). Additionally, these behaviours are often accompanied by a sense of loss of control; indeed, binges are required by definition to be accompanied by loss of control (American Psychiatric Association, 2013), and eating even small amounts in AN may be perceived as a loss of control, as is highlighted by the inclusion of 'subjective binge episodes' in the Eating Disorder Questionnaire (Cooper & Fairburn, 1987).

It was noted above that for behaviours to be defined as compulsive, not only should they be performed rigidly and repeatedly, but they should fail to lead to reward. Whether these behaviours lead to reward is less clear in EDs than in OCD, partly as EDs are often ego-syntonic or ego-ambivalent. This ego-syntonicity entails that many individuals with EDs feel that some or all of the disorder is consistent with their needs and goals (Sunday & Halmi, 1995). Initial weight loss is often accompanied by social approval, along with other rewards such as a sense of control, but continued weight loss often results in penalties, such as the worries of family and friends, health issues and cognitive difficulties (Godier & Park, 2014). Additionally, it seems that less than half of patients do truly experience their eating-disorder related rituals as ego-syntonic (and thus subjectively rewarding) (Sunday & Halmi, 1995), and it is clear that rituals and other ED symptoms do lead to significant functional impairment (Jenkins et al., 2011), even though insight into the problems caused may be poor.

Additionally, whilst ED behaviours may seem to be subjectively rewarding in some cases and therefore not to meet the definition of compulsivity, there is evidence for a disturbance of reward processing in EDs (Cowdrey et al., 2011; Harrison et al., 2010; Park et al., 2014). Patients may experience reward from the pursuit of thinness and dietary restraint; over time, this experience of reward may reduce, yet the associated behaviours continue (Park et al., 2014), in a manner akin to the wanting/liking dissociation present in substance abuse (Everitt & Robbins, 2005; Godier & Park, 2015b; Park et al., 2014). A study using self-report questionnaires found that those with AN-R were less sensitive to reward, but those with AN-BP are more sensitive to reward (Harrison et al., 2010). There also seem to be differences in the neural responses to reward in EDs. An fMRI study found that responses in the ventral striatum in those who have recovered from AN do not differentiate between reward and loss outcomes (Wagner et al., 2007), with recent research also finding elevated brain responses to reward prediction errors in frontostriatal regions in AN (Frank et al.,

2018). Thus, it seems likely that even if some subjective reward is derived from ED behaviours, perhaps it is unlikely that the outcomes of those behaviours would be rewarding to the same extent in individuals without EDs.

### 1.5.2 Comorbidities

#### *1.5.2.1 EDs, OCD, OCPD and OCRDs*

EDs appear to be phenomenologically similar to various disorders which feature compulsivity prominently. These (compulsive) disorders often also display elevated comorbidity with AN. Though there are many reasons why disorders might be similar or display comorbidity, a parsimonious one in this case might be that in such disorders compulsivity is either a causal or maintaining factor.

EDs are highly comorbid with OCD (Bienvenu et al., 2000; Kaye et al., 2004; Zaider et al., 2000). Those with a diagnosis of AN have been found to be around 10-fold more likely to subsequently receive a diagnosis of OCD, and those with OCD have been found to be 4-fold more likely than the general population to be subsequently diagnosed with AN in a large longitudinal cohort (Cederlöf et al., 2015). A large study of comorbidity found that over 4% of females with any ED had comorbid OCD, with BED showing the least comorbidity (1.6%) and AN-BP the most (7.7%) (Ulfvebrand et al., 2015). It is worth noting that despite the finding that major depressive disorder shows the highest comorbidity with EDs, OCD is less prevalent in the general population, such that the relative prevalence of OCD in EDs (AN in this case) is higher than the relative prevalence of depression (Jarry & Vaccarino, 1996; Serpell et al., 2001).

In a famous observational study of starvation in a non-clinical population of young men, compulsivity was dramatically increased (Keys et al., 1950), which might lead one to assume that compulsivity is purely a result of starvation. However, in both AN and BN, OCD

symptoms have been found to persist into recovery (Morgan et al., 2007; Råstam et al., 1996; von Ranson et al., 1999), indicating that these symptoms may not just be an epiphenomenon of the starved state (Serpell et al., 2001). In AN, there is also evidence of shared familial transmission, with those with AN having a higher proportion of relatives with OCD than would be expected at baseline (Strober et al., 2007), though other studies have not reported this (Bienvenu et al., 2000), or have reported an association with the related but distinct construct of OCPD (Lilenfeld et al., 1998).

The case for the importance of this comorbidity is also supported by the fact that the compulsive behaviours present in EDs are comparable to those present in OCD, in their stereotyped, rigid and repetitive manner, their negative consequences, and the fact that they may partly function to neutralise anxiety about a preoccupation (i.e. weight gain) (Steinglass & Walsh, 2006). AN and OCD patients have been found to have similarly elevated scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS), which measures the impairment resulting from obsessive and compulsive symptoms (Bastiani et al., 1996; Kaye et al., 1992).

OCPD, whilst a putatively distinct entity from OCD (see Section 1.4.2.2), also comprises compulsive symptoms (often in the form of 'rigidity' or set ways of performing tasks) as a key element (American Psychiatric Association, 2013; Serpell et al., 2001). This rigidity and perfectionism is also displayed in AN, and many behaviours (such as cutting food into a certain number of bites) also seem to be similar to the ritualistic behaviours of OCPD. The increased prevalence of OCPD in relatives of probands with AN indicates shared familial transmission (Lilenfeld et al., 1998). Furthermore, the presence of OCPD features as a child has been found to predict the subsequent onset of an eating disorder (Anderluh et al., 2003).

It has been suggested that there may be a common link between OCD, OCPD and EDs, perhaps genetic (Halmi, 2004), though, that said, one should recall that the association between OCPD and EDs other than AN is limited (Halmi, 2004; Lilenfeld et al., 1998; Serpell et al., 2001). However, there is some evidence for BN and OCPD links: whilst Braun et al. did not find any full cases of OCPD in their BN sample, 20% of their BN sample did have subthreshold symptoms of OCPD. Additionally, 14% of AN-BP patients studied met the criteria for OCPD, compared to only 6% of the AN-R patients, though they did not find a significant difference between ED diagnoses (Braun et al., 1994). This led Halmi et al. to conclude that OCPD traits such as perfectionism were, contrary to expectation, still found to an extent in those with binging and purging behaviour (Halmi, 2004).

Finally, it has been found that those with EDs are more likely to have first-degree relatives with OCRDs, regardless of any current OCRD diagnosis the proband has. This further suggests that compulsive disorders and EDs may share a common genetic substrate (Bellodi et al., 2001).

#### *1.5.2.2 EDs and BDD*

EDs can also be considered to have certain similarities with BDD, which is classed as an OCRD. Those with EDs and BDD often display preoccupation with perceived bodily imperfections, and compulsive behaviours such as mirror-gazing, other body checking rituals, or attempts to 'cover up' the perceived flaw (by clothing choice or make-up). There is a large overlap between the diagnostic criteria of BDD and the symptoms of an ED: the DSM-5 requires that if the preoccupations are solely about shape or weight, and the individual has a diagnosable eating disorder, that BDD isn't diagnosed (American Psychiatric Association, 2013). The reason for this exclusion is that researchers estimate that many of those diagnosed with AN (and some of those diagnosed with BN) might be also diagnosed with BDD if there was not a diagnostic hierarchy (Phillips et al., 2010). Therefore the diagnosis of BDD

alongside an ED often requires that the body preoccupation experienced is a separate concern to the shape or weight preoccupations present in EDs. It is notable that there is still a substantial comorbidity between the two disorders even given this diagnostic requirement (Dingemans et al., 2012; Grant et al., 2002; Ruffolo et al., 2006).

The issue of whether BDD and EDs are separate or related disorders has been discussed (Dingemans et al., 2012; Grant & Phillips, 2004), with the general conclusion being that the disorders appear to be distinct, for a number of reasons. Firstly, these disorders show a different response to treatment such as SSRIs, which is often effective in BDD but not in AN (Grant & Phillips, 2004) - though note that fluoxetine may reduce binges and depression in BN (McElroy et al., 2015). Secondly, comorbidity of the two is associated with more psychopathology and dissatisfaction with other body parts (Dingemans et al., 2012). Thirdly, the disorders also have a different gender distribution (Grant & Phillips, 2004). However, some of the other arguments, such that EDs do not respond to cognitive behavioural therapy (CBT) and that BDD has a higher comorbidity rate with OCD than EDs, do not stand up to further scrutiny. Notably, CBT-E has been recommended for a number of different EDs by NICE (National Institute for Health and Care Excellence, 2017), and the comorbidity with OCD further highlights that BDD is a disorder with a heavy compulsive component, as we hypothesise EDs also are. Indeed, one research group using principal components analysis found that a cluster of disorders which can be described as 'compulsive' includes OCD, BDD and EDs (Al-Asadi et al., 2014). Further discussion of this issue here is beyond the scope of this thesis; suffice it to say, the similarity between the EDs and BDD and the recognised compulsive elements of BDD provide evidence for the compulsivity of EDs.

### 1.5.3 Cognition

There are a number of neuropsychological tasks which are thought to measure various facets of compulsivity (Fineberg et al., 2014). One of these aspects, or 'neurocognitive

domains', is contingency-related cognitive flexibility, which can be measured by ability to perform reversal learning. There is some evidence that those with EDs are impaired in reversal learning (Brogan et al., 2010).

There is also evidence that those with EDs are impaired in task/attentional set-shifting (Holliday et al., 2005; Roberts et al., 2007; Tchanturia et al., 2003, 2012; Tchanturia, Anderluh, et al., 2004; Tchanturia, Morris, et al., 2004), though this should be interpreted with caution as good performance on many 'set-shifting' tasks also requires effective reversal learning (Wildes et al., 2014), which has distinct neural underpinnings (Rogers et al., 2000). The deficit in set-shifting in those with EDs persists into recovery (Roberts et al., 2010; Tchanturia et al., 2012), and is also found in relatives of those with EDs (Holliday et al., 2005; Roberts et al., 2010), indicating that this phenomenon is not likely to be solely the product of the 'ill' state of EDs.

Attentional bias towards and difficulty disengaging from disorder-relevant stimuli is another putative marker of compulsivity, with OCD patients showing a deficit in disengaging attention from disorder-relevant stimuli, but mixed evidence for a bias towards disorder-relevant stimuli (Bradley et al., 2016; Fineberg et al., 2014; Hezel & Mcnally, 2016). Those with EDs and those with body dissatisfaction also seem to have an attentional bias towards body-related stimuli (Aspen et al., 2013; Rodgers & DuBois, 2016). For food-related stimuli the evidence is mixed, with some studies finding enhanced ability to disengage attention from food stimuli, and others showing greater distraction (indicating difficulty disengaging) from food stimuli (Werthmann et al., 2015). This suggests that there are definite attentional biases in EDs, which are especially clear in relation to body-related stimuli.

Habit learning is also a neurocognitive domain of compulsivity. Habit learning is produced by a stimulus-response association, such that an external stimulus can elicit a

learned behaviour without conscious effort, and regardless of the outcome (Graybiel, 2008). It is thought to be on a continuum with goal-directed control, which may be defined as behavioural control based on action-outcome associations, in which the 'outcome' is congruent with the goals of the individual, and is rewarding. Behaviours which are initially rewarding might strengthen action-outcome associations until they are elicited by just the presence of the stimulus rather than requiring a conscious consideration of the outcome, such that a stimulus-response association – or a 'habit' – might result from an initially rewarding behaviour (Graybiel, 2008). One cognitive neuroscience hypothesis suggests that the underpinning of the perseveration of maladaptive behaviours in AN (e.g. restriction, exercising) is related to differences in habit formation (Steinglass & Walsh, 2006; Walsh, 2013). However, a recent investigation in AN found that there was no evidence of a general difference in habit learning (Godier et al., 2016), although this study was preliminary in nature and focused specifically on devaluation (the continual performance of an action after the reward value that was previously associated with it has been removed or limited). Conversely, binging behaviour seems to be more strongly related to abnormalities in habit formation. Binging on palatable foods has been found to induce habitual behaviour in rats (Furlong et al., 2014). Similarly, patients with BED seem to have a bias towards habit formation and away from goal-directed control (Voon et al., 2015). Using the same task as Voon et al. in a larger, online sample, this group found that there was a strong association between goal-directed deficits and self-reported EDs (Gillan et al., 2016), based on the 26-item Eating Attitudes Test (EAT-26) measure (Garner et al., 1979). This association was stronger than the association between goal-directed deficits in OCD and alcohol addiction, both of which disorders have been reported to display deficits in habit formation (Gillan, 2013; Gillan et al., 2011, 2014; Gillan, Apergis-Schoute, et al., 2015; Sjoerds et al., 2013; Voon et al., 2015).

### 1.5.4 Neural circuitry

The neural basis of compulsivity is beginning to be understood, and there is evidence to suggest that some of these differences are also found in EDs. The body of evidence strongly indicates that compulsivity is related to differences in frontal-striatal-thalamo-cortical circuitry (Alexander, 1986; Cummings, 1993; Fineberg et al., 2014, 2017; Grant & Kim, 2014; Groenewegen & Uylings, 2000; van den Heuvel et al., 2016). There are several of these circuits, and imbalances both within and between them may contribute to the development and maintenance of compulsive behaviours in both OCD and other compulsive disorders (van den Heuvel et al., 2016). The neural correlates of the neurocognitive domains which make up compulsivity (Section 1.5.3) have been investigated in several different disorders (though the majority of the research has been done in OCD); and as might be expected, the findings from separate disorders overlap but are not identical (Fineberg et al., 2017). Areas which show structural or functional differences between patients and controls in compulsive disorders include the orbitofrontal cortex, the prefrontal cortices, and the striatum: areas which (amongst other things) are involved in cognitive control, motor function, and reward (Chamberlain et al., 2008; Everitt & Robbins, 2005; Fineberg et al., 2017; Godier & Park, 2014; van den Heuvel et al., 2016; Whiteside et al., 2004). Some examples of the findings in OCD are presented in Table 2 below.

There is evidence of abnormalities in these same fronto-striatal-thalamo-cortical circuits in EDs (Kaye et al., 2011), including AN (Cowdrey et al., 2011; Fladung et al., 2010; Friederich et al., 2012, 2013; Godier & Park, 2014; Zastrow et al., 2009), BN (Marsh et al., 2009; Schäfer et al., 2010; Wagner et al., 2010) and BED (Balodis et al., 2013, 2014; Kessler et al., 2016; Schäfer et al., 2010). However, given that brain areas perform multiple functions, and that the functions which are outlined as being performed by these circuits (e.g. ‘reward’) are unlikely to be impaired specifically in compulsive disorders, further research is needed to

establish to what extent the same fronto-striatal-thalamo-cortical circuitry is impaired in EDs as in OCD and other compulsive disorders, whether these impairments are specific to compulsive disorders, and whether such impairments might lead to compulsive behaviours being performed.

*Table 2: A selection of studies which reported differences in corticostriatal circuitry in OCD.*

| | **Evidence** |
|---|---|
| **Structural MRI** | Smaller left and right OFC volumes compared to controls, greater thalamic volumes, greater white matter, trend towards different ACC volume, multiple correlations with YBOCS scores, no difference in caudate volumes (Atmaca et al., 2007)<br><br>Greater grey matter in posterior orbitofrontal and parahippocampal regions, decreased grey matter in left ACC, inverse correlations with OCD symptom severity and grey matter in medial thalamus, trend to reduction in right parietal associative cortex (Valente et al., 2005) |
| **Functional MRI** | Decreased connectivity strength between dorsal caudate and putamen to frontal regions in OCD; but ventral striatal-frontal connectivity increased in OCD (Vaghi et al., 2016)<br><br>Reduced activation of frontal regions including lateral OFC during reversal learning in OCD and relatives (Chamberlain et al., 2008)<br><br>Excessive habit formation associated with hyperactivity in the caudate; hyperactivity in OFC during acquisition of avoidance (Gillan, Apergis-Schoute, et al., 2015)<br><br>Decreased connectivity between limbic network and basal ganglia network, DMN, and executive network. Decreased connectivity within limbic network, stronger connectivity within executive network (Göttlich et al., 2014)<br><br>Greater activation in frontal regions, temporal regions, and right ACC during symptom provocation (Adler et al., 2000)<br><br>Altered connectivity between FPN seeds (primarily insula) and regions including PCC, medial frontal cortex, posterior inferior parietal lobule, and parahippocampus, and more connectivity between the FPN and thalamus, lateral frontal cortex (Stern et al., 2012)<br><br>Patients with OCD had greater functional connectivity along a ventral corticostriatal axis, including OFC; strength of connectivity between ventral caudate and anterior orbitofrontal cortex predicted symptom severity. Reduced connectivity between dorsal striatum and lateral prefrontal cortex, and ventral striatum and midbrain ventral tegmental area (Harrison et al., 2009) |
| **PET/SPECT** | Differences in radiotracer uptake in orbital gyrus and head of caudate nucleus in OCD (Whiteside et al., 2004) |

*Comparison is between OCD patients and controls unless otherwise stated. OFC = orbitofrontal cortex; YBOCS = Yale-Brown Obsessive-Complusive Scale, ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; DMN = default mode network; FPN = frontoparietal network.*

### 1.5.5 Neurotransmitters

Multiple separate neurotransmitters have been implicated in compulsivity (Fineberg et al., 2014, 2017), including the monoamine neurotransmitters (especially serotonin, dopamine and noradrenaline (NA)) (Fineberg et al., 2014, 2017) and glutamate (Naaijen et al., 2015). Different compulsive disorders respond differently to pharmacological treatments such as SSRIs, dopaminergic and glutamatergic agents (Fineberg et al., 2017). For example, whilst OCD is in general treated with SSRIs (Fineberg et al., 2017; Hollander, 1998), patients with OCD and tics may preferentially respond to antipsychotics, those with BDD may respond less to antipsychotics and high-dose SSRIs, and trichotillomania and excoriation disorder may respond to SSRIs and N-acetylcysteine (Bloch et al., 2006; Fineberg et al., 2017; Grant et al., 2009, 2016). This suggests that that there may be separate underlying neurochemical differences within these disorders, or additional factors which are responsible for the medication response, or lack thereof.

In addition to evidence from treatment-response, there have been several studies using MRS in OCD. This technique can shed some light on the underlying neurochemistry of the disorder by quantifying the levels of different neurochemicals present within certain defined brain voxels. This technique has not been used widely in compulsive disorders outside of OCD, and the studies which employ this technique in OCD do not paint a clear picture. A review by Brennan et al. indicates that there is no clear evidence of difference in either a measure of choline-containing compounds (including choline, phosophorylcholine, and glycerophosphorylcoline) or in glutamate-related neurochemicals (glutathione, glutamate, glutamine or $\gamma$-aminobutyric acid (GABA)) (Brennan et al., 2013). One study which was performed after this review found a difference in glutamate levels in OCD in thalamic regions which correlated with compulsion scores (Zhu et al., 2015). A more recent review found that overall evidence

indicates a potential increase in Glx (a composite MRS measure including glutamate and glutamine) in striatal regions across impulsive and compulsive disorders, which the authors relate to the underlying differences in fronto-striatal circuitry in these disorders (Naaijen et al., 2015). Furthermore, reduced glutathione levels in the posterior cingulate have been found in OCD patients in a proton MRS study, although this was not related to scores on the Yale-Brown Obsessive-Compulsive Scale (Brennan et al., 2016).

Relatedly, the glutathione-precursor and dietary supplement NAC has recently received attention as a possible agent for a number of psychiatric disorders, including conditions featuring prominent compulsive behaviours, such as trichotillomania (Grant et al., 2009), excoriation disorder (Grant et al., 2016), and addictions (Ducret et al., 2015). It is possible that NAC acts in these individuals to produce therapeutic benefit by reducing compulsive behaviours, but this is yet to be empirically tested.

In EDs, the pattern is similarly complex, with multiple different neurotransmitters implicated. These include serotonin (Bailer & Kaye, 2010), dopamine (Avena & Bocarsly, 2012; Friederich et al., 2013; Frieling et al., 2010), acetylcholine, and opioids (Avena & Bocarsly, 2012). A recent study from our group found evidence for reduced brain glutamate using MRS at 7 Tesla (7T) in a group of currently unwell AN patients (Godlewska et al., 2017). However, it is well-established that there are few effective pharmacological agents which reduce core ED symptoms, the existence of which could direct researchers towards potential neurochemical mechanisms underlying EDs. In AN, there is no recommended pharmacological treatment of value (Balestrieri et al., 2013), and, in contrast to OCD, no evidence that AN is improved by SSRI medication (Frank & Shott, 2016). Furthermore, none of the EDs have a pharmacological agent recommended as a first-line treatment by NICE (National Institute for Health and Care Excellence, 2017). However, it has been argued that olanzapine may reduce anxiety in AN (McElroy

et al., 2015). Additionally, there is some evidence that binging behaviours and mood in BN and BED can be treated using SSRIs (Bacaltchuk et al., 2000; Flament et al., 2012; McElroy et al., 2015) such as fluoxetine, and there have been successful trials indicating efficacy for lisdexamfetamine and naloxone (an opioid receptor antagonist) (McElroy et al., 2015, 2016).

As so many separate neurotransmitters are implicated in both compulsivity and EDs, it is difficult to ascertain the existence of a clear link between the two. Ideally, future transdiagnostic research might be able to shed further light on the neurochemicals which are affected in both compulsivity and EDs.

## 1.6 IMPULSIVITY

Impulsivity may be defined as responding prematurely and recklessly, without regard to the consequences of one's actions. Importantly, it is possible to argue that compulsivity and impulsivity should be considered together when it comes to the search for transdiagnostic factors (Fineberg et al., 2014; Robbins et al., 2012).

Historically, compulsivity and impulsivity were seen as 'diametrically opposed' (Fineberg et al., 2014), but they seem instead to be intertwined: disorders which are thought to be 'compulsive' in nature can be found to also display impulsivity (Grant & Kim, 2014). Sometimes, these two constructs are referred to as the 'impulsive-compulsive spectrum' (Claes et al., 2006; Fineberg et al., 2010; van den Heuvel et al., 2010). This association can either take the form of a simple transition from impulsivity to compulsivity over the course of the disorder (Everitt & Robbins, 2005), or involve more nuanced interactions including concurrent symptoms of each (Grant & Kim, 2014). Both are thought to result from failures to inhibit behavioural response (Robbins et al., 2012), and they both involve the corticostriatal system (Cardinal et al., 2004; Grant & Kim,

2014; Haber, 2003; Robbins et al., 2012; van den Heuvel et al., 2010). The interplay of spatially proximate cortico-striatal circuits may lead to the association between them (Robbins et al., 2012; van den Heuvel et al., 2010).

Some examples of the interaction between impulsive and compulsive behaviours include the presence of repetitive, compulsive gambling behaviour in gambling disorder, which is normally seen as an impulse-control disorder (Grant & Kim, 2014), or the presence of elevated impulsivity (which may be a marker of chronicity) in OCD (Grant & Kim, 2014; Kashyap et al., 2012). The most researched example is addiction, in which there is a well-characterised transition from impulsive drug-seeking and drug-taking to the compulsive, habitual drug-taking stereotypical of prolonged addiction (Everitt & Robbins, 2005).

## 1.7 ARE EDS IMPULSIVE DISORDERS?

EDs, along with displaying compulsivity as a key facet, are one of the disorders (along with addictions) which clearly also display impulsivity (Robbins et al., 2012; Waxman, 2009). One hypothesis is that EDs display a course much like addiction, in which certain behaviours displayed by the individual transition from impulsive in initial stages of the disorder to compulsive, fixed rituals which are hard to prevent (Godier & Park, 2014, 2015b).

### 1.7.1 EDs and impulsive behaviours

In terms of specific symptoms, both binging and purging have been linked to impulsivity as well as compulsivity (Hoffman et al., 2012; Raymond et al., 1999). Those with EDs who binge and purge were found to display higher impulsivity than those who do not perform these behaviours (Claes et al., 2005; Vervaet et al., 2004), with those who have AN-BP seeming to perhaps display less impulsivity still than those with BN (Claes

et al., 2005). Other research has found that different components of impulsivity may be related to many ED cognitions and behaviours, with one study finding that many disordered eating behaviours (binging, restricting, vomiting, exercise) were related to urgency, a facet of impulsivity (Black & Mildred, 2014). A separate study found that restraint, eating concern, shape concern and frequency of objective and subjective binges in the Eating Disorders Examination (EDE; see Fairburn & Cooper, 1993, and Section 2.4.2) were related to different facets of impulsivity (Lavender et al., 2017).

### 1.7.2 Comorbidities

EDs and attention deficit hyperactivity disorder (ADHD) have been found to have elevated comorbidity (Bleck et al., 2015; Nazar et al., 2016). Not only is it the case that those with ADHD are more likely to suffer from clinically significant binging behaviours (e.g. as in BED, BN, AN-BP), but they are also more likely to experience clinically significant restrictive behaviours (Bleck et al., 2015).

The elevated comorbidity between EDs and substance-use disorders (SUDs) has been well documented (Harrop & Marlatt, 2010; Holderness et al., 1994). SUDs have been described as impulsive in the early stages of the disorder (Everitt & Robbins, 2005), as have EDs (Robbins et al., 2012), and they have also been found to have qualitative similarities (Godier & Park, 2015b).

There also seems to be a higher association between EDs and impulse control disorders (a definition used by the World Health Organisation), including compulsive shopping and kleptomania (Fernández-Aranda et al., 2006, 2008).

### 1.7.3 Cognition

There is mixed evidence as to whether EDs display the typical differences in cognitive tasks that are thought to reflect underlying impulsivity. A review from 2009

identified four studies which tested performance on cognitive tasks which probe impulsivity and found no clear picture, with some studies showing differences, and some either not showing differences or showing differences between ED patients who perform binging behaviours and those who restrict (Waxman, 2009).

Impulsivity, similarly to compulsivity, is able to be fractionated into constituent 'neurocognitive domains' (Fineberg et al., 2014). One of these domains is motor impulsivity, which is demonstrated by greater stop-signal reaction times (SSRTs) in a Stop-Signal Task. In one more recent study, those with BN but not BED were shown to have deficits in inhibitory control shown by greater SSRTs (Wu et al., 2013), though another study found that those with BED also have an increased Stop Signal Response Time (Svaldi et al., 2014). A separate study found greater SSRTs in AN but not BN (Galimberti et al., 2012). This conflicting evidence indicates that there is not a clear picture for impulsivity in EDs, which might be expected if disorders can show impulsivity and compulsivity at separate times within the course of a disorder.

There are other tasks which have been used to measure impulsivity, such as the Delay Discounting Task (DDT) (which measures a domain of impulsivity known as 'choice impulsivity'). Here, the evidence is, again, complex. Those with AN have been demonstrated to have lower delay-discounting than is typical (Decker et al., 2015), though this does seem to normalise with treatment. Conversely, those with BED (and also obese women) show greater delay discounting (i.e. a lower value is given to rewards which are more distal in the future) (Davis et al., 2010). Increased delay discounting has also been observed in BN (Kekic et al., 2016).

Overall, this brief summary of impulsive cognition in EDs indicates that the picture is not yet clear, but there is a hint towards a difference between disorders, with lower impulsivity seen in AN, and greater impulsivity seen in binging EDs.

## 1.8 SUMMARY

It would appear that EDs have substantial similarities to compulsive disorders, not only in terms of the phenomenology of the symptoms, but also in terms of their underlying comorbidities, performance on cognitive tasks, neural circuitry, and the neurotransmitters which appear to be implicated. As impulsivity can be considered on a spectrum with compulsivity, with the two constructs often presenting in the same disorder in the same patients, and sometimes even during the same time period, the evidence indicating that EDs are impulsive disorders has also been considered. Whilst there is likely to be some association, it does appear that this may be stronger in the EDs which contain binging as a key component. The remainder of this thesis will present experimental work which aims to further characterise the construct of compulsivity (and, to a lesser extent, the construct of impulsivity) in EDs.

## 1.9 AIMS OF THESIS

The aims of this thesis, based on the research highlighted and summarised above, are as follows:

1) To investigate the neural basis of compulsivity in EDs, using a multimodal MRI approach and based on methods which have been used in disorders such as OCD;
2) To examine whether the cognitive inflexibility found in EDs is a result of difficulty learning adaptively, investigated using a computational modelling framework, and

whether this relates to NA, a neurotransmitter which has been implicated in cognitive flexibility and learning about uncertainty;

3) To investigate whether NAC, a dietary supplement which has been found to be of benefit in some compulsive disorders, reduces compulsive and impulsive responding in cognitive tasks; and whether it has potential for benefit in EDs.

# 2 GENERAL METHODS AND MEASURES

## 2.1 SUMMARY OF STUDIES

As the three experimental studies (discussed in Chapters 3 to 5) are referred to throughout this chapter in relation to the methodological considerations discussed, they are briefly summarised here.

The study referred to throughout this chapter as 'the MRI study' is discussed in Chapter 3, and included structural MRI, resting-state and task-based fMRI, and MRS. The participants were 20 individuals who had recovered from AN, and 20 individuals who had never experienced an ED. We were interested in examining the neural differences in these two groups in relation to compulsivity, and thus used a task which incorporated reversal learning and set-shifting, frontostriatal seeds for the resting-state analyses, and analysed glutamate levels in the ACC.

The study referred to throughout this chapter as 'the adaptive learning study' is discussed in Chapter 4, and included a behavioural task and pupillometry measures. This task manipulated volatility, and we examined the extent to which participants could adapt their learning rate as a result of these changes, predicting that participants from two clinically relevant groups (25 who had recovered from AN and 25 who scored highly on an ED symptom questionnaire but had no history of a diagnosed ED) would show reduced learning rate adaptation compared to the 32 control participants. We also predicted that they would show reduced pupil dilation responses to volatility.

The study referred to throughout this chapter as 'The NAC study' or 'The N-acetylcysteine study' is discussed in Chapter 5, and included 23 healthy participants with elevated scores on an ED symptom questionnaire. This study followed a double-blind,

placebo-controlled, within-subject design, and we compared participant performance on tasks which measure compulsivity and impulsivity after taking placebo and after taking N-acetylcysteine, a glutathione precursor with some efficacy in other compulsive disorders.

## 2.2 PARTICIPANT GROUPS

The participant groups selected for investigation in this DPhil represent a balance between a number of competing goals. Firstly, the research done in this thesis should be generalisable: the conclusions reached should be applicable to as large a segment of the population as possible, so ideally the groups selected should be representative of the segment of the population being studied. Secondly, the conclusions should be as free as possible from confounds, or variables which could provide alternative explanations for the phenomena observed. Thirdly, it should be feasible to recruit a sufficient number of participants for the experiments to be adequately powered to test the hypotheses proposed.

### 2.2.1 Key challenges

Some of the confounds that are especially important in ED research are the effects of malnutrition or starvation on behaviour (exemplified nicely by a classic study (Keys et al., 1950)). These effects of starvation or malnutrition also dramatically affect the brain, with one of the clearest effects seen on brain volume (Roberto et al., 2011). However, these authors found that these effects reduce significantly after weight restoration. The desire not to have results affected by the confound of malnutrition is related to the general desire to measure 'trait' rather than 'state' effects of a psychiatric disorder: one wishes to record the changes that do not result from currently being in an unwell state, but the persistent differences in those individuals that differentiate them from those who do not develop that particular disorder. Trait abnormalities are therefore potential markers of

vulnerability to develop a particular disorder and a possible target for preventative strategies. For further discussion on this point, see (Kaye et al., 2011).

Another confound, which has been alluded to earlier in this thesis (Sections 1.2.3, 1.5.2 and 1.7.2) is the issue of comorbidity. There is an elevated level of comorbidity in those who have current EDs, which is not surprising given the arguments already proposed for using transdiagnostic factors in psychiatric research (Section 1.3). However, this does pose a problem to research in some respects, as outcomes from cognitive tasks or MRI paradigms are reported to be abnormal in several different psychiatric conditions. Ideally, one would wish to be sure that the effects uncovered by experimental studies are due to the construct of interest (whether that be EDs or compulsivity), rather than due to comorbid and co-occurring psychiatric phenomena such as depression.

Another important confound is the use of psychoactive medications in this population. Many of those with current EDs are prescribed medication, often antidepressants or antipsychotics (de Vos et al., 2014). However, psychoactive substances by definition alter neural and cognitive responses to events, rewards and tasks. This creates a difficulty in disentangling the effects of medication from the effects of true phenotypic differences in those with EDs.

### 2.2.2 General criteria

Across groups, we required that participants were:

- willing and able to give informed consent for participation in research activities,
- free from current psychiatric disorders which might affect the results of the study - determined using the Structured Clinical Interview for the DSM (SCID) (First et al., 1996, 2015),

- free from psychoactive medication (e.g. antidepressants),
- free from recent use of illicit drugs,
- smoking fewer than 5 cigarettes per day (if smokers),
- fluent English speakers,
- over 18.5kg/$m^2$ in body mass index (BMI) (i.e. a weight that is above the 'underweight' cut-off).

From this starting point, we then determined groups based on the competing goals above and the aims of the research studies.

### 2.2.3 High ED symptom group

This group aims to represent the proportion of the population who have elevated ED symptom levels without having a formal diagnosis of an ED. This group might be thought to experience an elevated risk of subsequent ED diagnosis, and could be assumed to display similar cognitions to those who meet full diagnostic criteria for an ED - based on the hypothesis that ED symptoms are somewhat on a continuum, and the existence of a group of individuals who might be described as 'subsyndromal' (Dancyger & Garfinkel, 1995; Treasure et al., 2015; Tylka & Subich, 1999).

We used the EAT-26 questionnaire to identify individuals who had higher levels of ED symptoms than the average individual in the population (Garner et al., 1979). There is evidence that the EAT-26 is an appropriate metric to use to measure the continuum of ED symptoms within the population (Mintz & O'Halloran, 2000).

#### *2.2.3.1 N-Acetyl Cysteine Study*

For the study discussed in Chapter 5 (which was chronologically prior to the other studies presented in this thesis), we selected participants who scored between 9 and 19 (possible range 0-78) on the EAT-26. This group of participants would be expected to

have higher ED symptoms than the average individual in the population, based on percentile data (Garner et al., 1982), but scored below the putative clinical cut-off of 20 (Garner et al., 1982). The requirement to score below the clinical cut-off was designed to ensure that the individuals studied were not current ED cases, thus avoiding the confounding factors detailed above (Section 2.1).

#### *2.2.3.2 Adaptive Learning Study*

In contrast, we selected participants who scored above 20 (the putative clinical cut-off) on the EAT-26 for this study. This difference to the NAC study was in response to the observation that those who were recruited with scores of 9-19 often did not present as very symptomatic based on clinical interviews. All participants were required to have a BMI of over 18.5kg/$m^2$, to avoid any effects of being underweight (a key confound in studies in this population, as discussed above in Section 2.2.1).

### 2.2.4 Recovered AN group

In line with the reasoning used by other groups studying EDs, one way to ensure the measurement of trait (i.e. phenotypic) rather than state variables is to study those who have recovered from EDs (Kaye et al., 2011).

A number of criteria were used to determine 'recovery' from AN. Firstly, we required that the participant self-identified as recovered for over one year, met criteria for former AN and did not meet criteria for a current ED on the SCID. Participants were asked to self-report their estimated date of recovery. Secondly, participants were required to have a BMI of over 18.5kg/$m^2$, which represents the cut-off between 'underweight' and 'healthy weight' categories. This was measured at the time of the study by a researcher. They were also required to have had a BMI of over 18.5kg/$m^2$ throughout the last year (self-report). We subsequently recognised two sub-groups of recovered AN.

#### *2.2.4.1 Fully recovered AN*

As in previous studies from our research group (Cowdrey et al., 2011; Godier, 2015), full psychological recovery was defined as scores lower than one standard deviation above the global mean on the EDE (Cooper & Fairburn, 1987), a structured clinical interview which assesses ED symptoms, or the EDE-Q (Fairburn & Beglin, 1994), which is the corresponding self-report questionnaire. These criteria are similar to those defined by other researchers (Bardone-Cone et al., 2010) in terms of their focus on both psychological and physical measurements.

#### *2.2.4.2 Normal weight, partial psychological recovery*

These participants are differentiated from those who are fully recovered by a score greater than one standard deviation above the global mean on the EDE or EDE-Q.

## 2.3 ETHICAL APPROVAL

All studies received ethical approval from the Central University Research Ethics Committee (CUREC) at the University of Oxford. Both the adaptive learning and the MRI study received ethical approval after a CUREC 2 submission, and the NAC study received ethical approval after a CUREC 3 submission, and was sponsored by the Clinical Trials and Research Governance (CTRG) body for the University. The relevant ethical approval numbers are detailed in each section.

## 2.4 SCREENING AND THE SCID

### 2.4.1 Informed Consent

All participants were sent a copy of the participant information sheet (PIS) by email before the first study visit, and then were given another copy to re-read upon arrival at the first study visit. They were asked if they had any queries, and then provided full informed

consent. They were free to withdraw at any time without giving a reason, and without penalty.

### 2.4.2 The SCID

As highlighted in Section 2.2.2, we required participants to be free from any psychiatric disorder which might affect the results of the study. This was determined using the SCID. There are versions of the SCID which correspond to different versions of the DSM. In this research, the clinician version of the DSM-IV was used in the NAC study, due to its availability and common use in the research group, and the research version of the DSM-5 was then obtained and used in both other studies, as the DSM 5 definitions of psychiatric disorders were used in this thesis. The SCID is a semi-structured interview which provides guidelines for making the main DSM diagnoses, and provides a systematic way for making these diagnoses. The SCID also allows the characterisation of individuals not only in terms of current psychiatric disorders, but in terms of former psychiatric disorders they may have suffered from. These interviews were used to ensure that participants did not have excluding disorders (current psychiatric diagnoses which might interfere with the results of the experiments) or histories (e.g. a former ED in those in a high ED symptom group).

### 2.4.3 Physical health

Physical health was also taken into consideration in these studies. Study advertisements asked for 'healthy' individuals to take part, and basic questions about health were asked to determine likely current and former physical health issues. These were taken into account during these studies, and those with significant physical health issues which were likely to impact the study results or pose a risk to participants' comfort or safety were excluded.

Due to the fact that the study visits often took several hours, we also excluded participants who smoked more than 5 cigarettes a day, to prevent discomfort to them or excessive disruptions to the study protocol.

### 2.4.4 BMI

BMI was calculated on the day of the study visit, or the first study visit if there were more than one. Participants were weighed and their height measured, and the formula

$$BMI = \frac{weight}{height^2} \qquad Eq.\ 1$$

was used to determine BMI, with weight in kg and height in metres.

## 2.5 MEASURES

A number of questionnaires and other measures were used in the experimental studies that make up this thesis. They were used for varying reasons: to screen participants and select those who meet the criteria for the experimental groups; to provide continuous measures of other symptoms relating to psychiatric disorders which might influence the study results, to be used as nuisance covariates in analysis; or to further characterise the compulsivity and ED symptoms of those selected to take part in the research studies.

### 2.5.1 EAT-26

One of the questionnaires that was used extensively throughout this body of research was the EAT-26, which is a reliable and criterion-valid shortened version of the EAT-40 (Garner et al., 1979, 1982). It was originally designed to index AN symptomatology before BN was a distinct entity in the DSM, but appears actually to measure general eating pathology, with those with AN, BN or other EDs reliably scoring above the putative clinical cut-off of 20 (range 0-78) (Mintz & O'Halloran, 2000).

### 2.5.2 EDE and Eating Disorder Examination - Questionnaire Version (EDE-Q)

Both the EDE and EDE-Q were used in this body of work. The EDE is a semi-structured clinical interview which is used to determine eating disorder symptoms. The EDE-Q is the questionnaire version. Both instruments have been found to be reliable and have good criterion validity (Berg et al., 2012; Luce & Crowther, 1999). They both have a number of subscales: dietary restraint, shape concern, weight concern, and eating concern (Cooper & Fairburn, 1987; Fairburn & Beglin, 1994; Fairburn & Cooper, 1993). These questionnaires were used to determine the extent of recovery in participants who had a former diagnosis of AN (see Section 2.2.4). Items are generally rated on a 0-6 Likert scale, and sub-scores and total scores are calculated by summing the number associated with their answer and dividing by the number of items. Thus the range for each sub-scale and the global score is 0-6. The cut-offs used in this thesis are the mean plus one standard deviation of the norms of the global score: corresponding to 1.737 on the EDE, and 2.767 on the EDE-Q (Fairburn & Beglin, 1994).

### 2.5.3 Clinical Impairment Assessment questionnaire (CIA)

This is a sixteen-item self-report questionnaire designed by the same group as the EDE and EDE-Q (above, Section 2.5.2). It assesses the level of clinical or psychosocial impairment resulting from the presence of ED symptoms, and focuses on the past 28 days (Bohn & Fairburn, 2008). It has been found to have high internal consistency, satisfactory test-retest reliability and is sensitive and specific (Bohn et al., 2008). The putative clinical cut-off which is used to predict ED case status was found to be 16 (range 0-48), with a sensitivity of 76% and a specificity of 86% (Bohn et al., 2008).

### 2.5.4 The Self-Starvation Scale (SSS)

The SSS was previously constructed by our group to measure self-report compulsive self-starvation, as related to food restriction. It has 17 items (score range 0-

96), and showed good reliability and criterion-related validity in an initial sample (Godier & Park, 2015a).

### 2.5.5 Beck Depression Inventory-II (BDI-II)

The BDI-II is a twenty-one item (score range 0-63) self-report questionnaire which indexes depressive symptoms, ranging from sleep to suicidal ideation and hopelessness (Beck et al., 1996). It is widely used, and has good psychometric properties (Dozois et al., 1998). Scores of 0-13 are thought to correspond to minimal depression, 14-19 to mild depression, 20-28 to moderate depression and 29-63 to severe depression.

### 2.5.6 Spielberger State-Trait Anxiety Inventory (STAI)

This self-report questionnaire comes in two parts, which can also be combined. They assess state (current, these items alone form the STAI-S) and trait (general/over time, these items alone form the STAI-T) levels of different symptoms which indicate anxiety. There are forty items altogether, with twenty in each part, and each item is scored on a 1-4 Likert scale. Scores therefore range from 20-80 (Spielberger, 1983). This inventory has satisfactory psychometric properties (Spielberger & Vagg, 1984).

### 2.5.7 Hospital Anxiety and Depression Scale (HADS)

This is a self-report questionnaire which measures both depression and anxiety symptoms. This was used for the NAC study out of concern that the BDI-II contains a considerable number of questions relating to somatic symptoms, which may be present in those who are following extreme diets or restricting their caloric intake. The HADS, on the other hand, was created to avoid a reliance on somatic symptoms that could relate to general ill-health such as fatigue. It has 14 items (7 for anxiety and 7 for depression, with a 0-3 scale, such that scores for anxiety and for depression can range from 0-21) and is both reliable and valid (Zigmond & Snaith, 1983). A putative clinical cut-off of 8/21 has

been proposed (Bjelland et al., 2002). There is precedent for using it to assess anxiety and depression symptoms in those with EDs (Bydlowski et al., 2005; Corcos et al., 2000; Gilbert & Meyer, 2005), and it has been validated in large community samples (Bocéréan & Dupret, 2014).

### 2.5.8 Hamilton Depression Rating Scale (HAM-D)

The version of this scale used in this thesis (Hedlund & Vieweg, 1979), entails that the participant is rated by a researcher on 21 items, scored on a Likert scale with varying numbers of options (range 0 to 54). A score of above 20 is thought to indicate moderate or severe depression symptoms. The last four questions give further information about the depression, but are not part of the scale. It is valid for distinguishing those with depression from those without (Fava et al., 1982).

### 2.5.9 Obsessive-Compulsive Inventory – Revised (OCI-R)

Related to the concern of this thesis with compulsivity, the OCI-R was employed in a number of the studies presented in this thesis. This is also a self-report questionnaire, which measures OCD symptoms. It contains 42 items, and scores can range from 0 to 72. It has good reliability and validity, and is suitable for screening those with OCD, with a suggested clinical cut-off of 21, which shows good sensitivity and specificity (Foa et al., 2002).

### 2.5.10 The Yale-Brown-Cornell Eating Disorder Scale Self-Report Questionnaire (YBC-EDS-SRQ)

This is a slightly longer self-report questionnaire which is based on a structured clinical interview known as the Yale-Brown-Cornell Eating Disorder Scale (Bellace et al., 2012; Mazure et al., 1994). This questionnaire contains both a checklist and then some subsequent questions which assess the impact of the phenomena recorded in the checklist

on the individual. It contains separate checklists for preoccupations (mental events which are repetitive and outside of the individual's control) and rituals (behavioural events that are accompanied by a sense of being 'driven'). This scale is useful in recording ED-specific preoccupations and rituals, both at the current time and the self-defined 'worst' month of the participant's ED history. For each of the sub-scores (preoccupations and rituals) the maximum score is 16; and there is a sub-score for each of these for 'current' and 'worst' periods of symptoms. Maximum 'total score' is 32, and there is no suggested clinical cut-off by the original authors, as it was intended to index severity of the ED, rather than identify EDs. It has high validity and reliability (Bellace et al., 2012; Mazure et al., 1994).

### 2.5.11 Eysenck Personality Questionnaire (EPQ)

The EPQ is a self-report questionnaire, which asks participants to select yes or no to 90 questions. It aims to measure key personality traits, such as psychoticism, neuroticism, extraversion and 'lie', which is a measure of the tendency of the participant to respond in a socially acceptable way to questions (Eysenck & Eysenck, 1975). Scores on the extraversion scale and the lie scale range from 0-21, scores on the neuroticism scale range from 0-23, and scores on the psychoticism scale range from 0-25. Scores on the extraversion, neuroticism and lie scales generally have acceptable reliability and validity, but the psychoticism scale has poor reliability, and modest validity (Caruso et al., 2001; Wilson & Doolabh, 1992).

### 2.5.12 National Adult Reading Test (NART)

The NART (Nelson & Willison, 1991) is a way to estimate intelligence of English-speaking individuals. It includes a number of words in British English which have irregular spellings, and is supposed to measure vocabulary rather than ability to apply pronunciation rules to unknown words. An equation (Eq. 2) exists to convert the number

of errors made on the NART into the predicted intelligence quotient (IQ) of the individual.

$$Estimated\ Full\ IQ = 127.7 - (0.826 * NARTerrors) \qquad Eq.\ 2$$

## 2.6 COGNITIVE TASKS

### 2.6.1 Wisconsin Card Sorting Task (WCST)

The WCST (Berg, 1948) is a task which measures executive function. In particular, it measures set-shifting performance. Participants are presented with cards, which have a certain number of shapes displayed in a certain colour on them. They must sort (using trial and error) the card they see into one of four piles, each of which displays a different combination of colour, number and shape. The 'correct' sorting dimension may at first be by shape: thus all cards which show a square should be sorted into the pile which shows a card with a square. The 'correct' sorting dimension is learnt by trial and error – participants receive 'correct' and 'incorrect' feedback while sorting. The 'correct' dimension will shift at random intervals, and the participant must then use trial and error to learn the new 'correct' dimension with which to sort the shapes. Set-shifting performance on this task (indexed by number of perseverative errors, defined as errors caused by sorting cards by the former 'correct' dimension after a change in 'correct' dimension) has been shown to be impaired in AN and BN (Tchanturia et al., 2012), and this task is one of the set-shifting tasks with a high pooled standardized mean difference in AN (Roberts et al., 2007). The version we used is from the Psychology Experiment Building Language test battery (Piper et al., 2012).

### 2.6.2 Affective Go/No-go task (AGN)

The AGN task, used as part of the Cambridge Neuropsychological Test Automated Battery (CANTAB), requires participants to press the touch screen as rapidly as possible

whenever words of a certain valence are presented. The words presented are either positive or negative, and the 'rule' for response is indicated at the start of each block. Words are presented at the centre of the screen, and each word is displayed for 300ms. The inter-trial interval is 900ms. The blocks were in the following order: Positive, Positive, Negative, Negative, Positive, Positive, Negative, Negative, Positive, Positive. The shifting cost is the slowing of responses when the 'rule' changes or shifts from selecting positive to negative words, or vice versa. Affective response bias is the difference in response latency for correct responses to positively vs. negatively valenced words.

## 2.7 MRI: BASIC PRINCIPLES

MRI is a medical imaging technique. It relies on the fact that sub-atomic particles have a quantum-mechanical property known as 'spin'. Charged nuclei, such as protons, have a non-zero spin, and this creates a magnetic moment. The human body is made up to a great extent of water molecules, which contain two protons, or hydrogen nuclei. The main magnetic field of the scanner (abbreviated as $B_0$), which is generated by superconducting electromagnets, causes the magnetic moments of these protons to align with the direction of the field, either parallel to $B_0$ or anti-parallel (opposing the direction of $B_0$). Most commonly, the magnetic moments align with $B_0$, as this is a lower-energy state. However, the number that align anti-parallel depends on the strength of $B_0$. Whilst in an external magnetic field such as $B_0$, and aligned either parallel or antiparallel with $B_0$, the group of protons rotates (precession) around an axis along the direction of the field. The speed of precession is measured as the Larmor frequency (MHz), and determined by the Larmor equation:

$$w_0 = \gamma B_0 \qquad Eq.\ 3$$

where $\gamma$ is a constant for a particular type of nucleus (e.g. hydrogen) known as the gyromagnetic ratio. The precession of the protons parallel to $B_0$ leads to a net magnetisation along the direction of $B_0$, as all other magnetisation directions are cancelled out. This sum magnetisation is known as longitudinal magnetisation.

In order to generate detectable MR signal, one can excite particles out of longitudinal alignment using a pulse which has the same frequency as the Larmor frequency (or resonant frequency) of the particles. For protons, this is in the radio frequency (RF) range. Thus RF pulses are applied, which excites some of the protons out of parallel alignment, as the RF field transfers energy to them. This causes them to precess. Some protons move to the higher energy state of antiparallel to $B_0$. This results in some of the magnetisation parallel to $B_0$ being cancelled out by the antiparallel magnetisation, so longitudinal magnetisation decreases. The RF pulse also causes the protons to move in phase, rather than in random directions, resulting in transverse magnetisation – which is at a 90° angle to the main $B_0$ field. The precessing magnetisation can be detected with a RF receiver coil.

Subsequently, as the RF pulse ends, these protons both fall out of phase and also return to being in parallel with the $B_0$ field, which is known as relaxation. This can be described using a number of constants, which denote the rate of the exponential relaxation process. The T2 relaxation constant (where T equals time) indicates the rate at which protons lose phase coherence as a result of spin-spin interactions within the tissues, and the T2* relaxation constant indicates the rate at which protons lose phase coherence due to inhomogeneity within the local magnetic field. The T1 relaxation constant indicates the rate of longitudinal relaxation (which is when the longitudinal magnetisation increases to

its original level). An MR image where the difference in signal intensity between tissues is mainly due to difference in tissue T1 relaxation time is known as a T1-weighted image.

To differentiate between protons at different locations, spatially varying magnetic fields known as gradient fields are produced by gradient coils. At each point, the gradient field is parallel to $B_0$, but induces spatial variations in the magnetisation. The spins at each position are therefore at different frequencies, and the RF coils are able to detect these. Additional gradient fields are added in the x, y and z direction (where z is parallel to $B_0$).

The time between the centre of the excitation RF pulse and the centre of the echo is known as the echo time (TE). The repetition time (TR) is the length of time between corresponding points during a repeating sequence of pulses and echoes.

### 2.7.1 Structural MRI

A structural MRI image is a T1 image, with a short TR and short TE. This creates an image with grey matter (GM) appearing as dark grey, and white matter (WM) appearing as light, with cerebrospinal fluid (CSF) appearing black.

### 2.7.2 Functional MRI

When neural activity increases, so does the demand for oxygen. The response is an increase in blood flow to regions with this increased activity. Blood contains haemoglobin, which is diamagnetic when oxygenated and paramagnetic when deoxygenated, leading to differences in the MR signal of blood depending on the degree of oxygenation. These differences can be used to detect the increased amount of oxygenated blood, which is produced due to the increase in neural activity. This is known as blood-oxygen-level dependent imaging (BOLD).

### 2.7.3 MRS

MRS relies on the fact that within molecules, precessing nuclei experience different magnetic effects based on the environment they are in, due to shielding by electrons. This effect is known as chemical shielding, and allows the discrimination between different protons in different molecular environments. In this way MRS can be employed to determine the relative concentrations of a variety of biochemicals or 'metabolites' in the brain. Proton ($^1$H) MRS can reliably detect amino acids such as glutamate, which have been linked to the pathophysiology of compulsive disorders.

## 2.8 COMPUTATIONAL MODELLING

Computational modelling is a growing area of neuroscience research, which is increasingly being applied to psychiatric disorders. This is one of the areas that falls under the emerging field of computational psychiatry (Montague et al., 2012), which translates the ideas and techniques of computational neuroscience into theories about the aetiology and maintenance of psychiatric disorders.

Computational modelling attempts to use mathematical expressions to provide descriptions of certain processes, such as decision-making or learning. A number of 'models', (or mathematically-described schema) for the performance of particular tasks can be developed, and subsequently one can 'fit' the models to individual measures from participants. Free parameters of a model (i.e. the coefficients which fine-tune the behaviour of the model) can be estimated, and then the 'goodness of fit' of the model to each participant (and thus the group as a whole) can be estimated. These analyses allow us to formally answer a number of different questions about psychiatric populations:

- Are the governing equations for a particular process (say, deciding between two options) the same for different psychiatric populations? This is known as Model Selection or Model Comparison.
- Are the fitted parameters the same between psychiatric and control populations, or between different psychiatric groups?

### 2.8.1 Reinforcement Learning

One of the main fields that has been translated from computational neuroscience into psychiatric research is that of reinforcement learning. The biological validity of the use of reinforcement learning equations in human neuroscience results from the finding that the firing of dopamine neurons in the midbrain of animals resembles the 'prediction error' that is computed by reinforcement learning models (Schultz et al., 1997). 'Prediction error' can be defined as the difference between the outcome actually received and the outcome that the model predicted.

The fitting of reinforcement learning models to behaviour often involves modelling the choices made on each trial by the participant. The first part of this process is defined as the 'learning' model, which is one of the various algorithms by which an active agent learns. This step translates the outcomes observed by the participant into estimates of the 'values' of the options available to them.

One of the ways in which we can learn more about our environment is acting, which entails active probabilistic sampling between available options. This active sampling is modelled using 'selector' or 'choice' models, which translate the option values into the probability that each of the options is chosen by the participant. The simplest 'selector' model would just be a step function, whereby the agent chooses the option with the highest value. However, agents/humans are rarely this deterministic, and often their

choice behaviour can be described by sigmoid functions or similar (Stott, 2006). This type of function forms the second 'step' in modelling participant choice behaviour, and converts the values obtained after the reinforcement learning model is applied into choice probabilities.

Various different methods can be used to fit the model to the participant's choice data, but typically this involves computing the posterior probability of the choices the participant made, given the sequence of trials they were presented with and a set of possible parameter values. This is expressed using the following:

$$\Pi(\mathrm{P}(choice_{t=1:n})) \qquad Eq.\ 4$$

which essentially is the product of the probabilities of the choices the participant made during the sequence of trials.

In order to find the most likely estimate of the parameters used by the individual, one needs to identify the combination of parameters which maximises the posterior probability of the sequence of choices, also known as model likelihood. In this thesis, this has been achieved by:

1. Evaluating the model likelihood for each parameter combination,
2. Normalising these likelihoods by their total sum, such that it becomes a probability distribution with integrals summing up to 1,
3. Marginalise out the probability distribution for each parameter,
4. Integrate these distributions to get the weighted mean parameter value.

Following these four steps in sequence results in a set of estimated parameters which maximise the likelihood of the sequence of choices made by the participants. These parameters can then be compared between groups of participants, allowing one to make

inferences about how these groups might differ in learning processes and decision-making. If multiple models are used, the likelihood of each model given the 'best fit' parameters can be contrasted to estimate the model that best explains the choice behaviour of the participant cohort.

# 3 MULTIMODAL MRI INVESTIGATION INTO COMPULSIVITY IN THOSE WHO HAVE RECOVERED FROM ANOREXIA NERVOSA

## 3.1 INTRODUCTION

Whilst there has been extensive research into the neural correlates of compulsivity in the context of disorders such as OCD (see Section 1.5.4 and Chamberlain et al., 2008; Vaghi et al., 2016; van den Heuvel et al., 2016), it is important to see to what extent this can be generalised to the neural correlates of compulsivity in EDs. The aim of this study is to use multimodal imaging to investigate these neural correlates. The imaging modalities used in this study were structural MRI, task-based fMRI, resting-state functional imaging, and MRS, and we aimed to examine frontostriatal activity, connectivity and glutamate levels in those who had recovered from AN, and the association of these neural measures with compulsivity. The use of multimodal imaging allows us to determine whether these differences are observed using a task which probes set-shifting and reversal learning, which are key aspects of compulsivity (Fineberg et al., 2014); whether these differences are observed in functional brain connectivity patterns at rest; and whether there is any difference in the levels of glutamate (reported at 3 Tesla (3T) as a composite with glutamine known as Glx), which have sometimes been found to be altered in the anterior cingulate cortex (ACC) of OCD patients (Brennan et al., 2013; Gnanavel et al., 2013), and in those currently suffering from AN (Godlewska et al., 2017), and has been linked to compulsivity (Naaijen et al., 2015).

We studied a group of participants who had recovered from AN to try to identify any 'trait' differences in these measures, rather than examining those who are currently

underweight, a state which may not only affect the structure of the brain (Roberto et al., 2011), but also reward processing (Zink & Weinberger, 2010). There is also evidence that structural differences in participants with current EDs may affect connectivity estimates (Scaife et al., 2017). The use of a group who had recovered from AN also allowed us to recruit a group who are medication-free, as it is unclear to what extent psychotropic medications affect MRI measures (Haynos et al., 2018).

### 3.1.1 Structural MRI

There have been a number of studies of structural differences between those with AN and those who have recovered, with many studies reporting loss of grey matter volume in AN patients (Titova et al., 2013; Treasure & Friederich, 2007). It is often found that these losses are remediated after weight restoration (Mainz et al., 2012), such that there is no difference between those with EDs and control participants after 1 year of recovery (Wagner et al., 2006). This indicates that these structural changes are 'state' factors of the illness, either linked to nutritional status/malnourishment or to other factors relating to acute illness.

There are some exceptions to this, however, and it has been reported that in people with current and recovered AN there is an increase in volume of the medial orbitofrontal cortex (gyrus rectus) along with the right antero-ventral insula, with reductions in volume in the dorsal striatum (Frank et al., 2013a). Residual differences in volume in the precuneus have also been found when AN was accompanied by a very low BMI (Joos et al., 2011). There is some suggestion that the alterations that persist after recovery are related to reward circuitry (Frank et al., 2013b). Reward circuitry alterations have been implicated in addiction (Koob, 2001) and in OCD (Figee et al., 2011), and these potential differences compared to those who have never had an ED may either reflect or cause ongoing disrupted reward functioning and compulsivity.

Furthermore, it is important when performing any fMRI study to obtain a good estimate of whether the groups display structural brain differences which might partially explain or invalidate any functional findings, as any group differences in functional connectivity could be directly caused by differences in the neuroanatomy of that group.

We predicted that we would not find a structural difference in the gray-matter volume of those who have recovered from AN compared to control participants, as the literature seems to generally suggest that structural differences resolve after recovery.

### 3.1.2 Task-based fMRI

Using tasks in conjunction with BOLD fMRI allows researchers to probe the brain activity elicited by those tasks, where the 'clusters' of activation are, and whether they might differ between groups. EDs have been investigated previously using this method. One key finding includes differences in reward circuitry (Fladung et al., 2010), notably high ventral striatal activity when those with AN were looking at images of underweight women.

It is also possible to directly examine compulsive behaviours in those with AN using task fMRI. Two aspects of compulsive behaviour that could be studied are set-shifting - which has been suggested to be a trait factor in AN (Tchanturia et al., 2003; Tchanturia, Anderluh, et al., 2004) - and reversal learning (Fineberg et al., 2014). One study that has used a set-shifting task with fMRI in an AN group found hypoactivation in the ventral anterior cingulate-striato-thalamic loop, which is understood to be involved in reward and motivated behaviour (Kelley, 2004). This group also showed greater activation in frontoparietal circuitry during this task, perhaps reflecting increased cognitive control (Zastrow et al., 2009).

However, very few studies have investigated compulsivity using task fMRI in a group which is unlikely to be confounded by current low weight and malnutrition, such as those who have recovered from AN. Those who have recovered from AN are thought to be a population suitable for investigating trait vulnerabilities in AN (Kaye et al., 2011).

An MRI study in OCD identified hypoactivation in OCD patients and their first-degree relatives compared to controls in the lateral orbitofrontal cortex, lateral prefrontal cortex and parietal cortex during task fMRI of set-shifting and reversal learning (Chamberlain et al., 2008). The lateral OFC is thought to be responsible for maintaining the values of options, facilitating switching behaviour. We used the same task as the authors in this study to examine reversal learning and set-shifting in those who have recovered from AN, and predict that there would be reduced OFC activity compared to controls in those who have recovered from AN in both reversal learning and set-shifting conditions. Our primary outcome measure was OFC activity during the appropriate reversal learning contrast.

### 3.1.3 Resting-state functional connectivity (RSFC)

Resting-state analyses allow inferences to be made about functional connectivity within the brain. This technique is referred to as resting-state functional connectivity. During a short period of BOLD fMRI scanning (often as little as 5-10 minutes), participants lie in the scanner 'at rest', without performing a task or fixating on any particular stimuli. Low frequency (<0.1Hz) spontaneous oscillations are observed to be correlated across different regional nodes, suggesting that these nodes are functionally connected to one another.

Whilst it is important to ascertain functional differences in neural response to stimuli, this task-based approach has a number of limitations which make a

complementary resting-state approach useful. Firstly, the use of disorder-related stimuli (e.g. chocolate, Cowdrey et al., 2011) might lead to results that are specific to a particular disorder, or particular symptoms within a disorder, rather than results that might be extended in future work across transdiagnostic categories. Secondly, they may mask differences in groups or create artificial distinctions between groups if the two groups differ on how they relate to the stimuli, for example if participants who have recovered from AN are less sensitive to monetary wins.

RSFC has been used previously in OCD in a number of studies (e.g. Göttlich et al., 2014; Stern et al., 2012). One study in particular used RSFC to further elaborate the hypothesis that dysregulated fronto-striatal connectivity may underpin compulsive behaviours (Vaghi et al., 2016). Vaghi et al. (2016) found that OCD patients showed decreased connectivity between the dorsal caudate and putamen to frontal and parietal regions, but increased ventral striatal-frontal connectivity. They also found that there was a negative correlation between dorsal caudate connectivity with the ventrolateral prefrontal cortex and the number of errors made on the extra-dimensional shifting aspect of a cognitive flexibility task, such that those with the greatest error rate had the lowest connectivity. This suggests that this caudate connectivity might have an important role in cognitive flexibility.

Previous studies of RSFC in EDs have indicated that fronto-striatal circuitry may also be disrupted in AN, though with lack of consistency as to how this circuitry is disrupted (O'Hara et al., 2015). Some observations include increased fronto-accumbal connectivity (Cha et al., 2016), increased connectivity between the default mode network (DMN) and frontal regions (Cowdrey et al., 2014), decreased fronto-striatal activation during cognitive flexibility tasks (Friederich et al., 2013), and lower fronto-striatal connectivity from both ventral and dorsal regions of the striatum (Haynos et al., 2018).

Fronto-striatal regions in general have been found to be affected in AN (Cowdrey et al., 2011; Fladung et al., 2010; Friederich et al., 2012; Zastrow et al., 2009), BN (Marsh et al., 2009; Schäfer et al., 2010; Wagner et al., 2010) and BED (Balodis et al., 2013, 2014; Kessler et al., 2016; Schäfer et al., 2010). Interestingly, reduced fronto-striatal connectivity in AN-BP or BN was associated with response to dorsomedial repetitive transcranial magnetic stimulation, with connectivity between the dorsal ACC to the ventral striatum and anterior insula increasing during successful treatment (Dunlop et al., 2015); indicating this circuitry might be relevant for treatment response and recovery.

Importantly, differences in ventral fronto-striatal connectivity (i.e. between the nucleus accumbens, ventral caudate, ACC, and other frontal regions) are thought to reflect impaired reward and motivational processing, whereas differences in dorsal fronto-striatal connectivity (e.g. the dorsal caudate and putamen to frontal (executive) and motor regions) are thought to reflect an increased tendency to form habits (Haynos et al., 2018). One suggestion has been that the neural differences seen in AN may transition from ventral to dorsal regions of the frontostriatal circuitry, as the disorder progresses through impulsivity and reward-seeking weight-loss behaviour to rigid, compulsive behaviour (Godier & Park, 2014). Alternatively, anxiety-reducing restricting behaviour may gain reward value due to effects of starvation and social reward, resulting in reward circuitry differences later in the course of AN (Zink & Weinberger, 2010).

In the present investigation, we sought to determine whether the fronto-striatal dysregulation seen by Vaghi et al. in OCD patients was also a feature of functional connectivity in our group of individuals who had recovered from AN, and whether this connectivity was positively/negatively correlated with perseverative errors on the WCST as an alternative measure of cognitive inflexibility to the set-shifting paradigm used by

Vaghi et al. We predicted that similar dysregulation would be observed, with decreased dorsal-striatal-frontal connectivity, and increased ventral-striatal-frontal connectivity.

We obtained resting state data using a contemporary multi-echo echo-planar imaging (EPI) data acquisition. This aims to counteract the fact that micro-movements (<1mm) during resting-state acquisition are rarely fully corrected for in analysis, even when motion-correction pre-processing techniques are employed (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012). Importantly for this study, psychiatric groups may display greater head motion, which can lead to biased estimates of time series correlation (Kundu et al., 2013). Furthermore, typical pre-processing methods can alter the degrees of freedom for each individual in a poorly controlled way, and many of the steps are operator-dependent, which results in a certain degree of analytical flexibility and inconsistency between studies using these techniques.

Therefore, this study employed a unified protocol for both multi-echo acquisition, pre-processing and independent component analysis (ICA). The basic principle of this protocol is that components derived from an ICA which scale linearly with echo time correspond to T2* BOLD signal, whereas the components that do not are generally artefactual. The independent components which do not display echo-time-dependence are removed, and components whose signal change do display echo-time-dependence are accepted, and taken forward into group analysis (Kundu et al., 2013).

### 3.1.4 MRS

MRS data was collected in the present investigation with the aim of replicating a pilot finding in a sample of those acutely unwell with AN, which indicated that they had lower levels of glutamate across the three brain voxels studied (ACC, OCC and putamen) compared to control participants (Godlewska et al., 2017), and determining how the MRS

detectable profile of alterations in AN compares with other compulsive disorders. Understanding brain biochemistry in those with AN and those who have recovered from it may contribute to the successful development of pharmacological treatments for this disorder.

MRS data were collected from the ACC, as this voxel displayed the largest difference between patients and controls in glutamate (higher than the OCC and putamen) in the investigation of Godlewska et al. (2017), and it is part of the cortico-striatal circuit which has widely been reported to be disrupted in compulsive disorders such as OCD (Brennan et al., 2013; Vaghi et al., 2016, and see Table 2).

The reduction in glutamate reported in this study (Godlewska et al., 2017) may correspond to the reduction reported in Glx in the ACC in OCD patients compared to controls in two of eight studies reported in a review of MRS in OCD (Brennan et al., 2013), and the reduction of Glx in in the dorsal ACC in opiate addicted individuals compared to controls (Yücel et al., 2007). In contrast, other work has shown an increase in Glx in the ACC in OCD patients compared to their first-degree relatives, who themselves had higher Glx in the ACC compared to controls (Gnanavel et al., 2013). Greater levels of Glx have also been reported in the OFC in OCD patients compared to controls (Whiteside et al., 2006). A review of MRS in compulsivity and impulsivity suggested that Glx may be increased in the ACC in paediatric patients with ADHD and autism spectrum disorders compared to controls, but decreased in the ACC in adult patients with these conditions compared to controls (Naaijen et al., 2015). This age-dependent effect may be due to developmental changes in fronto-striatal glutamatergic circuitry.

We report the composite Glx metabolite here, due to concerns about the ability of 3T MRS to resolve glutamate and glutamine reliably (Stephenson, 2011). We predicted a reduction in Glx levels in the ACC in those who have recovered from AN.

## 3.2 METHODS

### 3.2.1 Ethical approval

The ethical approval reference for this study is R47959.

### 3.2.2 Participants

Based on the effect size ($d$ = 1.25) of the difference in OFC activation during the reversal learning contrast for OCD patients compared to controls reported in a previous study using the same in-scanner task (Chamberlain et al., 2008), we calculated that fifteen participants in each group would allow us to have a power of 0.95 to detect a difference between groups (based on an independent samples t-test). Recruiting twenty participants would allow us to detect a lower effect size ($d$ = 1.06). Thus, twenty participants who had recovered from AN (RA) and twenty control participants (HC) were recruited for this study.

The general inclusion and exclusion criteria for the present investigation are shown in Table 3.

*Table 3: General inclusion and exclusion criteria for the multimodal MRI study.*

| Inclusion criteria | Exclusion criteria |
|---|---|
| Participant is willing and able to give informed consent for participation in the study | Participant has a current diagnosis of a psychiatric disorder which, in the investigator's opinion, could impact study results (e.g. significant depression, anxiety, OCD) |
| Participant is female | Participant is currently taking any psychotropic medication |

| Inclusion criteria | Exclusion criteria |
|---|---|
| Participant is between the age of 18 and 40 | Participant has eyesight problems which would prohibit them from seeing the screen on which the task is displayed in the scanner |
| Participant has a BMI of over 18.5kg/$m^2$, which participant self-reports has been the case for the last year | Participant regularly smokes over 5 cigarettes per day |
| Participant is a fluent English speaker | Participant has recently used illicit drugs |
| Participant scores below one standard deviation above the global mean scores for young women on the EDE, which corresponds to a score below 1.737 (Fairburn & Beglin, 1994). | Participant's alcohol intake indicates alcohol abuse, or participant is unwilling to refrain from drinking alcohol the evening before the study visit |
| | Participant has any contraindications to MRI scanning (including claustrophobia) |
| | Participant is pregnant or breast-feeding |

*The inclusion and exclusion criteria which applied to all participants in the MRI investigation into compulsivity in those who have recovered from AN). All participants were required to meet the inclusion criteria and not meet the exclusion criteria. Some extra criteria were used to determine group membership.*

In addition, those in the RA group had to have a past diagnosis of AN (defined by DSM-5 criteria, and confirmed using the SCID-5-RV). The definition of 'recovery' for the purpose of this study is a score of below 1.737 on the EDE, a BMI of over 18.5kg/$m^2$ throughout the last year, and no current DSM-5 ED diagnosis.

### 3.2.3 Study procedures

#### *3.2.3.1 Pre-screening*

Participants were pre-screened online using the EDE-Q (see Section 2.5.2). Participants scoring below one standard deviation above the mean on the global scores (corresponding to a score of 2.767 on the EDE-Q) were invited to attend a screening visit.

#### *3.2.3.2 Screening*

The screening visit lasted 2.5 hours, and included a full explanation of the study for the provision of informed consent. Participants were asked to give their date of birth, and

their height and weight were measured and recorded. Subsequently, participants provided a summary of their medical and psychiatric history, including their lowest BMI and date of recovery if in the RA group. Three structured clinical interviews were performed: the SCID-5-RV was used to assess whether the participant had any current psychiatric diagnosis, the EDE was used to assess ED symptomatology (note that even if their scores were below 2.767 on the EDE-Q, which was used as a tool for pre-screening, their scores had to be below 1.737 on the full EDE interview), and the HAM-D was used to assess current depression symptoms. The participants also completed self-report questionnaire measures, including the STAI-T, EPQ, OCI-R and YBC-EDS-SRQ, to provide measures of relevant psychiatric symptoms (see Section 2.5 for more detail on these measures). Participants also completed the NART in order that their IQ could be estimated, and they were assessed for safety to undergo an MRI scan. Finally, participants completed two cognitive tasks: the WCST and AGN tasks (see Section 2.6), and were trained on the set-shifting task that they would perform in the scanner. This training involved them performing the task until such time as they felt comfortable with the task and had successfully completed a block following a reversal, and a block following a change in the stimulus set ('set change').

#### *3.2.3.3 Study visit*

The study visit lasted approximately 1.5 hours, with 1 hour of this being the MRI scan. Initially, the MRI safety screening was completed with the radiographer, and then the participant completed the BDI-II and STAI-S (Section 2.5). The scan was then performed, which included a structural T1-weighted scan, the resting-state fMRI scan, two runs of the task with concurrent fMRI scanning, and an MRS scan.

### 3.2.4 Scanner

Scanning was performed on a 3T Siemens PRISMA scanner (Siemens, Erlangen, Germany) equipped with a 32 channel transmit receive Siemens head coil.

### 3.2.5 Atlases and coordinates

We report all coordinates in 'Left-Right, Posterior-Anterior, Inferior-Superior' (LPI) order (used in MRI software such as FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and SPM (Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/spm/)) unless stated otherwise. To identify the regions of peak activation, we used the FSL command-line tool 'atlasquery', with the 'Harvard-Oxford Cortical Structural Atlas' for cortical coordinates, and the 'Harvard-Oxford Subcortical Structural Atlas' for subcortical coordinates. We also used the 'MNI Structural Atlas', where MNI stands for 'Montreal Neurological Institute', to confirm cerebellar locations.

Coordinates of peak activation or peak connectivity are reported rather than centre of mass coordinates in all cases.

The 'left' of the brain is displayed on the right of the image unless otherwise stated.

### 3.2.6 In-scanner behavioural task

The task used in the scanner is a type of attentional switching task, which requires participants to work out by trial and error which object is the target from a set of stimuli (Chamberlain et al., 2008; Hampshire & Owen, 2006). As this task distinguishes between intra- and extra- dimensional set-shifts, it is henceforth referred to as the Intra-Dimensional Extra-Dimensional task (IDED task). The set of stimuli are two faces and two buildings, with a face overlaid on each building, with one compound image presented on each side of the screen. An example screen is shown below (Figure 1).

*Figure 1: An example screen during the IDED task.*



*This screen shows the compound stimuli presented on the left and right of the screen to participants during the in-scanner set-shifting task.*

On each trial, participants indicated which side of the screen they believed the target was on, using two buttons from a button box. After that first trial, the compounds swap, such that the face stimuli are now superimposed on different building stimuli. After the participant responds to the side of the screen they believe the target is on for this second trial, the stimulus they were actually responding to can be uniquely identified, and they therefore receive feedback (thus, we can consider 'pairs' of trials as a unit). This feedback is presented on the screen for 0.6 seconds, indicating whether the object they had chosen was the target or not ('CORRECT' or 'INCORRECT').

An intra-dimensional shift (IDS) is defined as the participant choosing a stimulus on one pair of trials and then choosing the other stimulus from that dimension on the next pair (e.g. house A to house B). An extra-dimensional shift (EDS) is defined as the participant choosing a stimulus from the other dimension on the second pair of trials compared to the first (e.g. house A to face A).

After six trials (or three pairs of trials) of selecting the correct stimulus in a row, one of two things happens. Either the stimulus set changes (set change (SH), resulting in two new faces and two new houses), or there is a reversal learning event (RV), in which case the reward contingency changes (i.e. a different shape of the initial four is now 'correct'). After a reversal the participant would typically respond incorrectly for a pair of trials (as they do not know that the contingency has altered), and then must inhibit their responses to the recently rewarded stimulus whilst attempting to identify the 'newly correct' stimulus.

The behavioural performance of participants on this task was analysed using accuracy and reaction time. The pre-training of participants on this task was designed to ensure that the behavioural performance of the two groups was matched.

We calculated participants' accuracy for each type of event: intra-dimensional set changes, extra-dimensional set changes, intra-dimensional reversals (i.e. the new 'correct' shape was from the same dimension) and extra-dimensional reversals. The accuracy was entered into a repeated-measures analysis of variance (ANOVA), with between-subject variable of group membership, and within-subject variables of reversal (2 levels, reversal or set change) and the type of shift (intra- or extra- dimensional – note that this is distinct from when participants simply shift attention, thus not the same as the EDS and IDS conditions).

For reaction time, we calculated participants' mean reaction time (in seconds) for different trial-types for each run of the task. The trial-types for this analysis are IDS events (when the participant shifted their attention to another stimulus from the same 'dimension'), EDS events, RV events, SH events, and reaction time for non-shift events once participants have received 'correct' feedback (CN events). These reaction times were

analysed in a repeated-measures ANOVA, with the type of event as a within-subjects variable, and group as a between-subjects variable.

Greenhouse Geisser corrected values were used where the assumption of sphericity was violated.

### 3.2.7 Outside of scanner behavioural task analysis

The WCST and AGN were used in this study. These tasks are described in Section 2.6. In summary, the WCST was used to index poor set shifting performance, which is thought to imply cognitive inflexibility. The outcome measure used from this task was perseverative errors, which is the number of errors a participant makes to the previously 'correct' category after the 'rule' for card sorting has changed. The AGN can give a measure of shifting difficulty, but also a measure of affective response bias. Affective response bias can be measured as the latency to respond correctly to negative words (by pressing the touch-screen button) subtracted from the latency to respond correctly to positive words. For both of these tasks, trials were removed from further analysis if the reaction time was greater than the mean for that participant plus 3 standard deviations. Performance between groups on these measures was analysed using Welch's t-test (assuming unequal variance).

### 3.2.8 Structural MRI

#### *3.2.8.1 Acquisition*

The structural images were acquired using a T1 magnetization prepared rapid gradient echo (MPRAGE) sequence with the following acquisition parameters: TR 1900ms; TE 3.97ms; inversion time (TI) 904ms; flip angle 8°; field of view (FOV) 174*192mm; grid size 174*192mm; voxel size 1x1x1mm$^3$; 192 slices; 0.5mm inter-slice gap.

#### *3.2.8.2 Analysis*

Structural data was analysed with FSL-VBM (FSL's Voxel-Based Morphometry toolbox; Douaud et al., 2007; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised voxel based-morphometry (VBM) protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and grey matter-segmented before being registered to the MNI ICBM152 standard space using non-linear registration (Andersson et al., 2007a). The parameters used in this registration are the defaults distributed with FSL as found in the configuration file 'GM_2_MNI152GM_2mm.cnf'. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3mm. Finally, a voxel-wise general linear model (GLM) was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space. We used threshold-free cluster enhancement, which is a method for finding clusters within data without having to define clusters in a binary way (Smith & Nichols, 2009).

### 3.2.9 Task-based fMRI

#### *3.2.9.1 MRI Acquisition*

The IDED task was performed in two runs. Separate EPI T2* weighted images were obtained for each of these runs. The acquisition parameters were as follows: TR 1570ms; TE 30ms; flip angle 70°; multi-band acceleration factor 3; Parallel Acquisition Techniques (PAT) factor 2 (generalised autocalibrating partial parallel acquisition (GRAPPA)); FOV 216*216mm; grid size 108*108mm; voxel size 2*2*2mm; 72 slices;

no inter-slice gap. Slices were acquired using an inter-leaved pattern. The number of volumes acquired depended on the time taken for participants to respond (mean number of volumes 388), and there was a 20s count-down before the task began.

Field maps were acquired using a dual echo 2D gradient echo sequence with acquisition parameters as follows: TR 551ms; TE 4.92ms and 7.38ms; and the same spatial resolution as the EPI sequence.

#### *3.2.9.2 MRI Analysis*

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL. B0 unwarping was carried out using BBR (boundary based registration), which also performs simultaneous registration to the structural image (Greve & Fischl, 2009; Jenkinson, 2003, 2004). Registration to high resolution structural and/or standard space images was carried out using FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson & Smith, 2001; Jenkinson et al., 2002). Registration from high resolution structural to standard space was then further refined using FMRIB's Non-linear Registration Tool (FNIRT; Andersson et al., 2007b, 2007a). This used the default parameters found in the configuration file distributed with FSL, named 'T1_2_MNI152_2mm.cnf'. The following pre-statistics processing was applied; motion correction using the MCFLIRT toolbox (Motion Correction using FMRIB's Linear Registration Tool; Jenkinson et al., 2002); non-brain removal using FMRIB's Brain Extraction Tool (BET; Smith, 2002); spatial smoothing using a Gaussian kernel of full width at half maximum (FWHM) 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering using a cutoff of 90s (Gaussian-weighted least-squares straight line fitting, with sigma = 45.0s). Time-series statistical analysis was carried out using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich et al., 2001). Z (Gaussianised T/F) statistic

images were thresholded non-parametrically using clusters determined by Z > 3.1 (or 2.3 if stated in results) and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001).

Three levels of FEAT analysis were used. The first level of FEAT analysis was run individually for each run of the IDED task for each participant. The explanatory variables (EVs) examined in the general linear model were extra-dimensional shift, intra-dimensional shift, set changes, reversal events, correct and incorrect feedback during both the search phase and the phase of the task where they had previously received a correct response, and non-shifting events during both phases of the task. The onsets used for each of these EVs were the times that the stimulus was presented on the screen. The time periods modelled by each EV are defined as follows. Feedback EVs (for correct or incorrect responses, during the search phase and the phase during which they 'knew' the correct response) were modelled from the onset of the stimuli during the second trial of a pair of trials (i.e. the one for which they would receive feedback) until the end of the feedback was presented on the screen. All other EVs were modelled during the first 'trial' of each pair, i.e. when participants made their initial response but received no feedback, from the onset of the relevant stimuli until they were removed from the screen. The relevant pairs for extra-dimensional shifts were defined as a pair of trials on which the participant responded to a stimulus from the other category to the previous trial (e.g. a face rather than a house), and the relevant pairs for intra-dimensional shifts were defined when the participant responded to the other stimulus from the same category (e.g. the other house). Non-shifting events were pairs of trials during which a participant didn't change their response from the previous trials. Set-change EVs were modelled from when the new stimuli were presented until the participant responded, and reversal EVs were defined as the first pair after a reversal had happened that the participant responded to a

different stimulus (which typically indicated that they had understood that a reversal had occurred).

Each of these EVs were convolved with a default haemodynamic response function (γ function, with phase of 0s, standard deviation of 3s, and mean lag of 6s). We also added a temporal derivative (which addresses the differences in timing of BOLD response with respect to slice acquisition) and applied temporal filtering. The contrasts that were input to the model were extra-dimensional vs. intra-dimensional shifting events (EDS > IDS), reversal learning – set change events (RV > SH), 'incorrect' minus 'correct' feedback and vice versa, and switching events (RV, SH, EDS, IDS) minus non-switch when the target is known (CN). The second-level FEAT analysis combined the results of each run for each participant, to generate a 'mean' BOLD signal change per participant for each lower-level contrast. This used a fixed effects model. The third-level FEAT analysis contrasted the mean activation patterns for individuals (derived from the second-level FEAT) in the RA and the HC groups.

### 3.2.10 Resting-State Functional Connectivity

#### *3.2.10.1 Acquisition*

Functional images were acquired using a multi-echo EPI sequence, with acquisition parameters as follows: TR 1125ms; TEs 15ms, 34.42ms and 53.64 ms, flip angle 65°; multi-band acceleration factor 3; PAT 2 (GRAPPA); FOV 192*192mm; grid size 64*64; voxel size 3*3*3mm; 42 slices; no inter-slice gap. Participants were instructed to keep their eyes open and try not to fall asleep, and were not presented with any visual display in order to keep them from attending to any specific stimulus. An eye-tracking camera was used to monitor whether the eyes were open or closed in real time – if they closed, the participant was reminded to stay alert and avoid falling asleep.

#### *3.2.10.2 Preprocessing*

Data were pre-processed and analysed using Analysis of Functional NeuroImages (AFNI) software, version 17.2.09 (Cox, 1996), and associated functions (typically beginning with the prefix 3d). Multi-echo independent component analysis (ME-ICA) was used to denoise the data and reduce the effects of movement (Kundu et al., 2012, 2013). The python script meica.py (version 3.2, beta 1) was run using non-linear standard space normalisation to the MNI-152 template after affine registration, and slice timing information was specified manually to designate slice order (interleaved ascending). Broadly, this toolbox implements pre-processing, decomposition, and denoising steps for multi-echo EPI data.

In more detail, the meica.py script performs the following pre-processing: deobliquing, unifizing, skull-stripping and autoboxing the anatomical image; calculating and saving motion and obliquity parameters (after despiking the images from the first TE, motion correction parameters were estimated for each time-point by aligning the first TE images to the first-time point image using a rigid-body alignment procedure (3dvolreg), with quintic polynomial interpolation, and time-shifted to the average slice timing offset prior to spatial registration); slice-timing correction using 3dTShift (AFNI), despiking, and axializing all functional datasets; estimation of structural co-registration parameters by registering the skull-stripped first TE image from the first time-point to the skull-stripped anatomical image using an affine alignment procedure, then a nonlinear transform using 3dQwarp (AFNI); application of motion correction and anatomical co-registration parameters using 3dAllineate (AFNI); computing a brain mask from the mean image of the shortest TE (15 ms) time series (3dskullstrip (AFNI)), which was applied to all images. Then, the meica.py script decomposes the datasets into independent

components (ICs) using FastICA (AFNI), and performs TE-dependence analysis (which is expected to remove 'noise' components, see Section 3.1.3), then categorises ICs as BOLD or noise using their BOLD and non-BOLD weightings (measured as pseudo-*F* statistic Kappa and Rho values, respectively).

The outputs of this analysis include:

1) A denoised BOLD time series after basic preprocessing, T2* weighted averaging of echoes, and ICA denoising (using the procedure described above, where non-TE-dependent components were removed)

2) 'Raw' BOLD time series data after basic preprocessing and T2* weighted averaging of echoes

3) Component maps of accepted BOLD ICA components

4) Component maps of all (accepted and rejected) ICA components, and

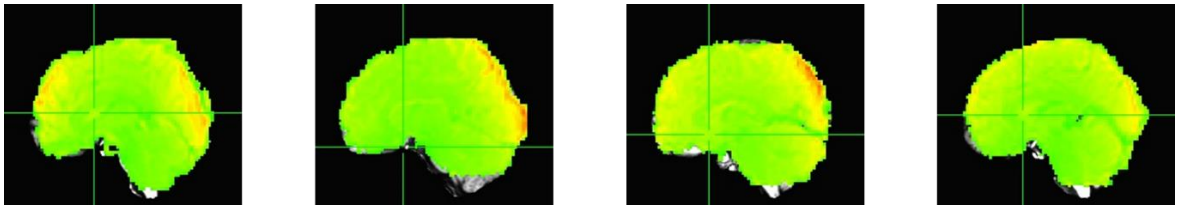
5) A table of components with kappa, rho and variance explained values.

The component maps of accepted ICA components (the third list item above) were taken forward into further analysis.

#### *3.2.10.3 Quality checks*

A number of quality check steps were performed to assess the quality of the data and the multi-echo ICA which was performed (Kundu et al., 2013; Vaghi et al., 2016). Initially, the quality of co-registration was examined by overlaying the denoised functional time series produced by ME-ICA with the structural image, allowing the overlap to be visualised. The co-registration was considered adequate: a sample of co-registration images is shown in Figure 2.

*Figure 2: Example co-registration for four participants.*



*The green/yellow overlay shows the area of the image after ME-ICA denoising, with the grey underlaid image being that participant's structural image.*

Secondly, the number and quality of BOLD-like components identified was inspected. These were visualised based on the coordinates of peak activation for all above-threshold activation (using the arbitrary threshold of 3), for all the accepted components. There was no difference between groups in the total number of accepted BOLD ICA components after ME-ICA denoising (Table 4), $t(37.89) = 0.56$, $p = 0.580$. The minimum number of components detected was 26, which is similar to the number of components for a 'low motion' participant in the paper introducing this method (Kundu et al., 2013), which was 32 components.

Thirdly, six degrees of freedom rigid body motion corrections were calculated and displayed, and visually inspected for abrupt motion.

Fourthly, framewise displacement (FD) was calculated for each timepoint. This is calculated as the sum of the first derivatives of the six motion parameters estimated from rigid body transforms (3 rotations and 3 translations, one in each dimension) to summarise head motion. Rotations were converted from degrees to mm by calculating displacement on the surface of a sphere of radius 50mm, which approximates the mean distance from the cortex to the centre of the head. There was no difference in mean FD (calculated for each individual across timepoints) between the groups (Table 4), and when a median-split was performed on all participants based on the sum of FD (an estimate of total motion), the number classified as having 'high motion' (above the median) and 'low motion'

(below the median) did not significantly differ between groups (Table 4). It is important to establish this as whilst the denoised time series resulting from the ME-ICA protocol shows no difference in temporal signal-to-noise ratio (SNR) between high and low motion datasets, there is still a difference in degrees of freedom, which reduces signal variability (Kundu et al., 2013)

Finally, the total variance in the BOLD signal explained for each participant by the ME-ICA decomposition was compared between groups, with no significant difference (Table 4).

*Table 4: Imaging motion analysis*

| **Variable** | **RA (n=20)** | **HC (n=20)** | $\chi^2$ | ***t*** | ***df*** | ***p value*** |
|---|---|---|---|---|---|---|
| **BOLD components** | 43.40 | 41.45 | | 0.56 | 37.89 | 0.580 |
| **Motion, high/low** | 11/9 | 9/11 | 0.1 | | 1 | 0.752 |
| **FD** | 0.12 | 0.12 | | 0.81 | 378.00 | 0.423 |
| **Variance Explained (%)** | 92.41 | 93.59 | | -0.85 | 37.99 | 0.399 |

*The mean and relevant statistics for group differences in these imaging motion parameters are shown. The accepted BOLD components (i.e. those considered to be 'signal' rather than 'noise' components) are shown in the first row. The second row shows the number of individuals in each group classified as high/low motion based on a median split. FD refers to framewise displacement (see above).*

#### *3.2.10.4 Main analysis*

We tested the hypothesis that there was dysregulated functional connectivity in fronto-striatal regions in the group of participants who had recovered from AN, which might underpin the common observation of cognitive inflexibility in this disorder (Tchanturia et al., 2012). Thus, we analysed functional connectivity between seed regions in the fronto-striatal network, and assessed the relationship between connectivity and WCST performance. This relationship was explored across groups (i.e. as a covariate), as there was no significant behavioural difference in performance on this task between the RA group and HC group.

The selection of corticostriatal seed regions of interest (ROIs) was based on those used in a previous study using a similar protocol in patients with OCD (Vaghi et al., 2016), which also examined the neural basis of compulsivity, finding that caudate connectivity was related to cognitive inflexibility in these patients. The ACC was also used as an ROI, as it is associated with corticostriatal circuitry along with the other ROIs (see Section 1.5.4). The ACC was also used as an ROI for the MRS data acquisition, to enable continuity of analysis between these two modalities. The seed ROIs, in full, were:

- bilateral dorsal caudate: DCd: centred on [±12, 6, 14], spherical with a 3mm radius, which covered the body of the caudate (Harrison et al., 2009; Vaghi et al., 2016)
- bilateral putamen: PUT: centred on [±24, -0, 3], spherical with a 3mm radius
- bilateral nucleus accumbens: NAc: centred on [±12, 8, -8], spherical with a 3mm radius
- bilateral ACC: centred on [±8, 32, 7], spherical with a 3mm radius, which corresponds to an area which is thought to be important in emotional regulation (Kelly et al., 2009).

The ME-ICA denoised data (unsmoothed, without additional band-pass filtering) were entered into 3dGroupInCorr (ANFI) to estimate functional connectivity, with degrees of freedom determined by the number of accepted components. 3dGroupInCorr extracts a time-course of signal from each seed region, and then computes the correlation map between the seed time series and every other voxel in the brain (using Pearson's correlation) for each participant. Fisher's r to z transform was used to derive standard scores. Voxel-wise t-tests are computed on the group correlation maps, with the probability of false positives controlled at a cluster level of $p < 0.01$ or $p < 0.05$, as stated in the relevant results section, after applying a per-voxel uncorrected height threshold of *p*

< 0.05. Rather than using Gaussian filtering when running 3dClustSim (AFNI) to calculate the cluster-level probabilities, we used the spherical autocorrelation function parameters obtained from running 3dFWHMx (AFNI) to do non-Gaussian long-tailed filtering, as fMRI data does not actually have a Gaussian-shaped autocorrelation function. The spatial domain was specified using a dataset mask, resulting in a grid size of 57*72*61.

We included perseverative errors on the WCST as a covariate of interest to examine whether this measure of cognitive flexibility was correlated with any differences in fronto-striatal connectivity. 3dGroupInCorr by default centers covariates (i.e. removes the mean) separately for each set of participants.

Where clusters were found that differed in connectivity between groups, we used these clusters as masks to extract mean z-scores of that connectivity for each participant (using 3dmaskave), in order to perform exploratory correlation analyses of connectivity and other behavioural or clinical measures (EDE global score and perseverative errors).

### 3.2.11 MRS

#### *3.2.11.1 Acquisition*

Participants underwent proton ($^1$H) MRS scanning. Spectra was measured from one voxel, the ACC (20 × 20 × 20 mm). Localisation was achieved using a semi-LASER sequence (Öz & Tkáč, 2011). The parameters used were: TR 3000ms; TE 28ms; 128 averages; 6000Hz bandwidth; 2048 data points. Voxels were positioned manually by reference to the structural T1-MPRAGE image obtained. Variable power and optimized relaxation delays (VAPOR) water suppression was used, VAPOR flip angle was 60°. Additionally, unsuppressed water reference spectra ('wref') were acquired from the same voxel by turning the VAPOR pulses off. These spectra were used to remove eddy current

effects. MRS data was not recorded for 9 participants as the MRS sequence used had not yet been set up on the scanner.

#### *3.2.11.2 Preprocessing*

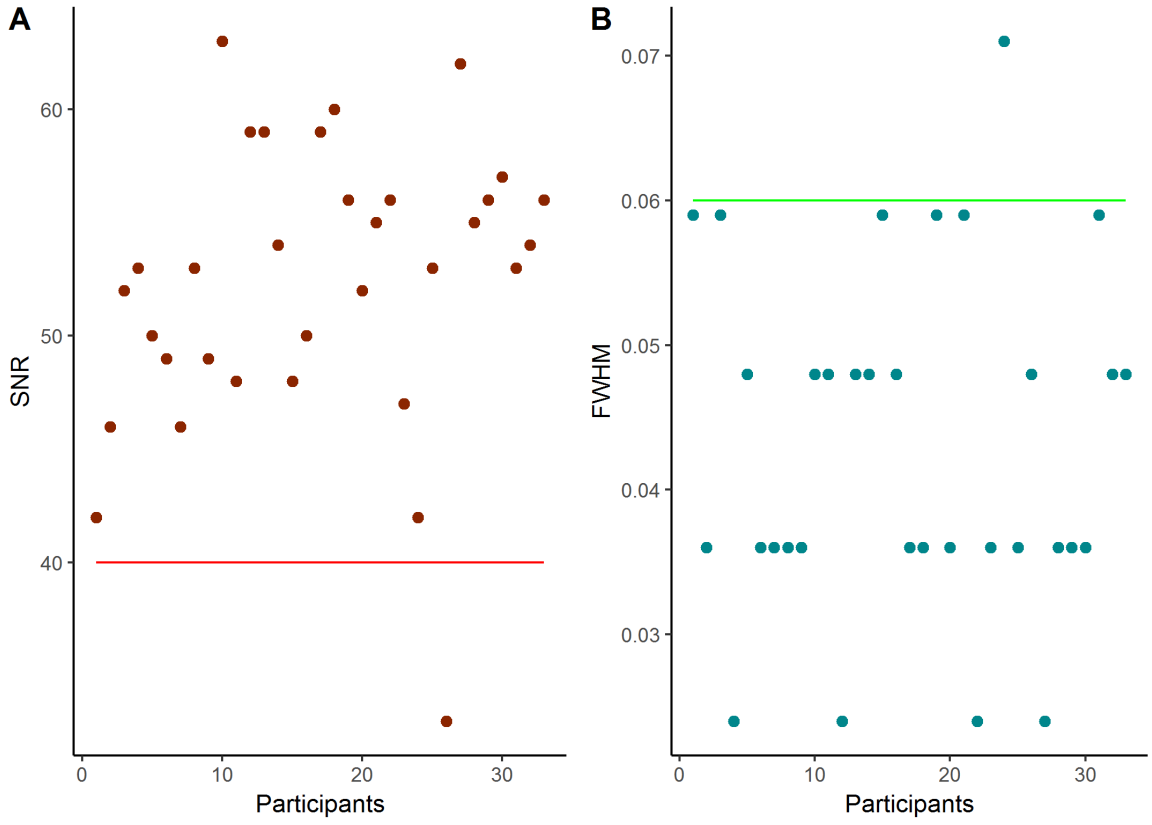
MRspa was used to perform frequency correction (using the amplitude absolute method) and phase correction (using the maximum intensity method).

Metabolites were quantified using LCModel (Provencher, 2001). The model spectra of alanine, aspartate, ascorbate/vitamin C, glycerophosphocholine, phosphocholine, creatine, phosphocreatine, $\gamma$-aminobutyric acid, glucose, glutamine, glutamate, glutathione, myo-inositol, lactate, *N*-acetylaspartate, *N*-acetylaspartylglutamate, phosphoethanolamine, scyllo-inositol, and taurine were generated based on previously reported chemical shifts and coupling constants (Govindaraju et al., 2000; Tkáč, 2008) by using the GAMMA/PyGAMMA simulation library of VeSPA (VErsatile Simulation, Pulses and Analysis) for carrying out the density matrix formalism. Simulations were performed with the same RF pulses and sequence timings as that on the 3T system.

Spectra that did not meet quality benchmarks were removed from further analysis. The benchmarks used were an SNR of over 40, and a FWHM less than 0.06ppm.

We also removed metabolites which had Cramér-Rao lower bounds (CRLB) (estimated error of the metabolite quantification) >30% for more than half of the participants. If the correlation between two metabolites was significant ($r \geq 0.5$), their sum was reported. We report Glx rather than individual glutamate and glutamine metabolites due to concerns about the ability to separately estimate these metabolites at 3T.

*Figure 3: Scatter plots showing spectra that were excluded as they did not meet quality thresholds.*




*Scatter plot of A) SNR and B) FWHM for the LCModel spectra that was output for participants' MRS data. Spectra with an SNR of below 40 were removed from further analysis, as were spectra with a FWHM of above 0.06.*

The T1 MPRAGE images were segmented using SPM8 segment (http://www.fil.ion.ucl.ac.uk/spm). Segmentation was used to determine the fraction of the voxel composed of CSF, GM and WM. SPM8 segmentation was used due to its higher precision compared to FSL; the estimates of voxel composition are closer to manual estimates (Tsang et al., 2008), and SPM segmentation is particularly accurate at distinguishing CSF from GM/WM (Kasiri et al., 2010)

Subsequently, the absolute concentrations of metabolites that were output by LCModel were corrected for voxel composition using the formula in Eq. 5.

$$CONC_{CORRECTED} = CONC_{ABSOLUTE} * \frac{43300f_{GM} + 35880f_{WM} + 55556f_{CSF}}{1 - f_{CSF}} \qquad Eq.\ 5$$

#### *3.2.11.3 Main analysis*

For our metabolites of interest, we performed unpaired t-tests between groups. The statistic used was Welch's t-test for unequal variances.

## 3.3 RESULTS

### 3.3.1 Participant characteristics

Participants were all female. There was no significant difference between the two groups (RA and HC) in handedness, age, BMI, or estimated IQ (calculated from the NART score). There was also no significant difference between RA and HC groups on the questionnaires measuring depressive or anxiety symptoms, or on any of the EPQ dimensions other than neuroticism. There was a significant difference between the RA and HC groups in the global EDE score, the EDE subscales, and the EDE-Q. All participants had a score on the EDE of below one standard deviation above the norm for global mean scores. Participants also differed on both worst and current YBC-EDS-SRQ scores, and OCI-R scores. See Table 5 below for further details.

*Table 5: Demographic and clinical characteristics of sample.*

| **Variable** | **RA (n=20) mean (sd)** | **HC (n=20) mean (sd)** | $\chi^2$ | ***T*** | ***df*** | ***p value*** |
|---|---|---|---|---|---|---|
| **Age, years** | 24.75 (4.8) | 24.25 (5.3) | | 0.31 | 37.66 | 0.757 |
| **Handed (r/l)** | 17/2 | 18/1 | 0.36 | | 2 | 0.835 |
| **BMI (kg/m2)** | 21.53 (2.6) | 22.74 (2.8) | | -1.42 | 37.83 | 0.163 |
| **Estimated IQ** | 113.6 (5.8) | 115.7 (3.5) | | -1.42 | 31.36 | 0.165 |
| **EDE** | 0.67 (0.5) | 0.26 (0.2) | | 3.41 | 25.97 | 0.002** |
| ***EDE eating*** | 0.26 (0.3) | 0.08 (0.1) | | 2.51 | 24.97 | 0.019* |
| ***EDE shape*** | 1.09 (0.7) | 0.44 (0.4) | | 3.43 | 29.19 | 0.002** |
| ***EDE weight*** | 0.88 (0.7) | 0.38 (0.3) | | 2.92 | 27.25 | 0.007** |

| Variable | RA (n=20) mean (sd) | HC (n=20) mean (sd) | $\chi^2$ | *T* | *df* | *p value* |
|---|---|---|---|---|---|---|
| ***EDE restraint*** | 0.46 (0.9) | 0.13 (0.3) | | 1.50 | 24.01 | 0.147 |
| **EDE-Q** | 1.06 (0.8) | 0.48 (0.4) | | 2.87 | 29.28 | 0.008** |
| **BDI-II** | 3.75 (4.3) | 2.90 (3.3) | | 0.70 | 35.39 | 0.488 |
| **HAM-D** | 3.95 (3.7) | 3.20 (2.7) | | 0.73 | 34.72 | 0.468 |
| **STAI-T** | 39.30 (7.2) | 35.05 (7.4) | | 1.84 | 37.94 | 0.073 |
| **STAI-S** | 33.25 (8.6) | 29.95 (7.0) | | 1.33 | 36.55 | 0.193 |
| **OCI-R** | 8.60 (5.5) | 5.00 (4.4) | | 2.28 | 36.10 | 0.028* |
| **YBC-EDS-SRQ: worst total** | 18.55 (4.4) | 1.35 (2.4) | | 15.19 | 29.46 | <0.001*** |
| ***YBC-EDS-SRQ: worst preoccupations*** | 9.80 (2.8) | 0.95 (1.9) | | 11.68 | 33.07 | <0.001*** |
| ***YBC-EDS-SRQ: worst rituals*** | 8.80 (3.4) | 0.40 (0.8) | | 10.70 | 21.55 | <0.001*** |
| **YBC-EDS-SRQ: current total** | 2.60 (3.1) | 0.70 (1.7) | | 2.41 | 29.77 | 0.023* |
| ***YBC-EDS-SRQ: current preoccupations*** | 1.40 (1.7) | 0.45 (1.1) | | 2.07 | 33.33 | 0.046* |
| ***YBC-EDS-SRQ: current rituals*** | 1.20 (1.9) | 0.25 (0.8) | | 2.08 | 25.45 | 0.047* |
| **EPQ: Neuroticism** | 10.85 (5.7) | 7.50 (4.1) | | 2.14 | 34.51 | 0.040* |
| **EPQ: Psychoticism** | 2.90 (1.9) | 2.30 (1.8) | | 1.03 | 37.59 | 0.312 |

| Variable | RA (n=20) mean (sd) | HC (n=20) mean (sd) | $\chi^2$ | *T* | *df* | *p value* |
|---|---|---|---|---|---|---|
| **EPQ: Extraversion** | 13.25 (3.9) | 14.25 (3.7) | | -0.83 | 37.93 | 0.410 |
| **EPQ: Lie** | 9.70 (4.7) | 9.25 (3.8) | | 0.33 | 36.28 | 0.742 |

*This table includes the relevant descriptive statistics (either mean or number with that characteristic from the cohort), and the statistics for the calculation of differences between groups. Note that the handedness information for two participants (one from each group) was missing, and this data is presented in count form. * p < 0.05, **p < 0.01, ***p < 0.001.*

### 3.3.2 Out-of-scanner behavioural task performance

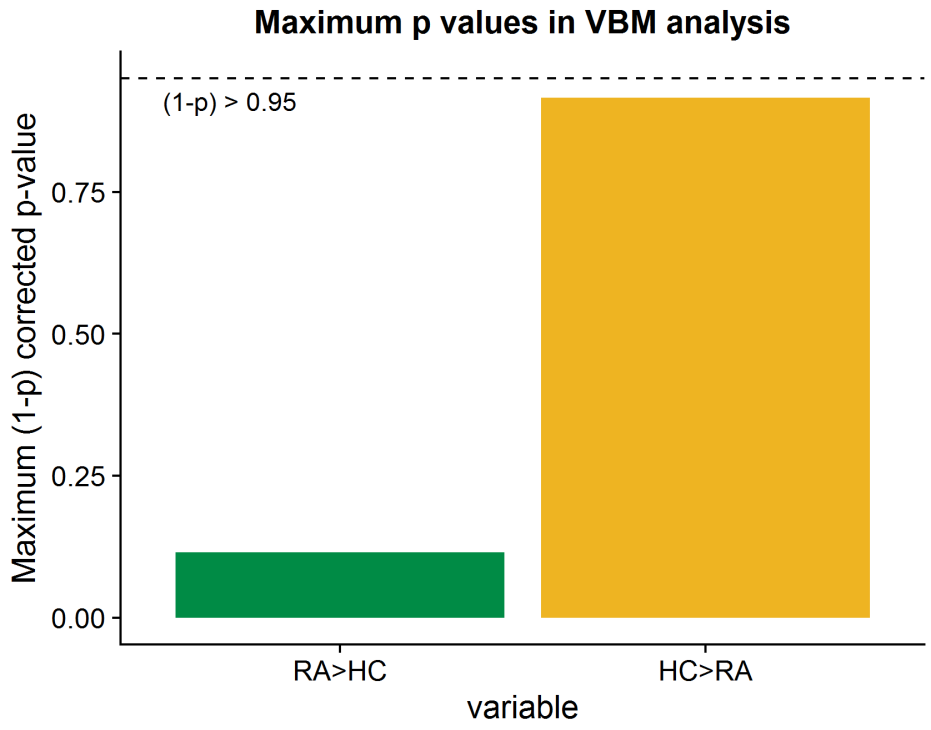
There was no significant difference between the RA and HC groups on total perseverative errors on the WCST, based on a t-test with group as the between-subject variable: $t(36.8) = -0.50$, $p = 0.620$.

There was also no significant difference between the RA and HC groups on either shift cost in the AGN: $t(36.5) = 1.02$, $p = 0.317$, or on affective response bias: $t(37.9) = 1.02$, $p = 0.316$.

### 3.3.3 Structural MRI

There were no significant ($p < 0.05$) differences in grey matter volume between patients and controls, using threshold-free cluster ehancement (TFCE). Figure 4 shows the maximum TFCE corrected (1-*p*) values for the two contrasts performed in the VBM analysis: RA > HC, and HC > RA.

*Figure 4: Graph of maximum TFCE corrected p-values for VBM analysis.*




*Bar chart showing maximum (1-p) threshold-free cluster enhancement (TFCE) corrected p-values for both of the voxel-based morphometry contrasts used. As can be observed, neither of them meet the threshold (grey dotted line) for a significance level of p < 0.05 (or >0.95 in this example using 1-p).*

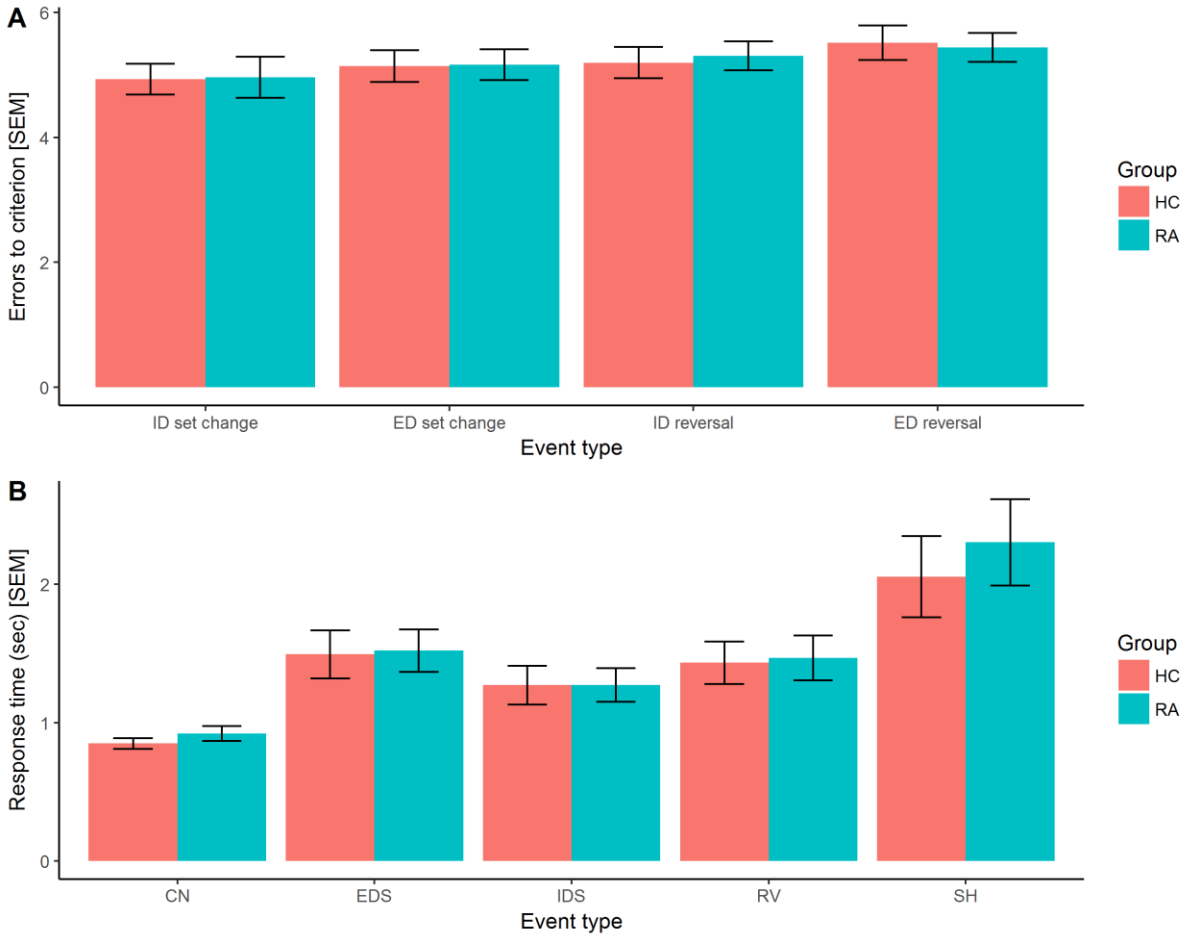
### 3.3.4 Task-based fMRI

#### *3.3.4.1 Behavioural analysis of IDED task performed in scanner*

Analysis of accuracy on the IDED task indicated that there were no group differences (no significant main effect or interaction effects including group, all $p > 0.05$). Across all participants, there was a significant effect of reversal on errors made: $F(1,38) = 10.88$, $p = 0.002$, with an increase in the number of errors made in the RV condition ($M = 5.35$, $SD = 1.53$) compared to the SH condition ($M = 5.06$, $SD = 1.92$). There was a trend towards an effect of set-shifting on errors made: $F(1,38) = 3.41$, $p = 0.073$, with an increase on errors made during the EDS condition ($M = 5.27$, $SD = 1.79$) compared the IDS condition ($M = 5.10$, $SD = 1.75$). The errors made are shown in Figure 5.

Analysis of reaction time on the IDED task also indicated that there were no group differences (no significant main or interaction effects including group, all $p > 0.05$). There was a significant effect of variable type on reaction time: $F(1.7, 64.7) = 60.3$, $p < 0.001$, with non-shift events after the participant knew they were correct having the lowest reaction time ($M = 0.89$, $SD = 0.15$), followed by IDS events ($M = 1.27$, $SD = 0.40$), RV events ($M = 1.45$, $SD = 0.49$), EDS events ($M = 1.51$, $SD = 0.51$), and SH events ($M = 2.18$, $SD = 0.95$).

*Figure 5: Behavioural analysis of participant performance (errors and RT) on the IDED task within the scanner by group.*

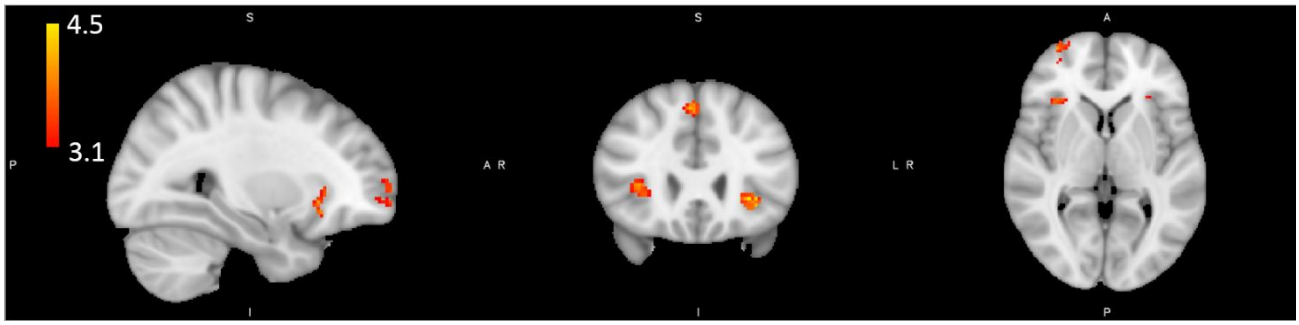



*Participant performance metrics are displayed in the bar graphs above. A) Errors to criterion (mean and standard error of the mean) for the control group and the RA group. The most errors were to reversal learning compared to set change events, with there being a trend towards an increase in errors for extra-dimensional rather than intra-dimensional shifting. B) Reaction times for different event types. CN stands for non-switch events when the correct outcome had been identified, EDS for extra-dimensional shifts, IDS stands for intra-dimensional shifts, RV stands for reversal events, SH stands for set change events.*

### *3.3.4.2 MRI BOLD activation analysis*

Initially, we analysed the activation for the contrasts described above across groups, using a voxel-wise height threshold of $Z > 3.1$, and a (corrected) cluster significance threshold of $p < 0.05$. Across all participants, experiencing reversal learning events compared to stimulus set change events (contrast RV > SH) was associated with significantly increased BOLD signal in a number of clusters in i) the superior frontal gyrus ([4, 22, 52]; *k* (size of cluster) = 203; *p* (cluster) < 0.001, *Z* (peak) = 4.52, *p* (peak) < 0.001); ii) the orbitofrontal cortex ([-32, 24, -6], *k* = 143, *p* (cluster) = 0.003, *Z* (peak) = 4.26, *p* (peak) < 0.001 ); iii) the frontal pole ([36, 50, 8], *k* = 148, *p* (cluster) = 0.002, *Z* (peak) = 4.42, *p* (peak) < 0.001); and iv) the insular cortex ([28, 22, -4], *k* = 83, *p* (cluster) = 0.005, *Z* (peak) = 4.16, *p* (peak) < 0.001) (Figure 6).

*Figure 6: Sagittal, coronal and axial views of the activation clusters for the across-group activation for contrast RV > SH (reversal learning).*



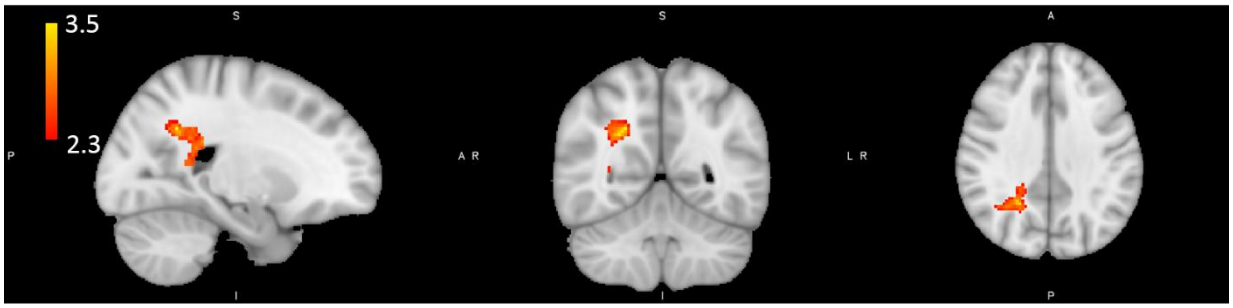

*Four significant clusters were identified with a voxel-wise height threshold of p<0.01:i) the superior frontal gyrus ([4, 22, 52]; k = 203; p (cluster) < 0.001, Z (peak) = 4.52, p (peak) < 0.001); ii) the orbitofrontal cortex ([-32, 24, -6], k = 143, p (cluster) = 0.003, Z (peak) = 4.26, p (peak) < 0.001 ); iii) the frontal pole ([36, 50, 8], k = 148, p (cluster) = 0.002, Z (peak) = 4.42, p (peak) < 0.001); and iv) the insular cortex ([28, 22, -4], k = 83, p (cluster) = 0.005, Z (peak) = 4.16, p (peak) < 0.001). This image is centred on x = 29, y = 25, z = 3. The colours represent the thresholded Z values for the corresponding coordinate of the brain.*

Additionally, at the lower voxel-wise height threshold of Z > 2.3, across participants there was a greater BOLD signal in response to switching compared to non-switching events in the intracalcarine cortex: [-14, -88, 8], *k* = 1177, *p* (cluster) < 0.001, *Z* (peak) = 3.37, *p* (peak) < 0.001. There was no across-participant activation for the EDS > IDS contrast, or for the correct vs. incorrect (and vice versa) contrasts.

No whole brain differences were found between groups using a stringent voxel-wise threshold of Z > 3.1 and a (FWE corrected) cluster significance threshold of $p < 0.05$.

Using a more lenient voxel-wise height threshold of Z > 2.3, there was a significant difference between groups for the contrast EDS > IDS (extra-dimensional set-shifting compared to intra-dimensional set-shifting) (Figure 7). There was significantly greater activation in the control group compared to the RA group on extra-dimensional shifting vs intra-dimensional shifting in a cluster with peak activation at the precuneus ([22, -54, 34], $k = 746$, $p$ (cluster) < 0.001, $Z$ (peak) = 3.57, $p$ (peak) < 0.001). This cluster overlapped with precuneus, superior lateral occipital cortex and angular gyrus. However, it is worth noting that there was no overall activation in response to the EDS > IDS contrast across the whole set of participants.

*Figure 7: Greater activation in HC compared to RA participants in response to extra-dimensional compared to intra-dimensional shifting.*




*This figure shows significantly greater activation in the controls compared to the RA participants in the precuneus/angular gyrus/superior lateral occipital cortex for the contrast EDS > IDS (or extradimensional-shifting compared to intra-dimensional shifting). With a voxel-wise height threshold of Z > 2.3, a cluster of greater activation in HC compared to RA was found in the precuneus/angular gyrus ([22, -54, 34], k = 746, p (cluster) < 0.001, Z (peak) = 3.57, p (peak) < 0.001). This image is centred on x = 22,y = -54,z = 34. The colours represent the thresholded Z values corresponding to that coordinate in the brain.*

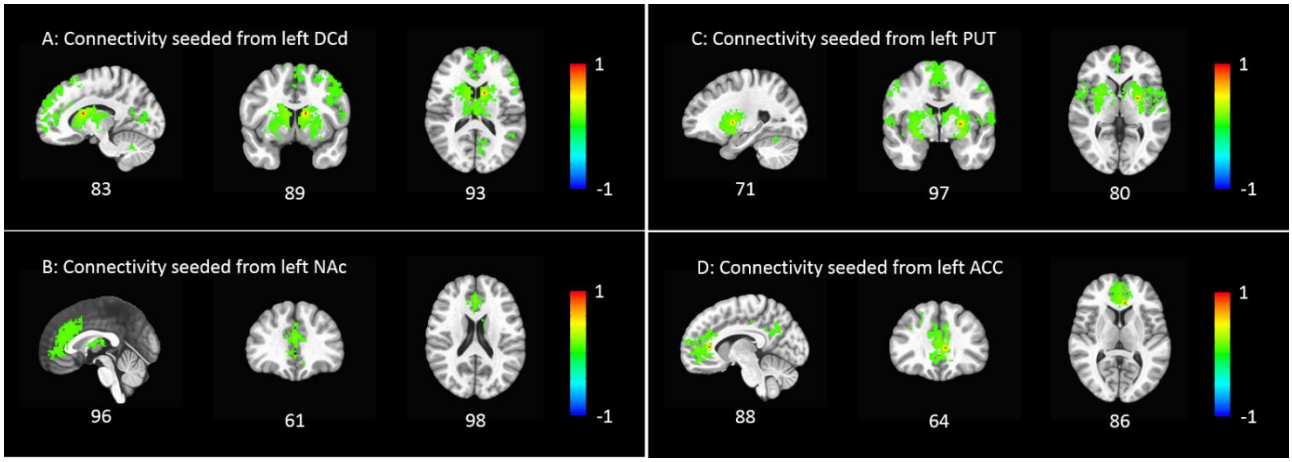
### 3.3.5 Resting-state fMRI

#### *3.3.5.1 Connectivity from seed regions across groups*

Within the control group, functional connectivity seeded from striatal regions successfully replicated and identified corticostriatal connectivity commonly reported elsewhere, i.e. that activity in the caudate and putamen was correlated with activity in motor and frontal regions, while activity in the nucleus accumbens and ACC was correlated with activity in emotional/reward-based circuitry (Alexander, 1986; Haber & Knutson, 2010) (Figure 8 and Table 6).

Specifically, (using a voxel-wise $p$ value of $< 0.01$), connectivity patterns were identified with a $p$ (family-wise error (FWE) corrected) $< 0.01$. In the present investigation, the activity in the dorsal caudate in control participants was most strongly correlated with activity in cerebellar regions, with correlations also to activity in superior occipital cortex, posterior cingulate cortex, intracalcarine cortex, inferior frontal gyrus and right superior parietal lobe. There was also a significant correlation between activity in the nucleus accumbens seeds and activity in the ACC and other subcortical regions such as the amygdala and caudate. The activity in the putamen showed significant correlation with activity in supplementary motor and superior frontal regions, and the precentral gyrus. ACC activity correlated with activity in the broader cingulate region, and posterior cingulate/cuneus regions. See Figure 8 and Table 6 for voxel coordinates and statistical summaries of correlations.

*Figure 8: Significant connectivity with seed regions in control participants during resting state scan.*




*Statistically significant connectivity with seed regions in control participants obtained by resting state analysis, showing the connectivity pattern with each of the seed ROIs. A) Connectivity from the left DCd seed, with the 83rd sagittal slice, 89th coronal slice and 93rd axial slice shown (x = -13, y = 7, z = 15). B) Connectivity from the left NAc seed, showing the 96th sagittal slice, the 61st coronal slice and the 98th axial slice (x = -0, y = 35, z = 20). C) Connectivity from the left PUT seed, with the 71st sagittal slice, 97th coronal slice and 80th axial slice shown (x = -25, y = -1, z = 2). D) Connectivity from the left ACC seed, showing the 88th sagittal slice, the 64th coronal slice and the 86th axial slice (x = -8, y = 32, z = 8). See Table 6 for further details on the significant clusters shown. The colourbar ranges from 1 to -1, and the colours on the brain surface represent the value of the (thresholded) correlation at that point, between 1 and -1.*

*Table 6: Clusters with significant connectivity with seed regions in healthy control participants.*

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation | *Z (p)* at peak |
|---|---|---|---|---|---|---|
| **Left DCd** | 6797 | -12.6 | 7.0 | 15.1 | Left caudate | 6.84 (<0.001) |
| | 1090 | 10.1 | -86.4 | -30.3 | Right cerebellum | 4.28 (<0.001) |
| | 722 | -53.0 | -61.1 | 35.3 | Left superior lateral occipital cortex | 4.52 (<0.001) |
| | 384 | -2.5 | -38.4 | 37.8 | Left posterior cingulate cortex | 4.34 (<0.001) |
| | 103 | -27.7 | -78.8 | -32.8 | Left cerebellum | 4.53 (<0.001) |
| | 95 | -65.6 | -28.3 | -7.6 | Left posterior middle temporal gyrus | 3.63 (<0.001) |
| **Right DCd** | 6085 | 12.6 | 7.0 | 15.1 | Right caudate | 7.28 (<0.001) |

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation | *Z (p)* at peak |
|---|---|---|---|---|---|---|
| | 613 | -10.1 | -73.7 | 12.6 | Left intracalcarine cortex | 4.38 (<0.001) |
| | 480 | -32.8 | -71.2 | -30.3 | Left cerebellum | 4.04 (<0.001) |
| | 266 | -55.5 | 17.0 | 5.0 | Left inferior frontal gyrus | 3.62 (<0.001) |
| | 258 | -2.5 | -53.6 | -35.4 | Left/central cerebellum | 5.06 (<0.001) |
| | 204 | 35.3 | -73.7 | -30.3 | Right cerebellum | 3.93 (<0.001) |
| | 202 | 35.3 | -51.0 | 50.4 | Right superior parietal lobule | 3.73 (<0.001) |
| | 182 | -50.4 | 7.0 | 32.7 | Left precentral gyrus | 4.04 (<0.001) |
| | 118 | -30.3 | -20.8 | -2.6 | Left putamen | 4.77 (<0.001) |
| | 93 | -25.2 | 52.4 | 17.6 | Left frontal pole | 3.25 (0.001) |
| | 90 | 5 | -83.8 | -30.3 | Right cerebellum | 3.34 (<0.001) |
| | 90 | 58.0 | -48.5 | 15.1 | Right angular gyrus | 4.34 (<0.001) |
| **Left NAc** | 832 | -0.0 | 34.7 | 20.1 | Anterior cingulate gyrus | 5.57 (<0.001) |
| | 421 | 7.6 | 9.5 | -2.6 | Right caudate | 3.66 (<0.001) |
| | 282 | -12.6 | 7.0 | -7.6 | Left accumbens | 7.07 (<0.001) |
| **Right NAc** | 264 | 12.6 | 7.0 | -7.6 | Right accumbens | 7.33 (<0.001) |
| | 198 | -12.6 | 1.9 | -10.1 | Left amygdala | 4.05 (<0.001) |

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation | *Z (p)* at peak |
|---|---|---|---|---|---|---|
| | 192 | -0.0 | 32.2 | 22.7 | Anterior cingulate gyrus | 3.90 (<0.001) |
| **Left PUT** | 1901 | -25.2 | -0.6 | 2.5 | Left putamen | 7.49 (<0.001) |
| | 1390 | 27.7 | -0.6 | -7.6 | Right putamen | 4.63 (<0.001) |
| | 766 | 2.5 | -5.7 | 60.5 | Right Supplementary Motor Cortex | 4.99 (<0.001) |
| | 212 | 2.5 | 54.9 | 2.5 | Right paracingulate gyrus | 4.55 (<0.001) |
| | 181 | 50.4 | -5.7 | 50.4 | Right precentral gyrus | 4.07 (<0.001) |
| | 145 | -55.5 | -8.2 | 47.9 | Left precentral gyrus | 4.15 (<0.001) |
| | 123 | 32.8 | -63.7 | -20.2 | Right occipital fusiform gyrus | 4.08 (<0.001) |
| | 108 | -17.7 | -53.6 | -12.7 | Left lingual gyrus | 3.23 (0.001) |
| **Right PUT** | 2099 | 25.2 | -0.6 | 2.5 | Right putamen | 7.73 (<0.001) |
| | 1842 | -27.7 | -0.6 | -10.1 | Left amygdala | 4.32 (<0.001) |
| | 483 | 12.6 | -3.1 | 68.1 | Right superior frontal gyrus | 5.49 (<0.001) |
| | 274 | 53.0 | 1.9 | 40.3 | Right precentral gyrus | 5.36 (<0.001) |
| | 171 | 35.3 | -56.1 | -25.3 | Right cerebellum | 4.40 (<0.001) |
| | 110 | 37.8 | 37.2 | 27.7 | Right frontal pole | 4.11 (<0.001) |
| | 100 | -20.2 | -66.2 | -22.7 | Left cerebellum | 3.21 (0.001) |

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation | *Z (p)* at peak |
|---|---|---|---|---|---|---|
| | 76 | 10.1 | -28.3 | 47.9 | Right precentral gyrus | 4.24 (<0.001) |
| **Left ACC** | 1419 | -7.6 | 32.2 | 7.5 | Left anterior cingulate gyrus | 7.23 (<0.001) |
| | 518 | 5.0 | -48.5 | 17.6 | Right posterior cingulate gyrus | 3.54 (<0.001) |
| | 147 | 45.4 | 12.0 | -7.6 | Right insular cortex | 4.08 (<0.001) |
| | 113 | 20.2 | 37.2 | 35.3 | Right frontal pole | 3.48 (<0.001) |
| | 87 | -40.4 | 14.5 | -12.7 | Left insular cortex | 3.28 (0.001) |
| **Right ACC** | 1521 | 7.6 | 32.2 | 7.5 | Right Anterior Cingulate gyrus | 6.97 (<0.001) |
| | 1439 | -0.0 | -61.1 | 25.2 | Precuneus cortex | 4.04 (<0.001) |
| | 177 | -2.5 | 7.0 | -7.6 | Left subcallosal cortex | 4.48 (<0.001) |
| | 159 | 35.3 | 37.2 | 35.3 | Right frontal pole | 4.38 (<0.001) |
| | 93 | 58.0 | -48.5 | 20.1 | Right angular gyrus | 3.81 (<0.001) |
| | 81 | -22.7 | 27.1 | 40.3 | Left superior frontal gyrus | 3.63 (<0.001) |
| | 74 | 32.8 | 17.0 | -17.7 | Right orbitofrontal cortex | 3.21 (0.001) |

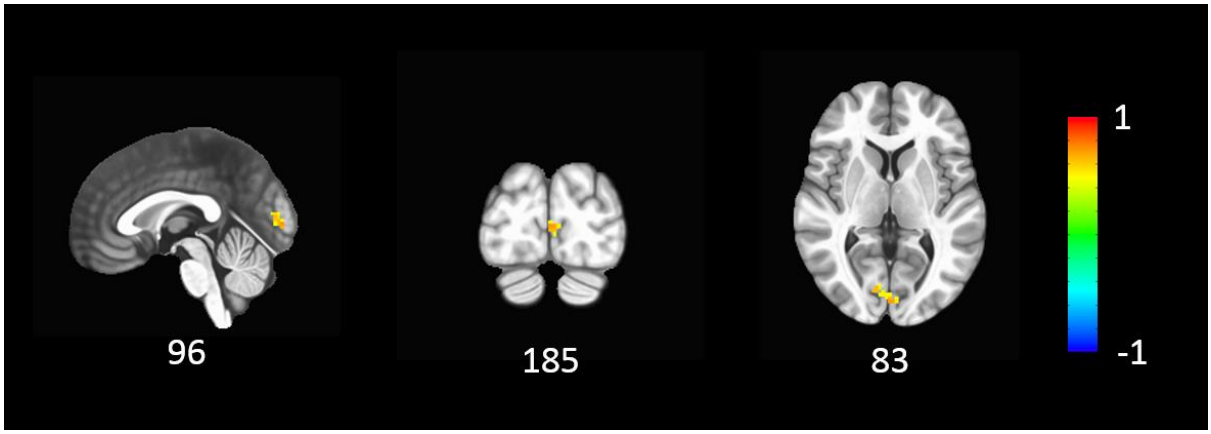
*For simplicity, we only include clusters here with a p(FWE corrected) of <0.001, DCd refers to dorsal caudate, NAc to nucleus accumbens, PUT to putamen, and ACC to anterior cingulate cortex.*

#### *3.3.5.2 Between-group differences*

Using a stringent voxel-wise threshold of $p < 0.01$, there was a single group difference in connectivity. This difference was significantly reduced connectivity between the right ACC and a cluster overlapping with the cuneus/lingual gyrus (peak activation in

the intracalcarine cortex at [-0.0, -88.9, 5.0], $k$ = 58, $p$ (cluster) < 0.010, $Z$ (peak) = 3.28, $p$ (peak) = 0.001) in the RA group compared to the HC group. For controls, the connectivity to the peak of this cluster was positive, but for the RA group, this connectivity was negative. In an exploratory correlation analysis, there was no association between this connectivity and EDE total score or perseverative errors on the WCST (all $p$ > 0.05).

*Figure 9: Lower connectivity between the right ACC to the cuneus in the RA group compared to HC group.*



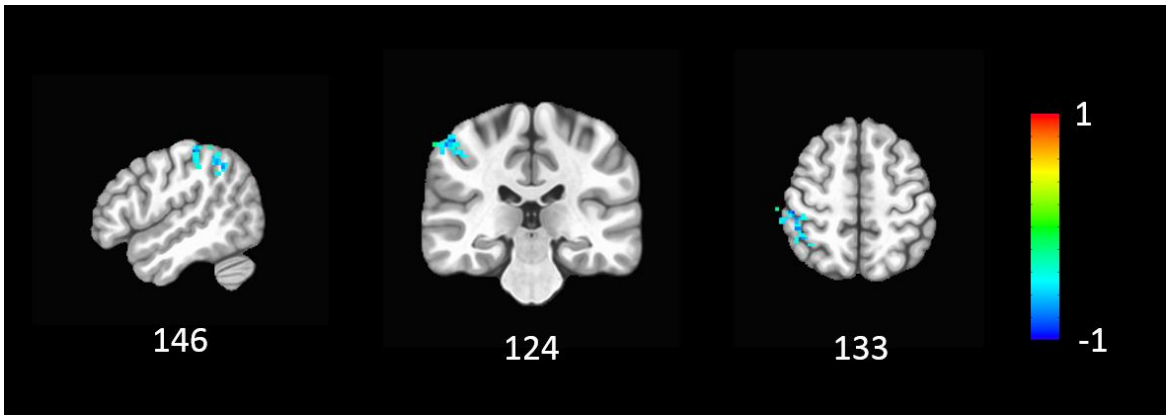

*The coordinates of the peak activation are -0.0, -88,9, 5.0. The slices used are the 96th sagittal slice, the 185th coronal slice, and the 83rd axial slice (x = -0, y = -89, z = 5). The scores are t-statistics converted to z-scores. The colours on the brain surface represent the difference of the correlation at that point, between 1 and -1.*

There were no other significant group differences in RSFC seeded from the nucleus accumbens, dorsal caudate, putamen and ACC using this stringent voxel-wise height threshold, nor in exploratory analyses of individual differences in connectivity associated with WCST performance. However, using a less stringent voxel-wise height threshold of $p$ < 0.05, another group difference could be observed.

This group difference was a significant increase in connectivity between the right nucleus accumbens and a cluster including the right inferior parietal lobule (I and right postcentral gyrus in the RA group compared to the control group, with the baseline connectivity between the right nucleus accumbens and this cluster being negative (but non-significant) in the control group and positive in the RA group: [ 50.4, -28.3, 55.4], $k$ =

188, $p$ (cluster) < 0.050, $Z$ (peak) = -3.85, $p$ (peak) < 0.001) The peak activation is in the right postcentral gyrus (Figure 10).

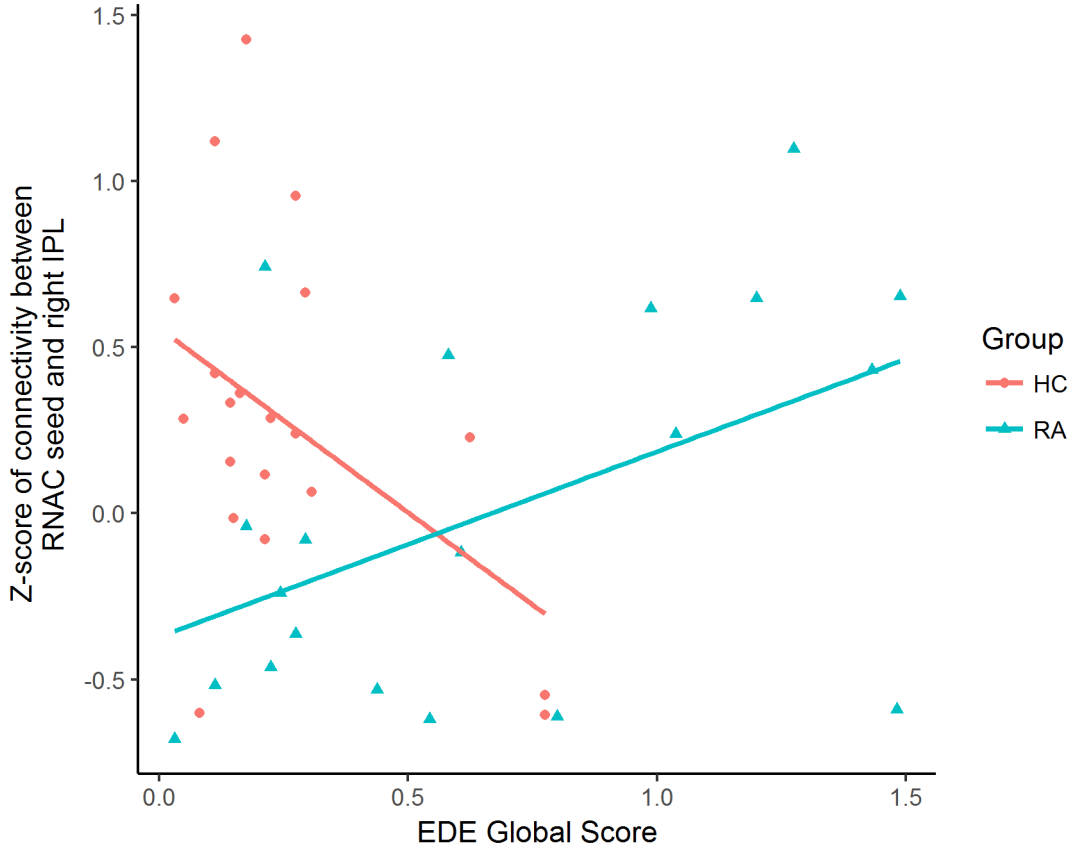
*Figure 10: Significantly greater connectivity between the right nucleus accumbens and the right inferior parietal lobule in the RA group compared to controls.*




*The coordinates of the peak activation are 50.4, -28,3 and 55.4. The slices used are the 146$^{th}$ sagittal slice, the 124$^{th}$ coronal slice, and the 133$^{rd}$ axial slice (x=50, y=-28, z=55). The scores are t-statistics converted to z-scores. The colours on the brain surface represent the difference of the correlation at that point, between 1 and -1.*

In an exploratory correlation analysis, we found that within the RA group, greater connectivity of the right nucleus accumbens with the right IPL is associated with greater global score on the EDE: $r(18) = 0.50$, $p = 0.026$, $R^2 = 0.16$. In the HC group, the correlation was in the opposite direction: $r(18) = -0.46$, $p = 0.043$, $R^2 = 0.10$ (Figure 11). There was no association between this connectivity and perseverative errors on the WCST ($p > 0.05$).

*Figure 11: Correlation between EDE total score and connectivity between the right nucleus accumbens and right IPL.*




*This scatter plot shows the EDE total score of that participant (x position) and the z-score of connectivity between the right nucleus accumbens seed and right IPL for each participant (y position), colour coded by group. There is a positive correlation in the RA group, and a negative correlation in the HC group, displayed using straight lines.*

#### *3.3.5.3 Correlation between cognitive flexibility and frontostriatal connectivity between groups*

We used perseverative errors on the WCST as a covariate of interest to explore whether there were any group differences in neural connectivity based on this measure of cognitive flexibility. Results here indicate a significant group difference in the slope of the correlation (arctanh) between the seed region and resulting cluster and WCST perseverative errors. Significant clusters are shown on Table 7. As this was an exploratory analysis, a relaxed $p$ voxel-wise height threshold of $p < 0.05$ was used.

*Table 7: Clusters showing a significant group difference in correlation slope between connectivity to a seed and perseverative errors.*

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation difference | *Z (p)* at peak | *p* (FWE corrected) |
|---|---|---|---|---|---|---|---|
| **Left DCd** | 199 | 20.2 | 22.1 | 65.5 | Right superior frontal gyrus | 3.98 (<0.001) | <0.040 |
| **Right DCd** | 194 | -45.4 | -17.0 | 50.4 | Left middle frontal gyrus | 3.20 (0.001) | <0.050 |
| **Left NAc** | 245 | -5.0 | -104.0 | -0.0 | Left cuneus/left lingual gyrus | -4.61 (<0.001) | <0.020 |
| **Left NAc** | 191 | 12.6 | -99.0 | 20.1 | Right occipital pole | -3.77 (<0.001) | <0.050 |
| **Left PUT** | 308 | 47.9 | -33.4 | 37.8 | Right supramarginal gyrus | -2.77 (0.006) | <0.010 |

*Clusters for which there is a significant group difference in the slope of the correlation (arctanh) between the seed region and resulting cluster, and WCST perseverative errors. A positive Z value indicates that the slope is greater in the HC group than the RA group, a negative Z value indicates that the slope is greater in the RA group than in the HC group.*

#### *3.3.5.4 Correlation between cognitive flexibility and frontostriatal connectivity within RA group*

Additionally, we investigated the links between functional connectivity and cognitive flexibility, again using perseverative errors on the WCST as a proxy for cognitive flexibility, within the group of participants who had recovered from AN. As this was also an exploratory analysis, a relaxed $p$ voxel-wise height threshold of $p < 0.05$ was used.

*Table 8: Clusters showing a significant correlation between connectivity with a seed and perseverative errors, in the RA group.*

| Seed | Cluster size *k* (voxels) | Peak X activation | Peak Y activation | Peak Z activation | Location of peak activation difference | *Z (p)* at peak | *p* (FWE corrected) |
|---|---|---|---|---|---|---|---|
| **Left DCd** | 204 | -2.5 | 24.6 | 68.1 | Frontal pole | 2.54 (0.011) | <0.04 |
| **Left NAc** | 211 | 15.1 | -91.4 | 25.2 | Right cuneus/ occipital pole | 4.17 (<0.001) | <0.03 |
| **Right PUT** | 337 | -5.0 | -93.0 | -12.7 | Occipital pole | -4.20 (<0.001) | <0.01 |
| **Right ACC** | 191 | 10.1 | 44.8 | 52.9 | Frontal pole/superior frontal gyrus | 2.32 (0.020) | <0.01 |

*Clusters shown are those for which there is a significant correlation with increased WCST perseverative errors and connectivity between the seed region and resulting cluster in the RA group. A positive Z value indicates correlation between the connectivity and errors is positive, a negative Z value indicates that the correlation between the connectivity and errors is negative.*

### 3.3.6 MRS

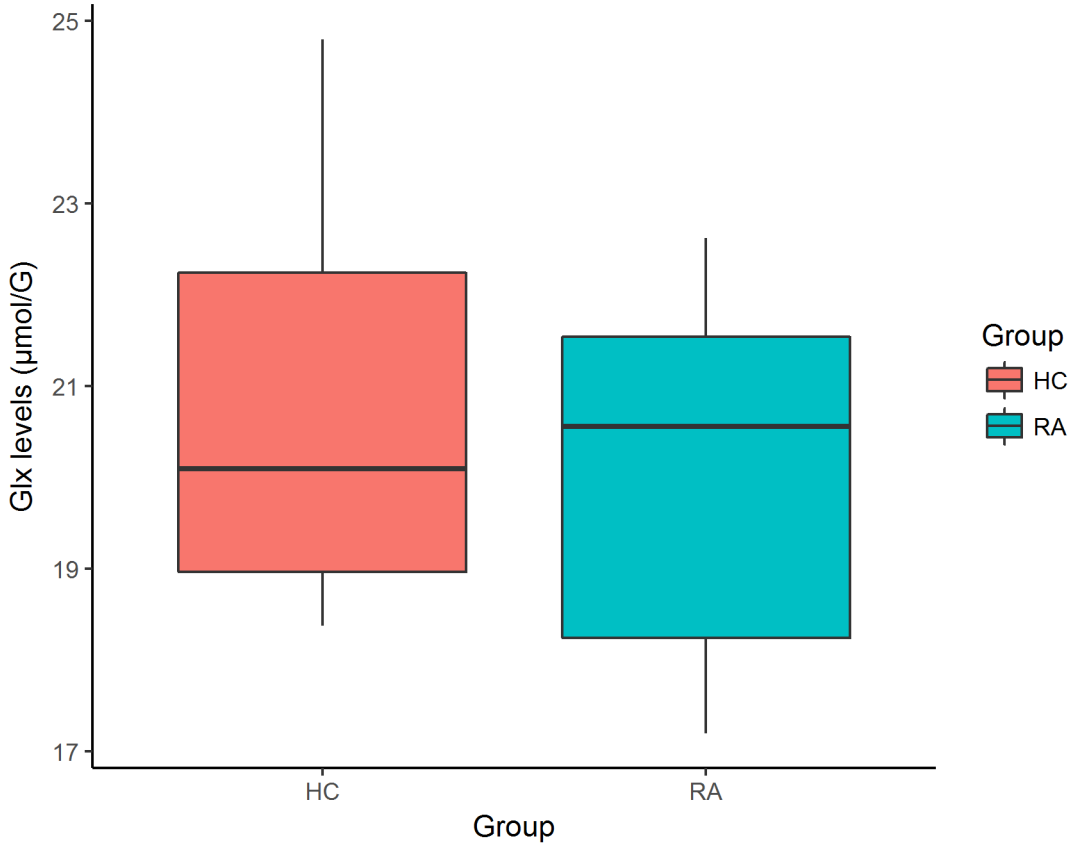
The spectra from two participants were removed as they did not meet the quality assessment standards outlined in Section 3.2.11.2 (data from one participant had a FWHM > 0.06, and one had an SNR of < 40). The spectra for alanine, lactate, phosphocholine, n-acetyl aspartyl-glutamate, taurine and scyllo-Inositol had CRLB > 30 for more than 50% of the participants so were removed from further analysis. No metabolites had a positive correlation of $r \geq 0.5$. As noted in the methods section, we report Glx as a composite metabolite of glutamate and glutamine due to concerns about the ability to independently estimate the levels of these metabolites at 3T.

There was no significant difference in voxel contents for GM, WM or CSF based on the SPM estimates (all $p > 0.05$). All metabolite concentrations are, however, corrected for GM, WM and CSF content as outlined in section 3.2.11.2.

Using unpaired two-sample t-tests, we analysed the differences between groups in Glx. In our sample, there was no significant difference in the levels of Glx between

groups, $t(28.24) = -0.92$, $p = 0.366$ (Figure 12). Notably, there was also no correlation between levels of Glx and symptom scores on the EDE: $r(29) = -0.39$, $p = 0.698$; or between levels of Glx and BMI: $r(29) = 0.09$, $p = 0.925$.

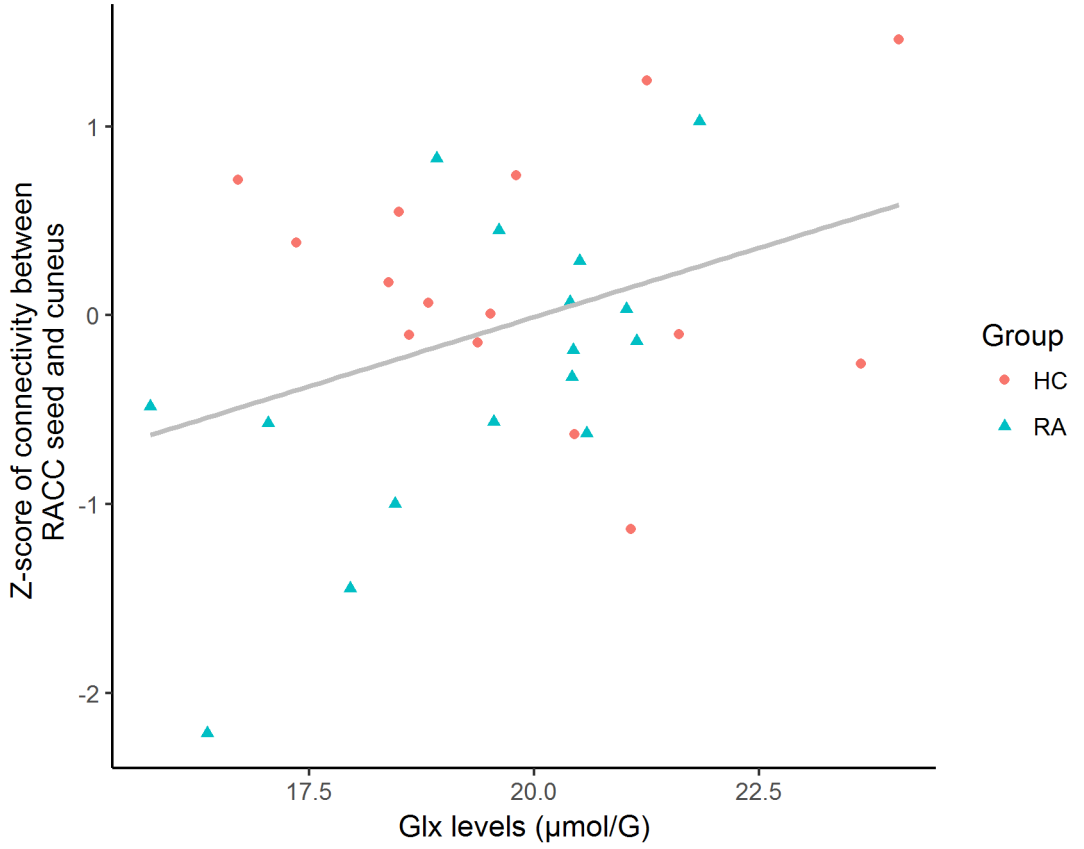
*Figure 12: Boxplot of Glx levels in the ACC by group.*




*This boxplot displays Glx levels (a composite of glutamate and glutamine) for both groups of participants in the ACC voxel. The metabolite levels were corrected for the (SPM estimate) of grey matter, white matter and CSF in the voxel. There was no significant difference between groups in Glx levels.*

Additionally, we correlated connectivity between the right ACC and the cuneus/lingual gyrus (which was significantly different between groups, see Section 0) with Glx across participants, as these measurements were made using the same brain region. There was a significant positive correlation between connectivity and Glx levels: $r(29) = 0.36$, $p = 0.044$, $R^2 = 0.13$, (Figure 13).

*Figure 13: Correlation between Glx and connectivity between the ACC and cuneus.*




*This scatter plot shows the level of Glx (measured in the ACC) and z-score of connectivity between the right ACC seed and cuneus for each participant, with points coloured by group. There is a positive correlation evident, displayed by the solid line.*

## 3.4 Discussion

In the present investigation, a multimodal MRI dataset was acquired and analysed: structural data were analysed using FSL-VBM; task-related fMRI data were analysed using FEAT in order to examine group differences in brain activation in response to set-shifting and reversal-learning events; RSFC data were analysed using corticostriatal seeds in order to determine group differences in functional connectivity; Glx group differences were analysed. The main results from the present investigation are as follows:

1. Structural MRI: No significant difference in grey matter volume, estimated using voxel-based morphometry, between groups.

2. Task-based fMRI: Significantly reduced activation of a cluster in the precuneus/angular gyrus during extra-dimensional versus intra-dimensional attentional switching for the RA group compared to the HC group, significant at a lower voxel-wise threshold of $Z > 2.3$. There were no differences in behavioural performance (either in terms of errors or RT) in the two groups on the in-scanner task.
3. Resting-state fMRI: Significant differences between groups in cingulate-cuneal connectivity, and (at a lower voxel-wise threshold of $p < 0.05$) in accumbal-parietal connectivity. The connectivity between the nucleus accumbens and parietal cortex was correlated positively with total EDE score in the RA group, and negatively in the HC group. There were also differences in the slope of correlation between perseverative errors on the WCST (performed outside the scanner) and connectivity. The RA group showed a lesser slope in the correlation between perseverative errors and connectivity between striatal areas and frontal regions, and a greater slope in connectivity between striatal areas and parietal/occipital regions. Greater connectivity between striatal and frontal regions within the RA group seemed to be linked to higher perseverative errors.
4. MRS: No difference in Glx between groups, or association with either BMI or eating-disorder symptoms (as measured by the EDE). However, Glx in the ACC did correlate with connectivity between the ACC and cuneus, which was different between groups.

Notably, the results of this multimodal MRI study do not match our predictions. Additionally, the majority of the results from this multimodal MRI study allow us to only highlight trends about neural differences between participants who have recovered from AN and healthy controls, due to the lack of significant results meeting more stringent statistical thresholds. The only result that arose from these analyses was of reduced connectivity between the ACC and cuneus in AN patients compared to controls. However,

at less stringent voxel-wise height thresholds (corresponding to $Z > 2.3$ or $p < 0.05$) there were additional neural differences between the participant groups in a number of different respects.

Importantly, there was no significant group difference in grey matter volume between the two groups. This indicates that the subsequent functional and neurochemical results are unlikely to be due to any difference in structure, either as the result of random chance or as the result of scarring from the malnourished/underweight state which many of the participants in the RA group will have experienced. This allows us to have greater confidence in the results from these functional analyses, though, as is common practice, we included the volume of grey matter, white matter and CSF in the ACC voxel used in the estimation of metabolite volumes in the MRS analysis.

Firstly, differences between RA and HC groups in the BOLD activation in the right angular gyrus/precuneus under the condition of extra-dimensional shifting compared to the condition of intra-dimensional shifting were identified, with the RA group showing a reduced difference in activation between the two conditions compared to the control group. The angular gyrus has been linked to reversal learning in a previous study using a set-shifting task (Rogers et al., 2000), and reduced grey matter in the right angular gyrus has also been reported in OCD patients (Valente et al., 2005). Additionally, the angular gyrus has been found to be more connected to other parts of the fronto-parietal network in patients with AN compared to control participants, and this is linked to self-reported persistence in control participants (Boehm et al., 2014).

The angular gyrus is activated in a variety of tasks and networks, including attention, the DMN, semantic and number processing. The angular gyrus can be considered to be a ‘node’, in which information from multiple domains is combined, and a

conceptual-level understanding is developed (Seghier, 2013). Greater activation of this area in control participants might indicate better abilities to respond to shifts in concept, as is required during extra-dimensional (but not intra-dimensional) shifts.

Alternatively, this difference in activation may be due to the previous experience of low body weight in our RA group. It has also previously been found that adolescent AN patients show higher activation in the angular gyrus during performance of a WM task compared to controls (Castro-Fornieles et al., 2010). Perhaps our finding of a result in the opposite direction in recovered patients is due to a compensatory process.

RSFC data were analysed between groups, with the hypothesis that corticostriatal connectivity would be altered in the RA group compared to HC. There was positive connectivity observed in RA participants between the left nucleus accumbens and the right postcentral gyrus, with the control participants displaying negative (but non-significant) connectivity between these regions. This connectivity was positively correlated with total EDE score in the RA group, and negatively in controls; perhaps indicating that in a vulnerable group, increased connectivity between these regions is related to worse ED symptoms. The parietal cortex is frequently suggested to be important in AN, with activity at rest low before treatment (especially during symptom provocation), and increased after treatment (Bär et al., 2015; van Kuyck et al., 2009). The parietal cortex integrates proprioceptive and visual information, along with information about appetite, and also modulates sustained attention. More broadly, this may reflect findings of altered frontoparietal circuitry function in compulsivity (Chamberlain et al., 2008; Menzies et al., 2008), with some arguing that the cortico-striatal model of compulsivity could be extended to include the parietal cortex (Göttlich et al., 2014). Frontoparietal network activity is important for appropriate attention and executive functioning, and differences in connectivity between this network and subcortical areas may lead to either under- or

over- attention and appraisal of fear signals, which may lead to compulsive behaviour (Göttlich et al., 2014).

Other researchers have argued that in compulsive disorders, limbic regions may be disconnected from fronto-parietal regions, whereas we seem to see the opposite in this study. However, studies have also found increased neural activity in the parietal cortex during symptom provocation in OCD (Adler et al., 2000; Rotge et al., 2008; Shapira et al., 2003), although reduced left inferior parietal activation has also been reported to food stimuli (which could be considered symptom provocation) in EDs (Uher et al., 2004). The increased connectivity between the parietal cortex and the nucleus accumbens in this population may be related to the unusual reward and attentional processing in relation to food/weight stimuli in ED groups (Cowdrey et al., 2011; Fladung et al., 2010; Park et al., 2014), but this hypothesis would require further investigation. A reduction in the thickness of parietal cortex in both adult and paediatric OCD patients was the main finding in a mega-analysis of 1905 OCD patients from 27 sites worldwide, further emphasising that the parietal cortices may play an important role in the psychopathology of compulsive disorders (Boedhoe et al., 2018).

Reports of hypometabolism in the parietal cortex in both AN and BN (Delvenne et al., 1999) may account for the increased BOLD signal in the HC group compared to the RA group in the parietal cortex in the extra-dimensional set-shifting contrast. However, this hypometabolism may normalise after weight restoration (Delvenne et al., 1996), and as such would not be expected to be a feature of the neural response to set-shifting in the recovered ED patients with healthy BMIs investigated here. Parietal hypometabolism is also unlikely to explain an increased RSFC between parietal regions and the nucleus accumbens in AN, because hypometabolism is likely to reduce the BOLD signal produced by a region, making a correlation with other brain areas less rather than more likely.

Notably, the findings of the present investigation differ to those found in a recent investigation of RSFC in current patients with AN-R using striatal seed regions (Haynos et al., 2018), despite similar sample sizes. However, there are a number of notable differences in the design of the present investigation and that of Haynos et al. (2018), primarily in the fact that their participant group had current AN-R, with a BMI of < 18.5kg/$m^2$, and were permitted to be taking psychotropic medication. Thus the differences between their findings and ours could be linked to either the use of medication, the underweight status of the participants (which has been highlighted as an issue earlier in this thesis, see section 3.1.1), or the fact that we recruited individuals who had recovered to attempt to identify RSFC differences related to trait ED status, rather than state ED or acute illness.

The other main between-group difference is the reduction in connectivity between the right ACC and cuneus/lingual gyrus in the RA group. This seems to be driven by a change in connectivity from positive to negative in the RA group compared to the HC group. This connectivity varies depending on the seed region and age of participants, with negative functional connectivity found in children and adolescents rather than adults using seeds closer to the most anterior parts of the cingulate (Kelly et al., 2009), but in this study, the connectivity in control participants was positive, and negative in the RA participants. This may be related to impulsivity, as a difference in connectivity between the dorsal ACC and lingual gyrus has been found in ADHD (Sun et al., 2012). Overall, the lingual gyrus is thought to be important for both vision and logic, with the ACC involved in impulse and emotional control, along with decision making. It is therefore possible that this connectivity is important for decision making, especially involving impulsivity. Those with current AN are thought to be less impulsive than control participants, and better able

to perform delay-discounting tasks, though this was found to normalise in recovery (Decker et al., 2015).

Additionally, this ACC-cuneal connectivity was found to correlate with Glx levels across all participants, which may imply that glutamatergic transmission, though not altered between groups, nevertheless is related to this connectivity difference. This is comparable to a finding in patients with major depressive disorder of correlation between lower Glx levels and lower postgenual ACC connectivity (Horn et al., 2010), and is in line with recent research suggesting that regional glutamate concentrations predict connectivity to other brain regions (Kapogiannis et al., 2013). Further investigation of this relationship may lead to a greater neurobiological understanding of how these RSFC differences arise, and whether neurochemical changes might precede connectivity changes, or vice versa.

Furthermore, there are differences in the slope of connectivity as WCST perseverative errors increase between groups: the RA group showed a lesser slope in the correlation between perseverative errors and connectivity between striatal areas and frontal regions, and a greater slope in connectivity between striatal areas and parietal/occipital regions. This might indicate that different connectivity underlies cognitive flexibility between controls and those who have recovered from AN, perhaps implicating a compensatory mechanism. However, in the absence of behavioural differences on this task, these connectivity differences had no observable impact on task performance in this case.

There was no evidence that indicated a difference in Glx in the MRS component of this study. There was a trend for numerically lower values in the RA compared to the HC group for Glx, but this was not statistically significant. It is possible that the metabolite

decreases seen in AN in some previous studies (Brennan et al., 2013; Godlewska et al., 2017) normalise after recovery, as has been observed for structural changes in both other studies (Mainz et al., 2012; Wagner et al., 2006), and in this one (Section 3.3.3). This would mean that these metabolite differences are likely to be a 'state' factor of the illness, and thus only an epiphenomenon of the underweight state. This is important information to be taken into account in future research, as state factors are unlikely to lead to new treatments. However, it is also possible that the sample size was too small to adequately detect a limited change in metabolite levels, especially given that the RA group was relatively noisy – at different stages of recovery, different ages, and with different illness durations. A larger sample could be recruited and these variables included as covariates.

Overall, the complementary findings of parietal differences in the RA group, in the absence of grey-matter differences, indicate that this is an important area to explore further in determining both the reason for and the effects of these differences. These findings support previous hypotheses of parietal involvement in the corticostriatal differences that lead to compulsivity, indicating that research could usefully consider the parietal cortex in more depth (Göttlich et al., 2014), as there are regions within it (here, the angular gyrus and the postcentral gyrus) which may be important in explaining the aetiology of rigid and inflexible behaviours.

# 4 ADAPTIVE LEARNING FROM ENVIRONMENTAL UNCERTAINTIES IN EATING-DISORDER RISK GROUPS

## 4.1 INTRODUCTION

One of the difficulties that pervades ED treatment is the relative lack of understanding of the cognitive processes that may be responsible for the maintenance of the highly compulsive, rigid behaviours that characterise this disorder (Godier & Park, 2014). One robust finding within the cognitive psychology research into EDs is that of cognitive inflexibility (Tchanturia, Anderluh, et al., 2004), especially in set-shifting paradigms (Roberts et al., 2007). This is thought to be present as a 'trait', i.e. not just a product of the disease-state (Holliday et al., 2005; Tchanturia et al., 2011). Cognitive inflexibility may be defined as a difficulty in flexibly altering responses given changes in the requirements of the task, the contingencies of the environment, or the goals that the individual is pursuing, and is a sub-domain within the broader endophenotype of compulsivity (Fineberg et al., 2014).

Changes in environmental contingencies or context result in a type of uncertainty known as 'unexpected uncertainty' (Yu & Dayan, 2005), which complicates many of the decisions and predictions that humans need to make. Therefore, representing and adapting your learning strategy to unexpected uncertainty is important. To better understand how cognitive inflexibility arises in ED groups, it is important to test whether there is a general inability to adaptively learn about unexpected uncertainty.

Changes in environmental contingencies should increase learning about the new predictive relationships in the environment (Behrens et al., 2007). The frequency of these changes is referred to as the volatility of the environment. Therefore, to cope with

unexpected uncertainty, one ideally needs to be able to distinguish between volatile and stable environments. If you imagine that you are organising a social event at the weekend, and trying to decide between a barbecue or a bowling trip, you would be sensible to start by examining the weather in recent days. During a typical 'British summer', you might have experienced more rainy days than sunny days over the last month. However, the last few days may have been abnormally warm, with no rain, and you might even have been wearing suntan lotion. Is this typical of a British summer, or does it tell you that the underlying probability of sunshine has changed, and is higher at the moment than it has been all month? If so, you are in a 'volatile' environment, and you should, when making your predictions about weather at the weekend, just account for the most recent days. However, if this is normal for a British summer, and does not reflect a fundamental change in the probability of sunshine, then you would be best to opt for the bowling trip – on average, after all, it has been rainy during the last month.

During this experiment, we used a task that manipulates volatility independently for positive and negative outcomes. For each of these outcomes, there are periods (blocks) where the associations between shape and outcome are volatile (volatile blocks) and blocks where the associations between shape and outcome are stable (stable blocks). As the volatility of the different outcomes (positive and negative) are manipulated independently, blocks may be volatile for one outcome, and stable for another. We take a computational modelling approach to analyse the learning rates of participants in this task. This modelling approach (summarised in Section 2.8) entails using a mathematical model of the transition from receipt of information to participant choice, which is fit to participant behaviour in order to infer the value of hidden variables such as the learning rate. A higher learning rate is equivalent to more heavily weighting recent outcomes compared to distal ones (as when the chance of sunshine is volatile, and the last few days

will give you a more reliable of the chance of sunshine than the average sunshine over the last month). Participants should thus use a high learning rate for volatile blocks and a low learning rate for stable blocks. We predict that the difference between these two learning rates will be lower in the ED risk groups, in line with the cognitive neuroscience evidence suggesting that those with EDs are cognitively inflexible, and struggle to adjust their behaviour (Holliday et al., 2005; Roberts et al., 2007; Tchanturia et al., 2011; Tchanturia, Anderluh, et al., 2004). A finding that those in ED groups adjusted their learning rates less would also correspond with a similar finding in anxiety disorders (Browning et al., 2015), which would be unsurprising given the high comorbidities between these two groups of disorder (Kaye et al., 2004).

Pupillometry data was also recorded and analysed. Pupillometry is thought to give an insight into the functioning of the central noradrenergic system (Joshi et al., 2016; Nassar et al., 2012), and NA is thought to signal unexpected uncertainty (Yu & Dayan, 2005). In their research, Nassar and colleagues found that changes in pupil diameter (i.e. phasic changes) correlated with environmental instability, with baseline diameter reflecting the uncertainty resulting from a recent environmental shift. Pharmacological manipulations that increase the release of NA are able to improve performance on attentional set-shifting tasks (which deliberately introduce a shift in context, and thus increase unexpected uncertainty) in rats (Devauges & Sara, 1990). Furthermore, NA deafferentiation in rats impairs set-shifting performance (McGaughy et al., 2008). However, not all of the evidence paints such a clear picture of the role of NA in signalling unexpected uncertainty: Jepma et al. found that atomoxetine (a NA transporter blocker) caused an increase in learning rate after an alteration in environmental contingencies (which they refer to as a ‘change-point’) if the baseline learning rate was low, but otherwise atomoxetine causes a reduction in learning rate (Jepma et al., 2016). Greater

pupil dilation in response to volatility (high frequency of 'unexpectedly uncertain' events) has also been observed previously (Browning et al., 2015; Pulcu & Browning, 2017), and pupil dilation may also be linked to surprise (Preuschoff et al., 2011). Therefore, pupillometry data might give additional insight into the participants' estimations of environmental uncertainty, and any deficits observed.

Participants with EDs often show deficits on set-shifting tasks (Roberts et al., 2007), and one might hypothesise that NA could be implicated in this impairment. Additionally, research has indicated that there is reduced NA functioning in ED patients, including those who have recovered (Kaye et al., 1984, 1985; Pirke, 1996), and a polymorphism in the NA transporter gene has also been linked to AN-R (Urwin et al., 2002).

The aim of this study was therefore to test whether individuals in ED risk groups adjust their learning rate in response to changes in environmental contingencies for both positive and negative outcomes to a lesser extent than control participants.

We predicted that those who were in the two ED 'risk' groups would show impaired learning rate adaptation when volatility altered, compared to the control participants. Therefore, the primary outcome measure was the difference in learning rate between volatile and stable blocks. We expected this reduced difference might be enhanced for negative outcomes than positive outcomes. We also predicted that there may be a reduced pupil dilation response to volatility in these 'risk' groups, commensurate with the prediction that they might show lower adaptation to changes in the environment, and informed by the fact that NA levels seem to be correlated to performance on set-shifting tasks in the animal literature.

## 4.2 METHODS

### 4.2.1 Ethical approval

The ethical approval reference for this study is R51898.

### 4.2.2 Sample size

There were no a priori estimates of the likely effect size in this study, as the previous study which has used the task in a clinical group used a correlational analysis rather than a case-control design (Browning et al., 2015). However, we performed a sensitivity analysis, and based on our chosen sample size of 25 per ED group and 32 control participants, we determined that we would have 0.95 power to detect an effect size of $d = 0.89$.

### 4.2.3 Participants

To investigate both trait and state effects of ED symptoms on learning about environmental contingencies, three groups of female participants were recruited (82 in total): those who had recovered from AN (RA), those who were highly concerned about their eating, shape and weight, but did not have a formal ED diagnosis (EA), and control participants who had never had an eating disorder and were below various markers on self-report questionnaires about eating, shape and weight (HC). It is thought that those with high levels of symptoms (the EA group) might allow insight into 'state' factors of EDs; and the RA group, as no longer meeting criteria for a diagnosis, might allow insight into 'trait' factors.

The total participant pool was comprised of 32 HC participants, 25 RA participants, and 25 EA participants.

All participants were aged between 18 and 45, fluent in English, and had a BMI of over 18.5kg/$m^2$ (to avoid the confound of malnutrition), which was measured during the study visit. All participants were also screened for current psychiatric diagnoses using the Structured Clinical Interview for the DSM-5, Research Version (SCID-5-RV). Those who appeared to have a current psychiatric diagnosis that would be likely to interfere with the results of the study were excluded (e.g. current depressive episode, current generalised anxiety disorder, current OCD, or a current substance use disorder). Participants did not smoke more than 5 cigarettes per day, and the number of cigarettes they did smoke (if applicable) was recorded. Participants were also excluded if they were taking a psychoactive medication such as an SSRI.

The RA group was defined by a self-reported former diagnosis of AN (reported as being made by a healthcare professional), confirmed by a SCID-5-RV interview indicating the presence of former AN, and no current ED diagnosis. They (as was true for all participants) were required to have a BMI of over 18.5kg/$m^2$, and to self-report as being recovered for over a year. Their current psychological recovery status was indexed in terms of the EDE-Q (Fairburn & Beglin, 1994), with full psychological recovery defined by a score of less than 1 standard deviation above the global mean, based on the norms. This was recorded but not used as an exclusion criterion.

The group who were concerned about their eating, shape and weight were defined by a score of above 20 on the EAT-26 (Garner et al., 1979). This is the putative clinical cut-off proposed by the original authors, and indicates significant concerns about shape, weight and eating, and corresponding behaviours.

The control group was required to score less than 1 standard deviation above the global mean on the EDE-Q, below 16 on the CIA (which measures impairment from ED-related symptoms) (Bohn & Fairburn, 2008), and below 20 on the EAT-26.

### 4.2.4 General procedure

The study involved the completion of pre-screening questionnaires: The EAT-26, EDE-Q, and CIA. If eligible, participants were invited for a single study visit. During that visit, the SCID-5-RV was performed. Subsequently, participants completed additional questionnaires online: the BDI-II to index depressive symptoms, the STAI to index anxiety symptoms, and the OCI-R to index obsessive-compulsive symptoms. They then completed the learning task reported in Pulcu & Browning (2017).

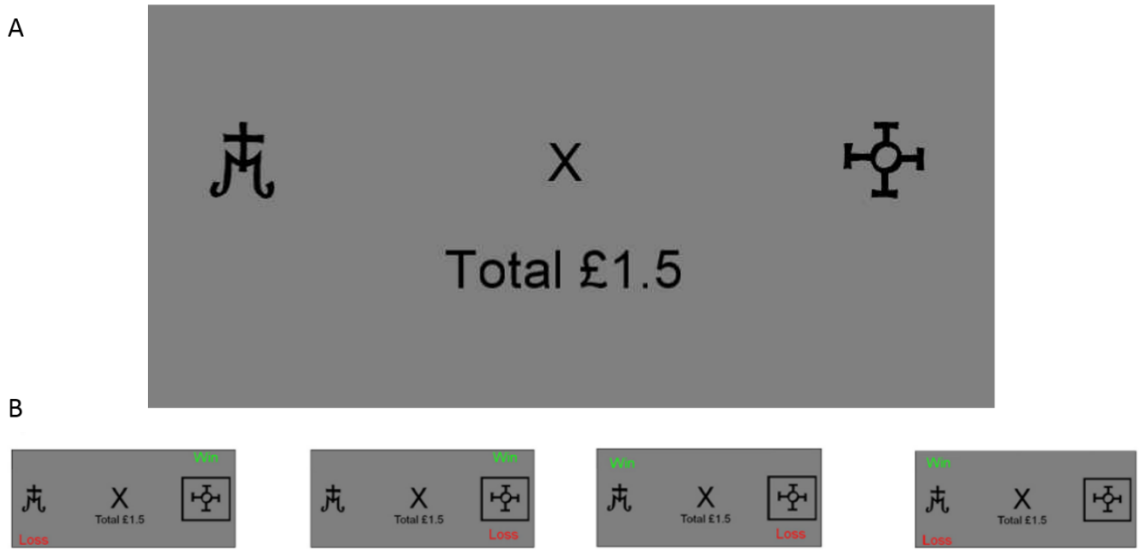
### 4.2.5 The volatility task

This study utilises a task which has been shown to produce adaptive learning in human participants. The volatility of outcomes (here defined as the frequency at which the associations between the stimuli and outcomes alter) is manipulated between blocks, which should produce an adjustment in learning rate. A 'learning rate' is a term frequently used in the field of reinforcement learning, which indicates to what extent the 'prediction error' (or difference between the expected and actual outcome of an action) updates the expectations or beliefs an agent has about their environment. Learning rates are bounded to be between 0 and 1, and can also be understood as the extent to which recent information is weighted compared to more distal information. As described in the introduction, it is optimal to have a higher learning rate when outcomes are volatile, as the more recent outcomes are relevant to inform the best choice, whereas older outcomes (particularly those before the contingencies shifted) are likely to be at best uninformative, and at worst actively misleading. Humans are able to adapt their learning rate in response to volatility in an approximately optimal way (Behrens et al., 2007).

A recent adaptation of the volatility task used by Behrens et al. (2007) has shown that not only are participants able to adjust their learning rate when volatility changes, but they are also able to maintain separate estimates of the volatility of different valence of outcomes ('wins' and 'losses') , adjusting learning rate for that outcome in response to these estimates (Pulcu & Browning, 2017). This novel task was used in the present study, so that both adaptive learning in general, and adaptive learning about positive and negative outcomes separately, could be probed in these participants.

The task used in this study is thus the same as reported in Pulcu & Browning (2017). On each trial, two abstract shapes (letters selected from the Agathodaimon font) were displayed, one on either side of the screen (Figure 14A).

*Figure 14: An example screen (A) and the various possible outcomes of making a choice (B).*




*An example screen, showing the two stimuli (abstract shapes, referred to as 'A' and 'B' throughout this chapter for convenience), a fixation cross in the centre of the screen, and the participant's monetary total below the fixation cross. In panel A, the screen at the point that a participant would have to make a choice is displayed. Below, in panel B, the different possible outcome associations for that trial are displayed: left to right, these are win associated with shape B and loss associated with shape A, both win and loss associated with shape B, win associated with shape A and loss associated with shape B, and both win and loss associated with shape A. The box around shape B reflects the choice they made on that trial (so, in this instance, they selected shape B).*

Participants then chose one of the shapes, having been instructed to try to maximise their wins and minimise their losses. They were then shown the outcome of their choice,

as ‘win’ and ‘loss’ appeared on the screen, above the shape with which they were associated on that trial (Figure 14B). Win and loss outcomes were independent, such that any shape could be associated with either a win, or a loss, or both a win and a loss, or neither. Wins had a value of 15p, and losses had a value of -15p. Therefore, if ‘win’ appeared by the shape they had chosen, they won 15p, if ‘loss’ appeared, they lost 15p, but if both ‘win’ and ‘loss’ (or neither) appeared by the shape they had chosen their total money stayed the same. Their ‘total money’ was displayed below a fixation cross for the duration of the task, and started at £1.50.

As the win and loss outcomes were independent, an optimal performer would learn separate estimates of which shape was associated with the win, and which shape was associated with the loss.

The task included three blocks, of 80 trials each. Participants were allowed to rest in between blocks. Shapes were changed between blocks, but not within – so the same two shapes were used throughout a block. The side of the screen the shapes appeared on was randomised. The total probability within a block that wins and losses were associated with shape A averaged to 50%, such that the task did not systematically favour either of the shapes within a block. ‘Shape A’ here just refers to one of the two abstract shapes (see Figure 14), with the probabilities for the win/loss outcome being associated with Shape A and Shape B summing to 1.

Volatility was manipulated block-wise throughout the task. When a particular outcome was ‘volatile’, its probability of being associated with shape A shifted between 0.15 and 0.85 (and vice versa) in segments ranging from 14 to 30 trials. When an outcome was not volatile (i.e. it was ‘stable’), it had a 0.5 probability of being associated with shape A. This meant that the ‘stable’ blocks could also be defined as ‘uninformative’ – the

outcome of previous trials does not allow for a better prediction of the outcome in subsequent trials.

During the first block, both ‘win’ and ‘loss’ outcomes were volatile. During the second and third block, in a counterbalanced order between participants, either the ‘win’ outcome was volatile whilst the ‘loss’ outcome was stable, or vice versa.

The task was presented on a VGA monitor connected to a laptop computer running Psychopy version 1.85.2. Participants were encouraged to keep their head still, and to assist in this they rested on a head-and-chin rest placed 42cm from the screen. An eye-tracking system was mounted on the rest, (Eyelink 1000 Plus; SR Research, Ottawa, Canada). The eye-tracking device was set up to record from both eyes (binocularly): it recorded participants’ gaze coordinates and pupil area, at a rate of 500Hz. A fixation cross was presented in the centre of the screen. Either side were the abstract shapes, offset by about 9 degrees visual angle. Below the fixation cross the ‘total money’ was displayed, and updated at the start of each new trial to reflect the outcomes from the last. The ‘win’ and ‘loss’ outcomes were presented separately in a random order, and were displayed for a jittered interval of 2-6 (mean 4) seconds. Sounds were played when the ‘win’ outcome appeared by the shape chosen by the participant (‘cha-ching’ sound), and when the ‘loss’ outcome appeared by the shape (‘buzz’ sound).

Participants were paid the money they obtained during the task, on top of the reimbursement for time and travel from the study as a whole.

Behavioural models were fitted to the participant’s choices to obtain estimates of their learning rates in different blocks of the task. This is discussed in more detail in the model section below.

### 4.2.6 Behavioural analysis

Participants who showed no evidence of learning during the task (those whose total money won was the same or less than the £1.50 they started with) were removed from further analysis (n = 4; comprised of two control participants, and one from each of the 'risk' groups).

Our primary outcome measure was the difference in learning rates for win and loss outcomes between volatile and stable blocks. We created reinforcement learning models based on previous work using variants of this task (Behrens et al., 2007; Browning et al., 2015; Pulcu & Browning, 2017), performed model selection to ascertain which model best described participants' behaviour, and then used the winning model to estimate the difference in learning rates for each participant per block. Below, the winning model is described, along with the alternative models we considered.

#### *4.2.6.1 Best-fitting model*

The model we use for analysis in the remainder of the chapter has four parameters: two learning rate terms, one inverse temperature term, and one bias term. This is referred to as 'Model 5' (see Table 9).

The first step for the model was to estimate the probabilities with which the win and loss outcomes were associated with shape A (Eq. 6 and Eq. 7). This was done using a Rescorla-Wagner learning rule (Rescorla & Wagner, 1972). Note that here there is a learning rate $\alpha$ for both wins and losses separately: these were estimated separately by the model as the win and loss outcomes were independent (though we also included in the model comparison an alternative model with a single learning rate).

$$P(win)_{A,t+1} = P(win)_{A,t} + \alpha win * (win_{A,t} - P(win)_{A,t}) \qquad Eq.\ 6$$

$$P(loss)_{A,t+1} = P(loss)_{A,t} + \alpha loss * (loss_{A,t} - P(loss)_{A,t}) \quad \textit{Eq. 7}$$

Above, $P(win)_{A,t}$ is the probability on trial *t* that the 'win' outcome is associated with shape A, and $P(loss)_{A,t}$ the probability on trial *t* that the 'loss' outcome is associated with shape A. Note that the probability of the win/loss being associated with shape B for any given trial is 1 minus the probability of the win/loss being associated with shape A. These are both initialised at 0.5, assuming that participants have no reason to believe that the outcome is associated with a specific shape at the start of each block. $win_{A,t}$ and $loss_{A,t}$ have a value of 1 if that outcome is associated with shape A, and 0 if associated with B, on the current trial *t*, and $\alpha win$ and $\alpha loss$ are the separate learning rates for 'win' and 'loss' outcomes, bounded between 0 and 1. As a reminder, a higher learning rate is equivalent to more heavily weighting the recent outcomes when updating the probability that the outcome is associated with shape A.

These separate probabilities are then combined into a *'value'* variable.

$$value_{A,t} = P(win)_{A.t} - P(loss)_{A,t} + bias \quad \textit{Eq. 8}$$

Here, $value_{A,t}$ is the value of shape A on trial *t*, which is just the participant's estimated probability of winning when choosing shape A on trial *t* minus the probability of losing when choosing shape A on trial *t*, with a *bias* term added, which is the preference an individual has for a particular shape (estimated per block), that slightly skews the value towards that shape. This can take values between -1 and 1.

Subsequently, these decision values were translated into choice probabilities. Participants rarely use a stepwise function to convert probability to choice, but are somewhat inconsistent or exploratory. In simple terms, if $value_{A,t}$ (defined as in Eq. 8) > $value_{B,t}$, one might assume the participant would choose shape A every time, leading to a

probability of 1 for choosing shape A. Vice versa would be expected for shape B: when $value_{B,t} > value_{A,t}$, one might assume that the participant would choose shape B with a probability of 1. However, individuals are more likely to make choices which are imperfect or probabilistic. This behaviour can be captured using a sigmoid function, such that probabilities increase to 1 the more the values differ.

$$P(chooseA) = \frac{1}{1 + e^{-(\beta * value_{A,t})}} \qquad \textit{Eq. 9}$$

Here, the $\beta$ term is an inverse temperature parameter, which is multiplied by the *value*, calculated as in Eq. 8. The term 'inverse temperature' is a relic of the fact that, for two choices, the sigmoid function often used to capture choices is the same as the Boltzmann function in statistical mechanics. This parameter governs the stochasticity of choices that the participant makes. As $\beta$ tends to 0, choices tend towards complete randomness; as $\beta$ tends to infinity, choices tend to complete determinism.

This leads to four free parameters, $\alpha win$, $\alpha loss$, $\beta$, and *bias*, which are all estimated separately for each block. This is achieved by calculating the full joint posterior probability of each combination of parameters, given the series of choices made by the participant, and calculating the expected value of the parameters from the marginalised probability distributions, as in the previous work using this task (Pulcu & Browning, 2017), and also as explained in Section 2.8.1 of this thesis. This estimation is done separately for each task block, and for each participant. We removed 10 trials of each block at the stage of calculating the choice probabilities using the softmax function. These trials were excluded on the basis that we also removed them from the pupillometry analysis due to adaptation to luminance effects (see below).

#### *4.2.6.2 Alternative behavioural models*

We compared this model with a number of alternative behavioural models, which were also fitted to participant choice data. This was done in order to find the model most likely to produce the choice sequences we observed; as two of our three groups were recruited to have specific clinical features, we could not expect that previous models found to best explain choice behaviour on this task would be the best fitting models in our experiment.

The models can be classified into two different 'families'. The majority of them fall into the same family as the model already described, in that they assume that participants are learning about wins and losses separately. There is one model from another 'family', which assumes that participants combine the information about wins and losses early on, into an 'outcome', and learn the associations of those outcomes with different shapes. This is Model 4. The models are outlined in more detail below - though note that Model 5, as the 'best-fitting' model (see Section 4.3.2.1) is outlined above. See Table 9 for a summary of the models compared.

Model 1 was the same as in (Pulcu & Browning, 2017), with two learning rate terms (as in Eq. 6 and Eq. 7), and two linear scaling parameters. These parameters are akin to the inverse temperature mentioned above, except that they separately multiply the probabilities of winning and losing, whereas an 'inverse temperature' modulates the overall shape of the sigmoid function (i.e. $\beta win * P(win)_{A.t} - \beta loss * P(loss)_{A,t}$).

Model 2 used a single learning rate parameter, and two linear scaling parameters as in Model 1. Therefore, for this model, the separate $\alpha win$ and $\alpha loss$ terms in Eq. 6 and Eq. 7 are replaced with a single $\alpha$ term. Notably, the probabilities of wins and losses being associated with different shapes are still estimated separately, just using the same value

for the learning rate term. Parameters for each block were also estimated separately, as in Model 1.

Model 3 has two learning rate terms and one inverse temperature parameter, and is identical to the winning behavioural model (Model 5) except that it lacks the *bias* term.

Model 4 has a single learning rate and a single inverse temperature parameter, which is thought to reflect a 'model-free' (Daw et al., 2011) strategy for performing the task. Participants using this strategy are thought to lack a 'model' of the structure of the task or environment, including the different states one can be in. In our task, this would entail not learning independently about wins and losses, but learning just about the values of actions based on the outcome of each shape on the previous trial. Thus, the 'value' is calculated as:

$$value_{A,t+1} = value_{a,t} + \alpha * \left(outcome_{A,t} - value_{A,t}\right) \qquad \textit{Eq. 10}$$

where

$$outcome_{A,t} = win_{A,t} - loss_{A,t} \qquad \textit{Eq. 11}$$

Model 5 is the model described above, in Section 4.2.6.1.

The models were all fitted using the same procedure, which entailed obtaining the full joint posterior probability and then calculating the expected values of the parameters from the marginalised probability distributions (see also Section 2.8).

*Table 9: Summary of models fitted to participants' choice data.*

| Model | Number of learning rate terms (α) | Number of linear scaling parameters (β) | Extra terms | Notes |
|---|---|---|---|---|
| **1** | 2 | 2 | 0 | Original model used for this task (Pulcu & Browning, 2017) |
| **2** | 1 | 2 | 0 | |
| **3** | 2 | 1 | 0 | |
| **4** | 1 | 1 | 0 | Also referred to as 'model-free' |
| **5** | 2 | 1 | bias | Model used in rest of analysis |

#### *4.2.6.3 Model comparison*

Akaike information criterion (AIC) scores were calculated for all models. The AIC is an approximation to the log model evidence, and enables comparisons between different models, to see which best fits the data. The calculation incorporates the log likelihood of the model, and then contain a term which penalises models for complexity, in order to avoid overfitting (which would impair generalisability of the model to a new population). A lower score indicates a better fit of the model to the data, given the parameters used.

$$AIC = -2\mathrm{y} + 2k \qquad \textit{Eq. 12}$$

where $k$ is the number of parameters, and y is the log model likelihood at the estimated value of the parameters, which is just calculated as the sum of the logs of the individual probabilities of each of the sequence of choices made by the participant. This is equivalent to the log of the product of the individual probabilities of each trial. The log likelihood is used as the likelihood of a sequence of choices is often very small, so the log is taken for convenience.

$$y = sum(\log(\mathrm{P}(Choice_{t=1:n}) \qquad \textit{Eq. 13}$$

The winning model was calculated using the sum of AIC, and was confirmed using the SPM Model Selection procedure (from SPM12, version 5842 https://github.com/neurodebian/spm12/blob/master/spm_BMS.m). This procedure allows for the possibility of heterogeneity within the sample (i.e. different participants using different models) and outliers. We used the negative of the AIC as a proxy for the log model evidence. This takes models as random effects, and uses a hierarchical model based on variational Bayes. In brief, this method estimates the parameters of a Dirichlet distribution to describe the probability densities of the models included (Rigoux et al., 2014; Stephan et al., 2009).

#### *4.2.6.4 Statistical analysis of model parameters*

The parameters obtained from the behavioural models were transformed to the real line before analysis. This required a logit transform for learning rates, a log transform for inverse temperatures, and a logit transform for the absolute value of the bias term. Figures are shown non-transformed for clarity.

Initially, we replicated the behavioural effect reported previously (Pulcu & Browning, 2017). To do this, we performed a repeated-measures ANOVA on the learning rates with order (i.e. which order the second and third blocks were in) as a between-subject factor, and block volatility (both volatile (block 1), win volatile or loss volatile) and valence as within-subject factors. The effect of interest for this analysis was the interaction between volatility and learning rate valence (i.e. $\alpha win$ or $\alpha loss$), which would indicate that participants are able to adjust their learning rates independently for positive and negative outcomes, in response to changes in volatility.

The primary analysis of this study aimed to see if there were group differences in ability to alter learning rate between blocks, which we examined using a repeated-measures ANOVA on the difference in each learning rate between volatile and stable blocks (volatile-stable). As described above, in block 1 both outcomes were volatile. Thus, the difference in learning rate was calculated by taking the mean learning rate of the two volatile blocks for that outcome (e.g. for wins), and subtracting the learning rate for the stable block for that outcome. The between-subject factors were group and order, and learning rate valence was the single within-subject factor. These ANOVAs used estimated parameters from all three blocks.

### 4.2.7 Pupillometry analysis

#### *4.2.7.1 Preprocessing*

Data obtained using the Eyelink 1000 Plus system was preprocessed as in Pulcu & Browning (2017). This involved the following steps. Firstly, blinks were identified using the system's build-in filter and removed. Secondly, a low-pass Butterworth filter with a cut-off of 3.75Hz was applied. The data was then z-transformed across the whole task (Nassar et al., 2012). Thirdly, the pupil dilation response to win and loss outcomes was extracted separately based on the time they appeared in each trial (which outcome appeared first was randomised). The time-window that was extracted for each outcome was from 1s before until 6s after outcome presentation. This was then baseline corrected, by subtracting the mean of the 1s before the outcome was presented (the baseline) from each timepoint within the time window. Fifthly, data was interpolated when blinks or saccades to outside the area caused us to remove it.

Individual trials were excluded from analysis if more than 50% of the data in that trial was interpolated (Browning et al., 2015; Pulcu & Browning, 2017), and participants

were removed if more than 50% of their trials were removed for this reason (n = 2). Another participant had to be removed as the end of their pupillometry data was lost due to a power outage. For the remainder of the participants, the mean percentage of trials excluded was 7%.

As in the previous studies using this task, and as mentioned above, the first 10 trials from each block were not included in analysis, as initial pupil adaptation is likely in response to luminance changes during this period (Browning et al., 2015; Nassar et al., 2012).

These steps culminate in two sets of time series for each participant: one set including the portion during each trial corresponding to the display of the 'win' outcome, and one set including the portion during each trial corresponding to the display of the 'loss' outcome.

Subsequently, for both win and loss outcomes, we separated the time series into two: one based on the pupil response when the outcome was received (i.e. when that outcome was associated with the shape they had chosen), and one based on the pupil response when the outcome was not received (i.e. when that outcome was not associated with the shape they had chosen). The difference between these two time series (chosen and unchosen) was then calculated, leading to a time series for each outcome of pupil dilation in response to receipt vs. non-receipt of that outcome (i.e. a time series for chosen-unchosen loss outcomes). These two resulting time series (for wins and losses) were binned into bins of 1s, to allow a repeated measures ANOVA to be performed.

#### *4.2.7.2 Statistical analysis of pupil data*

The two (one per outcome) binned pupil time series of pupil dilation for chosen – unchosen outcomes were analysed using a repeated-measures ANOVA with time-bin,

block volatility, and valence of learning rate as within-subject factors, and group and order as between-subject factors.

In all analyses, significant interactions were followed up by standard post-hoc tests, using Welch's t-test (assuming unequal variances). If the assumption of sphericity in any ANOVA was violated, Greenhouse-Geisser corrected values were used.

## 4.3 RESULTS

### 4.3.1 Participants

Participant groups did not differ in mean age, BMI, state anxiety (measured by the STAI state), or OCD symptoms (measured by the OCI-R). However, participant groups did differ in mean eating disorder symptoms (measured by the EDE-Q and the EAT-26), and also differed in how much those symptoms affected their daily lives (measured by the CIA). Groups also differed in their mean depressive symptoms (measured by the BDI-II) and mean trait anxiety levels (measured by the STAI trait).

*Table 10: Summary of participant demographics and questionnaire measures*

| | **EA** | **RA** | **HC** | **Group difference** |
|---|---|---|---|---|
| Age | 23.78 (5.15) | 23.48 (3.77) | 25.03 (6.38) | None ($p = 0.469$) |
| BMI | 21.76 (2.78) | 21.79 (2.43) | 23.09 (4.81) | None ($p = 0.123$) |
| EDE-Q | 3.16 (0.77) | 1.49 (1.23) | 0.99 (0.84) | $F(2,79) = 36.37$, $p < 0.001$ |
| EAT-26 | 28.52 (6.80) | 7.43 (12.21) | 5.33 (5.00) | $F(2,79) = 61.39$, $p < 0.001$ |
| CIA | 19.52 (9.02) | 9.09 (8.84) | 3.73 (4.11) | $F(2,79) = 32.69$, $p < 0.001$ |
| BDI-II | 8.39 (9.39) | 5.61 (5.68) | 2.60 (4.65) | $F(2,79) = 5,74$, $p = 0.005$ |
| STAI trait | 38.74 (13.21) | 40.26 (9.83) | 29.63 (8.03) | $F(2,79) = 8.77$, $p < 0.001$ |
| STAI state | 32.83 (12.65) | 31.74 (5.44) | 27.53 (9.45) | None ($p = 0.103$) |

| | EA | RA | HC | Group difference |
|---|---|---|---|---|
| OCI-R | 7.65 (7.37) | 6.78 (6.63) | 5.40 (6.57) | None ($p$ = 0.428) |

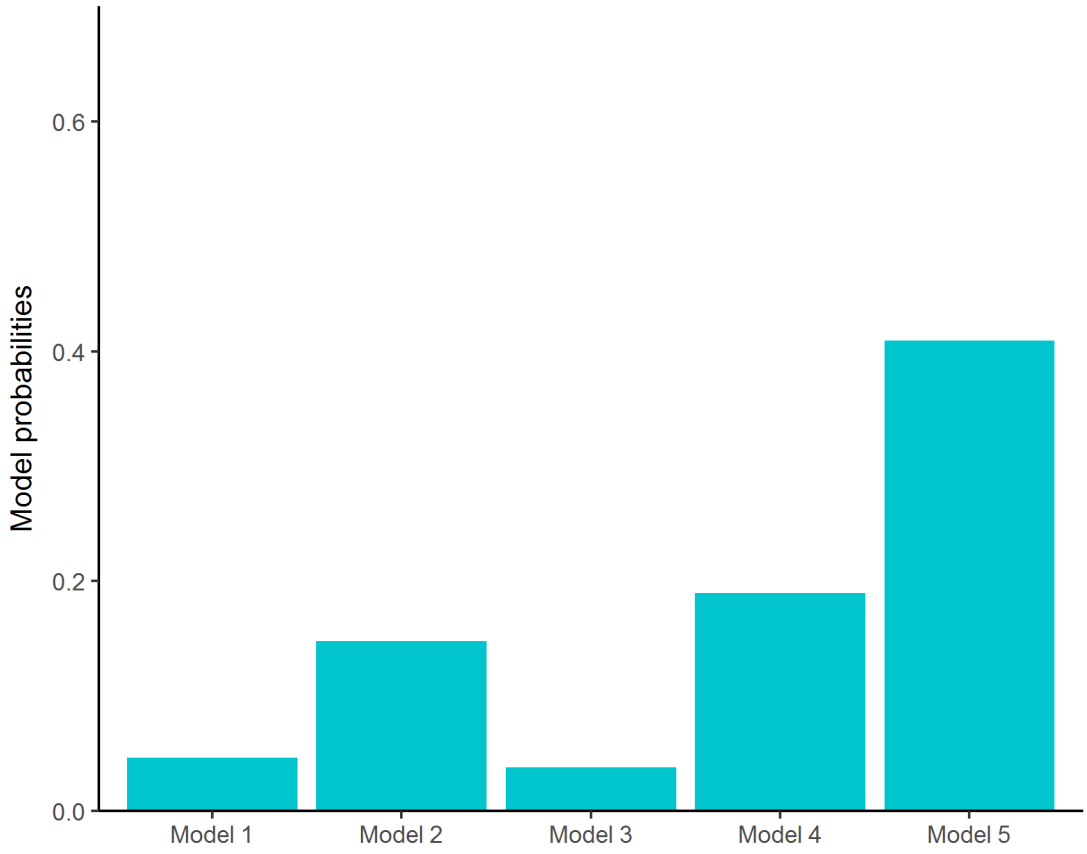
*Mean, standard deviation scores, and ANOVA results (with 3 levels of 'group') are displayed. There was a significant group difference in EDE-Q, EAT-26, CIA, BDI-II and STAI trait, and no significant group differences in STAI state, OCI-R or BMI.*

### 4.3.2 Behavioural results

#### *4.3.2.1 Modelling the volatility task*

The model with the lowest sum of AIC scores was Model 5. We confirmed this using the Bayesian Model Selection procedure outlined above (Stephan et al., 2009). This is displayed below in Figure 15.

*Figure 15: Results of model comparison*



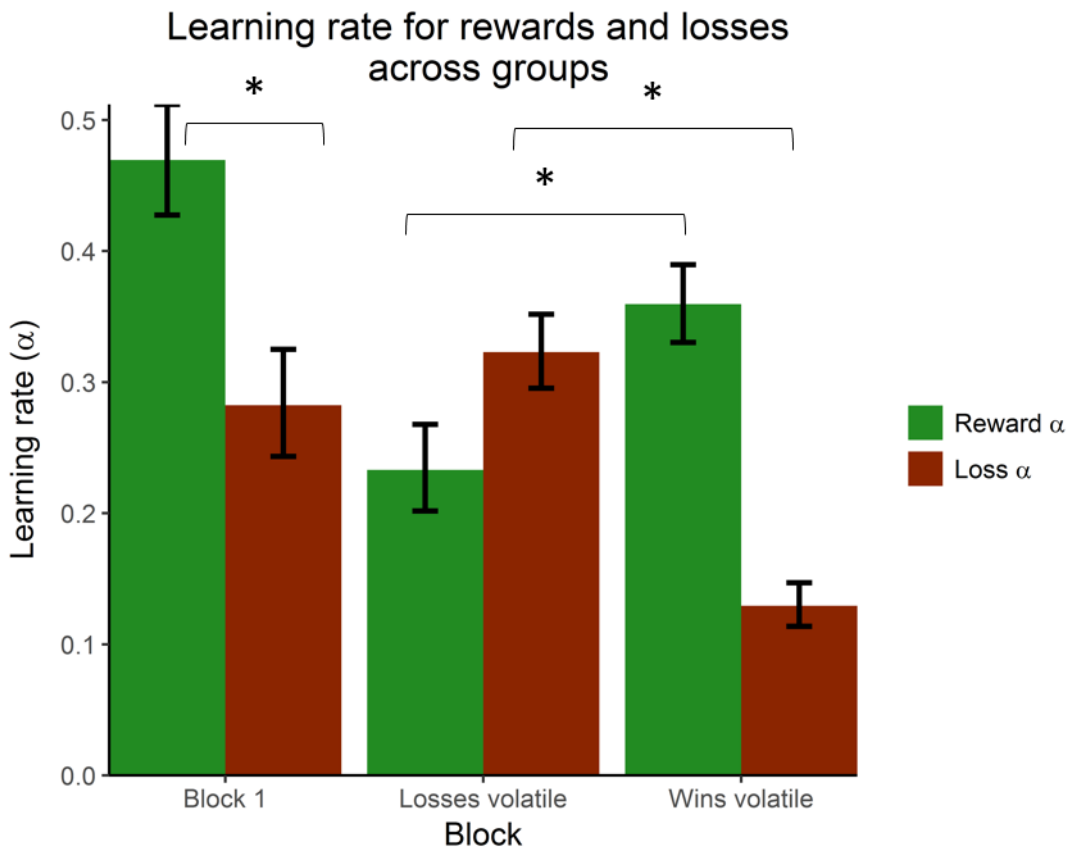

*Model probabilities for the different models of participant choice behaviour given the fitted parameters. These model probabilities are calculated using the random effects Bayesian Model Selection procedure in SPM12, using AIC as a proxy for log model evidence. Here, a higher probability for a model indicates that it is a better fit to the data.*

#### *4.3.2.2 Overall behavioural effects*

Across groups, and in support of previous work, participants were able to adjust their learning rates, increasing them when an outcome was volatile, and decreasing when an outcome was stable (Behrens et al., 2007; Browning et al., 2015; Pulcu & Browning, 2017): $F(1.95,148.21) = 46.94$, $p < 0.001$ (Figure 16). This was calculated using a repeated measures ANOVA as described in the Methods section. Post-hoc t-tests indicated that learning rate to positive outcomes in both of the blocks where they were volatile was higher than when they were stable, and this was the same for negative learning rates (all $p < 0.05$).

There was a significantly higher learning rate for win outcomes compared to loss outcomes in the first block (when both outcomes were volatile): $F(1,76) = 17.07$, $p < 0.001$. Both of these effects remained when the participants who performed poorly on the task were included.

*Figure 16: Learning rates for rewards and losses by block and group.*




*Bar plot (with standard error of the mean as error bars) showing the learning rate for wins and losses depending on the block and volatility. In the first block, both wins and losses are volatile; in the 'losses volatile' block, wins are stable; and in the 'wins volatile' block, losses are stable. Participants are able to increase their learning rate when outcomes were volatile separately for win and loss outcomes. There is a significant bias towards a higher learning rate in the first block. Significant effects of interest ($p < 0.05$) are indicated with a *.*

#### *4.3.2.3 Group effects*

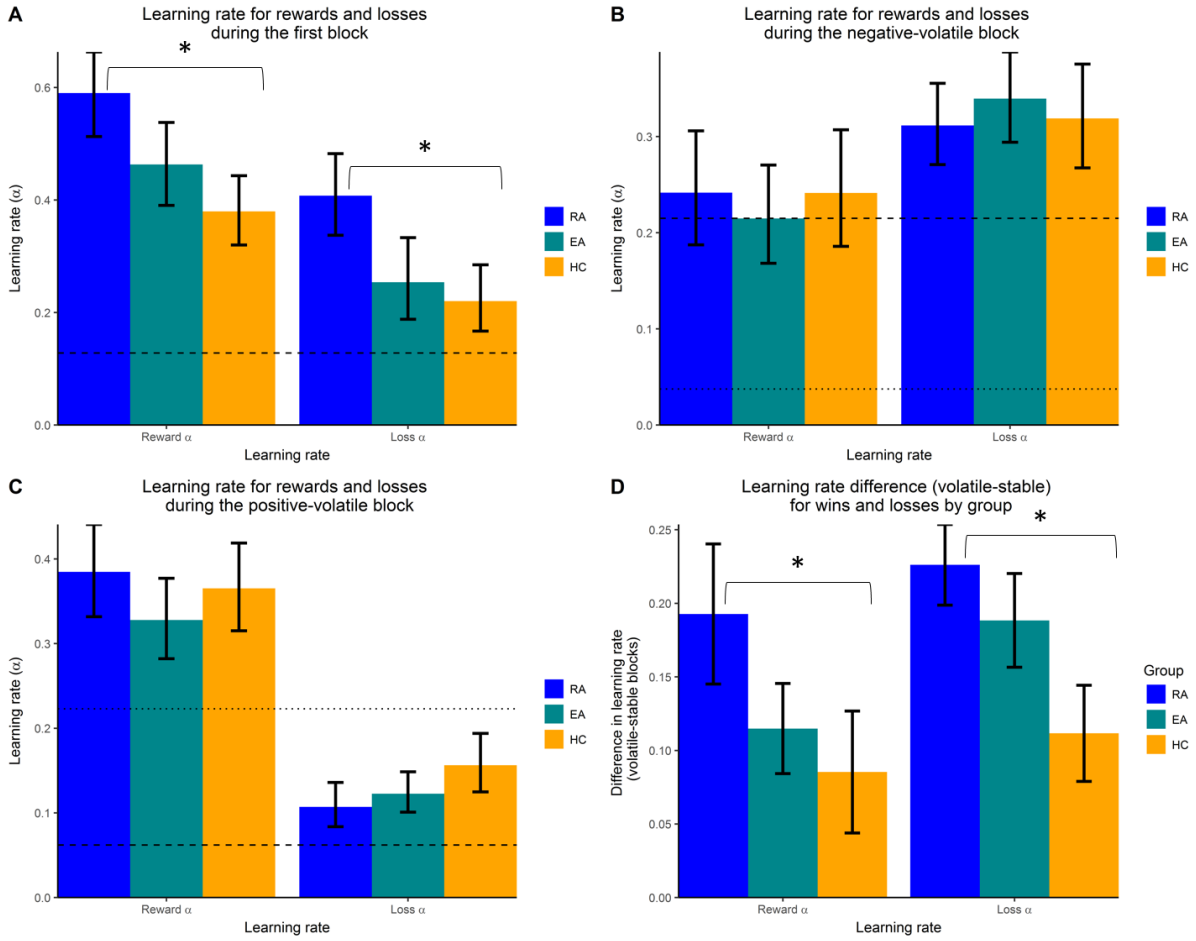
There was no difference in money won between groups: $F(2,72) = 0.28$, $p = 0.757$ [RA group: $M$ = £6.85, $SD$ = £2.01; EA group: $M$ = £7.29, $SD$ = £1.87; HC group: $M$ = £6.99, $SD$ = £2.32].

Using Model 5, there was a significant main effect of group in the repeated measures ANOVA which used the difference between learning rates (α) in volatile and stable blocks (described in more detail in the Methods section above): $F(2,72) = 4.31$, $p = 0.017$. (Figure 17D). We performed post-hoc ANOVA analyses for differences between RA and HC, and EA and HC. There was a significant difference in learning rate adjustment for RA compared to HC: $F(1,50) = 7.28$, $p = 0.010$; but no significant

difference in learning rate adjustment for EA compared to HC: $F(1,50) = 2.14$, $p = 0.150$; and no significant difference in learning rate adjustment for EA compared to RA: $F(1,44) = 2.40$, $p = 0.128$. Learning rate adjustment was highest in the RA group: $M = 0.21$, $SD = 0.19$, second highest in the EA group: $M = 0.15$, $SD = 0.16$, and lowest in the HC group: $M = 0.10$, $SD = 0.20$ (Figure 17D).

For completeness, we analysed this data by valence (i.e. difference in win learning rates; and difference in loss learning rates) and by block. Both valence effects were found to be in the same direction, with elevated learning rates for both wins and losses in the RA group compared to the HC group. This effect was only statistically significant for loss outcomes (using t-tests examining difference in learning rate separately for valence of outcome): $t(51.83) = -2.68$, $p = 0.010$, but was not statistically significant for win outcomes: $t(48.81) = -1.70$, $p = 0.095$. It is worth noting, however, that there is no evidence that this effect is specific to negative outcomes: in the ANOVA reported above, there was no significant interaction effect with valence: $F(2,72) = 0.18$, $p = 0.834$.

*Figure 17: Learning rates per block (A to C) and per group, and difference between learning rates in volatile and stable blocks (D) by group.*




*Bar plots with error bars of +-SEM. A-C: learning rates per block (A: block 1, B: negative volatile block, C: positive volatile block) by group, where both wins and losses are volatile. A to C also display 'ideal' learning rates, extracted from choices for the block in question derived from the Bayesian ideal observer model, collapsed over different block order schedules. In block 1, the same 'ideal' learning rate was found for both wins and loss outcomes, which is represented by a dashed line. In panels B and C, the dotted line represents the 'ideal' reward learning rate, and the dashed line represents the 'ideal' loss learning rate. D: the difference in learning rates (volatile block for that outcome – stable block for that outcome) by group, and by valence of learning rate (reward/loss). Significant effects of interest ($p < 0.05$) are indicated with a *.*

As stated above, we also examined learning rates by block, to further understand this effect (Figure 17, panels A-C). There was no significant effect of group in an ANOVA of the learning rates in block 1, but there was a trend towards such an effect: $F(2,72) = 2.99$, $p = 0.057$. This was not the case for the block in which wins were volatile: $F(2,72) = 0.24$, $p = 0.785$, or the block in which losses were volatile: $F(2,72) = 0.01$, $p = 0.989$. In a post-hoc analysis looking pairwise between groups, the RA group had a significantly higher learning rate in the first block (where both outcomes were volatile)

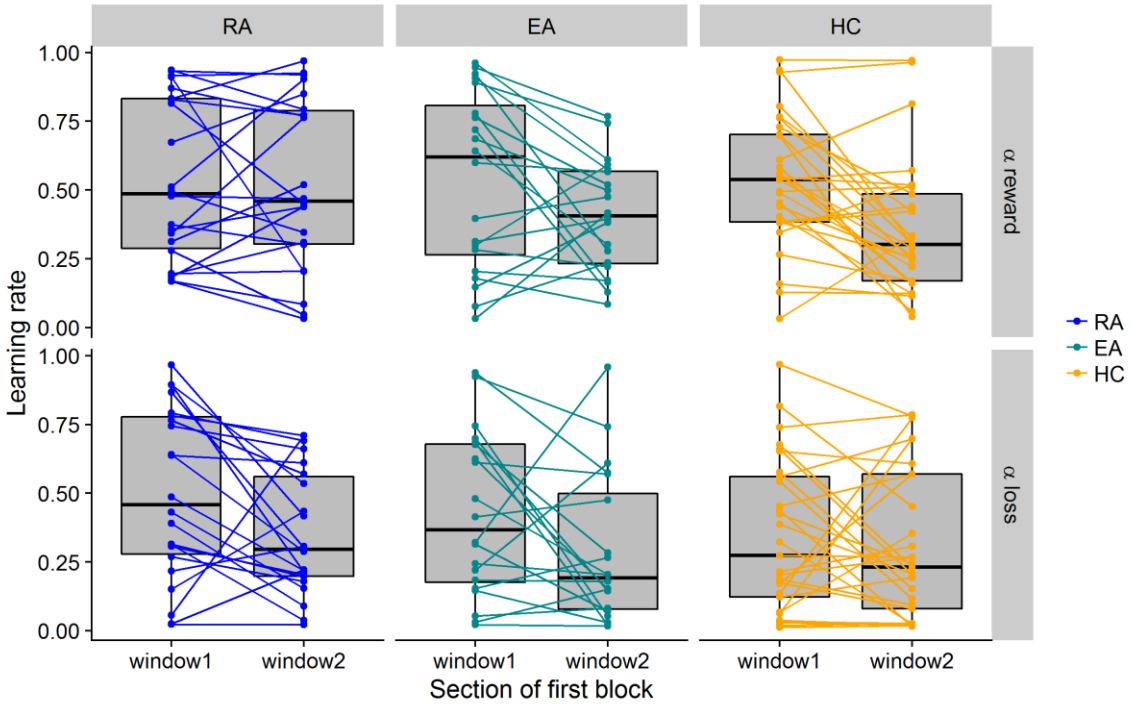
than the HC group: $F(1,50) = 7.19$, $p = 0.010$. There was no difference between the EA group and healthy control participants: $F(1,50) = 0.60$, $p = 0.442$. All groups had significantly different learning rates in block 1 compared to the 'ideal' learning rate (dashed line in Figure 17A, all $p < 0.05$, using t-tests), with the exception of the loss learning rate in the HC group ($p = 0.06$). The 'ideal' learning rate was calculated using the bias model (with 0 bias, and an inverse temperature parameter that caused deterministic behaviour) based on simulated choices from a Bayesian ideal observer (BIO) model's estimates of the probabilities of win and loss outcomes.

The observed difference in learning rates in block 1 may cause the initial finding of a greater difference in learning rates between volatile and stable blocks in the RA participants. When only learning rates when the respective outcome was stable were included, there was no group difference: $F(2,72) = 0.22$, $p = 0.801$. When all learning rates when the respective outcome was volatile were included (i.e. not just block 1), there was also no group difference: $F(2,72) = 1.46$, $p = 0.238$. We also re-ran the ANOVA for learning rate difference (volatile-stable) with only the second and third block included; the main effect of group on learning rate difference was no longer present: $F(2,72) = 0.41$, $p = 0.666$, although this may be due to the fact that the number of trials used for analysis reduced by a third, reducing power to detect differences. It is also worth noting that there is a confound in the structure of the task, in that both outcomes are always volatile in the first block. This means that a significant group effect on the difference between volatile and stable outcomes is hard to disentangle from a significant group effect linked to the start of a new task.

Learning rate is sometimes high at the start of tasks when participants are learning about how to perform well. If the increased learning rate in the RA group is for this reason, it might be expected that the learning rate should decrease during the course of the

first block. However, when the first block was divided into two, there was no significant difference in the learning rates of the RA group between the first and second half: $t(93.98) = 1.58$, $p = 0.119$. In contrast, the EA group did decrease their learning rates between the first and second half: $t$ (91.25) = 2.10, $p = 0.039$, and there was a trend towards the HC group doing the same: $t$ (117.89) = 1.92, $p = 0.057$. There were no significant differences between the RA and HC group in the first half, $t$ (101.90) = 1.69, $p = 0.093$; or in the second half, $t$ (101.28) = 1.91, $p = 0.058$, though there was a trend for learning rates to be higher in the second half in the RA group compared to the HC group ($M = 0.40$ vs. 0.27, $SD = 0.37$ vs. 0.38). This is shown in Figure 18 below.

*Figure 18: Plot of learning rates in the first and second half of block 1 by group and valence of learning rate.*




*Each facet represents a different group and a different learning rate (wins or losses), and there are scatter plots for the learning rates of individuals (joined to the same participants' learning rate in the other half of the block by a coloured line), superimposed over boxplots. 'Window 1' refers to the first 40 trials of block 1, and 'window 2' refers to the second 40 trials. These learning rates are displayed using a scatter plot, with each point representing the learning rate for one participant estimated during one of the windows in the task. Below, in grey, are boxplots of the median (central line), first and third quartiles (hinges), and largest/smallest value no further than 1.5 * inter-quartile range (whiskers).*

We also investigated the relationship between the learning rates in the first block and scores on clinical questionnaires. We created a linear model for each of the different

learning rates for block 1 (i.e. $\alpha win$ and $\alpha loss$), group, and each of the questionnaire measures. We inspected the model for collinearity: there were no factors with a Variance Inflation Factor > 4. There were no significant effects of any of the questionnaire measures on either $\alpha win$ or $\alpha loss$ in block 1.

#### *4.3.2.4 Relationship between anxiety and ability to adjust learning rate*

Due to previous findings linking ability to adjust learning rate to trait anxiety (Browning et al., 2015), we used a linear mixed model to estimate the effect of trait anxiety on ability to adjust (with fixed effects of order, valence (i.e. shifting for reward outcomes or loss outcomes), and group, and a random effect of participant). There was no significant effect of trait anxiety on ability to shift, $\beta = 0.001$, $p = 0.482$. The direction of this effect is different to the previous finding, such that ability to shift slightly increases as trait anxiety does.

#### *4.3.2.5 Other model parameters*

There was no significant main or interaction effect of group on the inverse temperature parameter (all $p > 0.05$). There was also no significant main or interaction effect of group on the absolute value of the bias parameter (all $p > 0.05$).

### 4.3.3 Pupillometry results

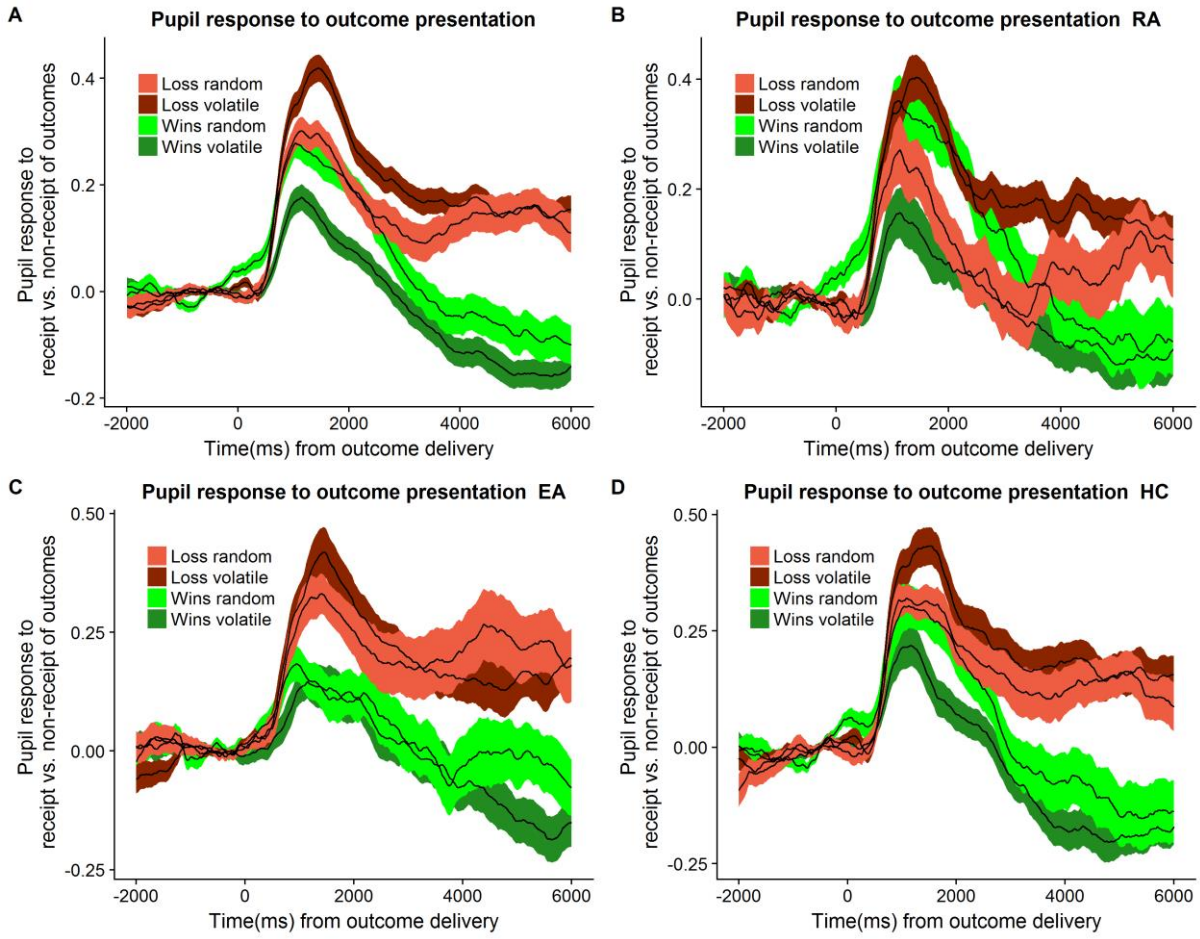
#### *4.3.3.1 Pupil dilation across participant pool*

The initial analysis of pupil data indicated no main effect of volatility, but an interaction effect between volatility and valence, with volatile outcomes causing greater pupil dilation than stable outcomes for loss outcomes, but vice versa for win outcomes: $F(1,69) = 10.32$, $p = 0.002$ (Figure 19A).

#### *4.3.3.2 Pupil dilation between groups*

There was also an interaction effect between group, volatility and time-bin: $F(5.07,175.00) = 2.73$, $p = 0.020$. To understand the source of this effect, we performed individual ANOVAs for each time-bin, with group and order as between-subject factors, and volatility and valence of outcome as within-subject factors. The only time-bin for which there was a significant effect including group was the one for the time-bin between 1000 and 2000ms after outcome presentation, where there was an interaction effect between group, volatility and valence: $F(2,69) = 3.21$, $p = 0.046$. This effect seemed to be present when the outcome was stable, when this result was broken down further by volatility: $F(2,69) = 4.57$, $p = 0.014$. Post-hoc t-tests indicated that the EA group seemed to have a reduced pupil dilation response when the 'win' outcome was stable compared to the HC group: $t(49.94) = 2.26$, $p = 0.028$, $M = 0.14$ and 0.28 respectively, and $SD = 0.21$ and 0.25 respectively.

*Figure 19: Pupil dilation responses to the presentation of outcomes*




*Line graph of pupil dilation response to outcome presentation by the volatility of that outcome, for receipt – non-receipt of outcomes. Coloured bands represent the standard error of the mean. A shows the total participant group, B the RA group, C the EA group, and D the HC group.*

## 4.4 Discussion

In this chapter, we found an increased difference between volatile and stable learning rates in the RA group (Figure 17D). This is unexpected, as we predicted a decreased difference in the ED risk groups, reflecting impaired cognitive flexibility. Either this result indicates greater flexibility in ED groups, and greater sensitivity to alterations in environmental contingency, or this effect may be driven specifically by an initial effect in the first block (Figure 17A) rather than a general effect across blocks. The evidence for the effect being specific to the first block is that there was no significant effect of group in any other block, nor when analysing by volatility (ANOVAs for stable

outcomes and volatile outcomes separately, see Section 4.3.2.3). However, the confound in this task between block order and volatility, in that both outcomes are always volatile in block 1, reduces the ability to disentangle effects specific to the first block from effects specific to volatility.

There are a number of potential reasons for a finding of heightened learning rate in the first block. Firstly, it may be that when a novel task is presented, the RA participants use a higher learning rate due to an exaggeration of the normal process of heightened uncertainty in response to novelty. However, if this were the case, their learning rate would be expected to decrease between the first half and second half of the first block (which takes between 10 and 15 minutes for most participants to complete), which we did not find. In contrast, we found that the other two groups decreased their learning rates more during the first block. There were, however, no significant group differences between either the first half or second half alone; but a trend towards the RA group having a higher learning rate in the second half compared to the HC group. Future work might investigate whether the novelty of a task has a longer-lasting effect on the behaviour of participants who have recovered from AN, which might explain the higher learning rates during the initial block, and the fact that they did not decrease.

Secondly, learning rates may be especially high in RA participants in blocks where there is high volatility for multiple outcomes. There may be difficulty pinpointing the source of the uncertainty, or difficulty in estimating the effects of the volatility on the task, resulting in a higher learning rate (which corresponds to a greater reliance on recent task outcomes, including the previous trial). Further work could reorder the task blocks, such that novelty is de-confounded from volatility.

Importantly, we have shown that the 'ideal' learning rate for this first block, as estimated based on outputs from a BIO model (Behrens et al., 2007), is significantly lower than almost all of the learning rates used. Only the loss learning rate in the HC group was not significantly different from the ideal (Figure 17A). The use of the BIO model allows us to have some gauge on how an idealised agent might perform this task; indeed, how a Bayesian agent (or, one who updates the probabilities of an event based on a combination of experience and the prior probabilities of that event) might perform this task. Whilst there is debate about what extent we are Bayesian (Williams, 2018), deviation from the responses that an idealised Bayesian agent might give usually come with some penalty, often in terms of obtained reward. Therefore it is likely that the RA group, with higher learning rates in this block of the task, might experience difficulties if this finding translates to their real-world learning strategies. However, there was no difference in total money won at the end of the task between groups.

Additionally, the task did cause participants to adjust their learning rates in response to the volatility of the environment, and to do this specifically and independently for both win and loss outcomes (Figure 16). This replicates findings from previous studies (Behrens et al., 2007; Browning et al., 2015; Pulcu & Browning, 2017).

Secondly, in our pupillometry analysis, across groups we found the expected volatility effect for losses (higher pupil dilation when outcomes were volatile), but not for wins. When we analysed pupil dilation by group, we found that there was an interaction effect between group, volatility and time-bin to pupil dilation to outcomes; specifically, the EA group showed reduced pupil dilation when win outcomes were in 'stable' blocks compared to HC participants (Figure 19). This finding is unexpected, as we predicted a reduced pupil dilation to volatility, and a reduced difference between pupil dilation responses to volatile and stable environments. Previous cognitive neuroscience studies

have shown that changes in pupil diameter may reflect a number of different influences, from cognitive effort, to uncertainty, to surprise, to changes in the world (Nassar et al., 2012; Preuschoff et al., 2011). In particular, pupil change has been found to reflect change-point probability (i.e. the likelihood of a change in the underlying state of the environment), but also individual differences in learning rate, learning rate on next trial, and uncertainty after a change (Nassar et al., 2012). However, the findings from our pupillometry analysis do not seem to relate to the behavioural findings, so they are hard to interpret.

Pupil change is also affected by arousal, which may have differed between groups at different points in the task. Nassar and colleagues found that there was an effect of arousal on learning rates consistent with a Yerkes-Dodson curve: when pupil diameter was above average, additional arousal reduced learning rates; and vice versa (Nassar et al., 2012). The pupillometry measures in this study are not sufficient to examine absolute pupil diameter, which could be worth controlling for in future studies.

It is important to note that the effect of reward surprise on pupil dilation in the EA group is different to what one might hypothesise. We hypothesised a reduced pupil dilation response to volatility in both of the ED risk groups, so future work should attempt to replicate this finding, and see if it affects behaviour or cognition in these participants.

There are a few limitations to this study which should be mentioned – random noise is not orthogonal to volatility. In the blocks which were ‘stable’, i.e. the associations between wins/losses and shapes did not fluctuate, these associations were set at a probability of 0.5. Essentially, this means that there is a 50% chance of the ‘win’ being associated with shape A, and a 50% chance that it is associated with shape B (and the same for losses), if that outcome is defined as ‘stable’. Therefore, the ‘stable’ outcomes

also have high levels of random noise, which participants may struggle to disentangle from volatility. Indeed, there is evidence to suggest that humans do not learn optimally about noisy outcomes, and that random noise may affect learning rates (Pulcu & Browning, in prep.).

Additionally, the difference in the RA group does not necessarily reflect a trait difference. It is also possible that the RA group have simply experienced more severe ED symptoms over their life, or that the effects are a result of 'scarring' from their illness.

In sum, whilst we did not find the hypothesised effect of under-sensitivity to environmental change in the ED-risk groups, we found greater learning rate adjustment in the RA group, which may be driven by a greater learning rate for both rewards and losses in the first block. This may be due to effects of novelty, or difficulty in estimating volatility in environments with multiple sources of volatility. Additionally, we found a difference in reward surprise in individuals with high levels of current ED symptoms (the EA group). This may indicate a difference in how environmental changes are estimated. More sensitive behavioural tasks should be designed to elucidate whether this effect on pupil dilation has any effect on behaviour, and, at a broad level, whether this could impact on cognitive flexibility in individuals with ED symptoms.

# 5 How do Glutathione levels affect compulsivity? A double-blind, placebo-controlled study

## 5.1 Introduction

NAC is a dietary supplement and glutathione precursor, which has been found to produce therapeutic benefit in certain disorders with components of compulsivity (Section 1.4.2), for example, trichotillomania, nail biting, and cannabis dependence (Deepmala et al., 2015; Oliver et al., 2015). NAC's neuropsychological mechanism of action in these disorders has not yet been investigated, but one might hypothesise that it produces benefit by acting directly on compulsivity or some related process, such as impulsivity. Despite the fact that impulsivity (acting rapidly with limited consideration of the consequences, Section 1.6) is sometimes seen as an opposite construct to compulsivity, recent studies suggest that impulsive and compulsive behaviours may share pathophysiological mechanisms, and co-exist in the same disorders (Fineberg et al., 2014). Thus it seems that if NAC acted by altering either compulsive or impulsive responding it might well be of benefit in conditions marked clinically by increased compulsivity.

As noted above, NAC has been investigated recently in a number of different compulsive disorders, either as a sole treatment or an adjunctive therapy. Whilst the literature is sometimes contradictory, there is evidence for improvements in trichotillomania (Grant et al., 2009), along with excoriation disorder (Grant et al., 2016) and gambling disorder (Grant et al., 2007). There have been studies in OCD (Afshar et al., 2012; Costa et al., 2017; Paydary et al., 2016; Sarris et al., 2015), but the overall body of

evidence suggests only a small benefit in this condition (Couto & Moreira, 2018). Additionally, there seems to be therapeutic utility specifically in reducing craving in Substance Use Disorders (Duailibi et al., 2017). This demonstrated benefit in some compulsive disorders may indicate that NAC acts by reducing compulsive responding.

NAC is readily available as a dietary supplement in the UK, and is also used for the treatment of acetaminophen overdose in hospitals. It is an acetylated version of the naturally occurring amino acid cysteine, and is converted to cysteine in the body (Dringen & Hamprecht, 1999). Cysteine is a precursor to glutathione, which is a major cellular antioxidant in mammals. NAC is used to increase glutathione levels in the brain as it more bioavailable than cysteine. Preclinical and clinical research has confirmed that NAC is able to increase levels of glutathione in the brain (Dean et al., 2011; Dringen & Hamprecht, 1999; Holmay et al., 2013).

The initial promise shown by NAC in the treatment of compulsive disorders led us to consider whether, due to the evidence for compulsivity in EDs, and informed by a transdiagnostic approach, NAC might be helpful in the treatment of EDs. Clinical EDs are often severe, as has been discussed in the introductory chapter of this thesis (Section 1.2.4) and difficult to treat. If it were possible for the impulsive and compulsive behaviours present in EDs to be modified by a nutritional supplement such as NAC, this would augment current treatment options.

The aim of this study was twofold: both to investigate whether sub-acute NAC administration could modify impulsive or compulsive task behaviour, and to see whether this might be a potential approach of relevance to EDs: thus we selected a relatively healthy participant group, who could be considered ‘at-risk’ for EDs based on their response to a self-report questionnaire of ED symptoms. Our primary outcome measure was perseverative errors on the WCST.

## 5.2 METHODS

### 5.2.1 Ethical approval

The ethical approval reference for this study is R44271.

### 5.2.2 Sample size

We were unable to locate any previous studies of NAC on psychological tasks designed to tap impulsivity or compulsivity. However, a previous study from our group found an effect of the anti-oxidant and lithium-mimetic, ebselen, to decrease impulsivity ('delay aversion') in the Cambridge Gambling Task (CGT), using a randomized, placebo-controlled, cross-over design in 20 healthy participants (Masaki et al., 2016). We therefore followed the same design in the present study. We calculated the effect size on the Cambridge Gambling task for this study to be 0.49, and based on this, we calculated that we needed a total sample size of 38 (or, 19 participants in total in a cross-over design) in order to have a power of 0.90 to detect a difference of a similar size on a cognitive task between groups (based on a matched samples t-test). We recruited a small number of extra participants in case of noncompliance or data exclusion, and thus recruited 23 participants for this study.

### 5.2.3 Participants and recruitment

Participants were 23 English-speaking females aged 18-40 (mean 23.7, range 19-37) with a BMI over 18.5kg/$m^2$ (mean 22.6, range 19.1-27.7). They were selected to score between 9 and 19 on the EAT-26 questionnaire, which corresponds to a score higher than 60% of the population, but below the putative 'clinical cut-off' (mean 14.1, range 9 to 18).

All participants were screened using the SCID-IV, to assess whether they were currently suffering from a psychiatric disorder. All participants who met criteria for an

Axis I psychiatric disorder based on this structured interview were excluded. No participant was taking psychotropic medications.

### 5.2.4 Study procedures

All participants completed a pre-screening questionnaire, which was the EAT-26 (Garner et al., 1979). They then attended three study visits.

The first was a one-hour screening visit, in which the study was fully explained to the participant and fully informed consent was taken. Participants provided an overview of their medical history and any current medication. Subsequently, the SCID-IV was completed, as were the SSS (Godier & Park, 2015a), which indexes compulsive self-starvation, and the HADS (Bocéréan & Dupret, 2014), which measures anxiety and depression symptoms without the focus on somatic items such as fatigue which might skew the results of those who are engaging in dieting or fasting behaviours. The EAT-26 questionnaire was also repeated. During this screening visit participants were randomised to receive either NAC or placebo first, and were given the requisite number of capsules in a bottle to take at home. They were informed about how to contact a researcher if any side effects caused them discomfort. They were also asked to record the time they took each dose during the administration period, and completed a side-effects questionnaire each day, in which they rated a number of side effects (e.g. nausea) from 0 (not present) to 3 (severe).

After the first day of administration, they were emailed to ask if they were experiencing any side effects.

On the 9$^{th}$ and final day of the administration period, participants returned for the first of two three-hour testing visits. During this visit, a small (5ml) venous blood sample was taken for measurement of glutathione levels. Those who did not wish to give blood

were not excluded. Participants then completed the three key questionnaires again: the EAT-26, HADS, and SSS. This took approximately 20 minutes. After this was complete, they carried out several computer-based tasks, taking around two hours. The tests are described in further detail in Section 5.2.7. Participants were asked about any adverse effects experienced, and also asked to make a guess as to whether they had taken NAC or placebo. Participants were then given the capsules for the other arm of the study (placebo if they had previously had NAC, and vice versa), and were instructed to take these after a 7 day washout period.

Participants were reminded of the start of the second arm of the study (post-washout period) by email. They were also asked after the first day to report any adverse effects.

After the 7 day washout period and 9 day administration period, the participants returned again for the third study visit. The procedures followed were as during the second visit.

### 5.2.5 Drug manipulation

Participants were randomized to receive either NAC or placebo first. During the NAC condition, participants took an initial two days of 1200mg NAC (one capsule in the morning, and one in the evening), followed by 7 days of 2400mg NAC (two capsules morning and evening). The dose was based on the typical dose used in previous studies, based on the therapeutic effect and safety profile (Deepmala et al., 2015), and was slightly higher than the mean effective dose used in a pathological gambling pilot investigation (Grant et al., 2007). During the placebo condition, participants took an equivalent number of placebo capsules each day. Between doses there was a 7-day washout period. Note that the main researcher was blinded for the drug manipulation.

### 5.2.6 Blood glutathione

During both study visits, a small (5ml) venous blood sample was collected. The blood sample was collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged, then stored at -30°C. Samples were analysed for glutathione levels by a collaborator (Professor Helga Refsum). Plasma concentrations of 19 analytes (amino acids including total sulphur amino acids, taurine and creatinine) were measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS) using a modified version of a previously described method (Antoniades et al., 2009). Briefly, isotopically-labelled internal standards were added to plasma followed by reduction of disulphides using dithioerythritol [100 mM] and then protein precipitation using 5-sulfosalicyclic acid [10%]. The extracts were diluted with an aqueous solution of formic acid [0.5%] and heptafluorobutyric acid (HFBA) [0.3%] prior to analysis. LC-MS/MS was carried out using a Shimadzu LC-20ADXR Prominence LC system (Kyoto, Japan) coupled to a Sciex QTRAP5500 mass spectrometer with a Turbo V ion source and TurboIonspray probe (Framingham, MA, USA). Chromatographic separation was achieved on a Phenomenex Kinetex Core Shell C18 (100 x 4.6 mm, 2.6 μm) LC column (Torrance, CA, USA) with an aqueous solution of formic acid [0.5%] and HFBA acid [0.3%] and acetonitrile gradient mobile phase. Positive mode multiple reaction monitoring was used for detection. Linear calibration curves of the peak area ratios of analyte and internal standard were used for quantification. Coefficient of variation for the analytes were 3.4 – 6.7%. The method was validated for 16 of the 19 analytes using spiked serum QA samples from an external quality assurance scheme ERNDIM (www.erndim.org).

### 5.2.7 Psychological tasks

The tasks completed by participants were selected in order to measure both impulsivity and compulsivity, and to probe different cognitive aspects of each of these

constructs. The cognitive tasks measuring compulsivity were the WCST, the Attention Switching Task (AST, CANTAB), the AGN, and the Two-Step Task; the tasks measuring impulsivity were the CGT (CANTAB) and a delay discounting task (DDT). These tasks and their relevant outcome measures are outlined below.

*Table 11: Table of tasks used in the NAC study.*

| **Task** | **Measures** |
|---|---|
| WCST | Perseverative errors (compulsivity) |
| AST | Switching cost during shift vs non-shift blocks (compulsivity) |
| AGN | Shifting cost to RT when rule changes (compulsivity) |
| Two-Step Task | Model-based index (compulsivity) |
| CGT | Delay aversion (impulsivity) |
| DDT | Delay discounting (impulsivity) |

*Participants performed these tasks after 9 days of either NAC or placebo administration. Also displayed are the primary outcome measures for each task. Note that RT means reaction time.*

In the WCST, participants are presented with cards, which they have to sort into one of four different piles based on number, colour or shape (Berg, 1948; Piper et al, 2012). They receive feedback of 'correct' or 'incorrect', and from this they must attempt to ascertain the correct dimension to use to sort the cards. However, this may subsequently change: the only indication of this change is an increase in 'incorrect' feedback when using the dimension that was previously correct. Here, the outcome measure used is perseverative errors, which are errors in which participants sort using the previous dimension rather than the current correct dimension after a shift has occurred.

The AST is a task in which participants are shown arrows on either side of the screen, pointing to the left or to the right. They are tasked with selecting either left or right depending on a rule. The rule can either be that they must respond to the side of the screen the arrow is on, or the direction that it is pointing. In the final block, the rule is displayed on the screen in a trial-wise manner, rather than varying block-wise during the training. The switching cost is the difference between response latency during blocks where the rule changes in a trial-wise manner, compared to the latency of response during the blocks where the rule is held constant across the block.

The AGN task is outlined in the General Methods section (Section 2.6.2). To briefly recap, this task requires participants to press a touch-sensitive button on the screen when words that are either positive or negative are presented. The valence that should be responded to (either positive or negative) is indicated at the start of each block. The shifting cost is the slowing of responses when the 'rule' changes or shifts from selecting positive to negative words, or vice versa.

The Two-Step Task (Daw et al., 2011; Gillan et al., 2016) involves two steps of participant action per trial. Initially, participants are presented with two fractals, and they choose one. Probabilistically, the state then shifts to one of two final states (coloured orange and blue in this case), which also contain two fractals. The participant must choose between these, and is then either rewarded or unrewarded. The probability of the final fractals being rewarded is determined by a Gaussian walk, and the probability of a given initial fractal leading to the two final coloured states is constant at 0.7 and 0.3. A 'common' transition is thus from a given fractal to the coloured state which has a 0.7 transition probability, and a 'rare' transition is from a given fractal to the coloured state which has a 0.3 transition probability. A model-free learner will respond largely to the outcome of the previous trial (rewarded or unrewarded) when deciding whether to repeat

their initial choice; a model-based learner will base their knowledge of the transition probabilities of the initial fractals to the coloured states when deciding whether to repeat their initial choice. Put another way, if a model-based participant chooses fractal A, and then is given a choice between fractals 3 and 4, then chooses 4 and wins money, they would choose fractal A again if the transition between A and the state containing fractals 3 and 4 is common, and B if the transition between A and the state containing fractals 3 and 4 is rare. Here, the model-based index indicates to what extent participants use that model-based strategy.

The CGT involves participants being shown a set of ten squares, some of which are coloured red, and the remainder of which are coloured blue. They are instructed to guess whether a yellow token is hidden behind one of the blue-coloured or red-coloured squares. After making their guess, they may bet a certain number of their points on whether or not they are correct – these points range from 5% of their total to 95%. There are two 'modes' – ascending and descending. In ascending mode, the points they can bet are shown in ascending order, and they bet by pressing the touch-screen square. In the descending mode, the points they may bet are presenting in descending order. Delay aversion is the difference in the proportion bet depending on whether the mode is ascending or descending: i.e. corresponding to how averse participants are to waiting for a longer time to bet a smaller (and thus less risky) amount.

The DDT displays choices for participants between an immediate or a delayed reward, with the delay ranging from 12 hours to one month, and the reward ranging from £5 to £16. They have to select whether they would rather have the immediate or delayed reward on each trial.

### 5.2.8 Data analysis

#### *5.2.8.1 Outcome variables from psychological tasks*

For the WCST, the outcome measure we used was the number of errors in which a participant sorts a card incorrectly, based on the previous rule rather than the current one. Outlier trials were classified as those with a reaction time of greater than the mean reaction time plus three standard deviations, and were removed.

The switching cost in the AST is the difference between mean response latency in blocks in which the rule is shifting trial-wise and blocks in which the rule is held constant. Outlier trials were again classified as those with a reaction time of greater than the mean reaction time plus three standard deviations, and were removed.

Shifting cost in the AGN task was calculated as the mean latency for correct responses in shift blocks, minus the mean latency for correct responses in non-shift blocks. Outlier trials were again classified as those with a reaction time of greater than the mean reaction time plus three standard deviations, and were removed.

The Model-Based Score for the Two-Step Task was derived using logistic regression, using the established procedure (Gillan et al., 2016). Participants who missed more than 100 trials were excluded from task analysis (n = 1). This analysis was performed in R, version 3.3. The switch/stay behavior of participants on the current trial (switch = 0, stay = 1) was the dependent variable, with the regressors being the reward on the previous trial (rewarded = 1, unrewarded = -1), transition type (common = 1, rare = -1), and an interaction term between reward and transition type. The key effect is a significant interaction between reward and transition type, as this indicates the extent of model-based learning present in the choices made by participants. The algorithm used was Bound Approximation by Quadratic Optimisation. In Table 14, the interaction between

reward, transition type and condition is reported, where a significant interaction would indicate that model-based learning is modulated by NAC.

Delay aversion in the CGT is calculated as the mean proportion of the current total points that the participant chose to risk on gamble test trials for which they had chosen the more likely outcome, for descending trials minus ascending trials. Outlier trials were classified as those with a reaction time of greater than the mean reaction time plus three standard deviations, and were removed.

In the DDT, delay discounting area under the curve is calculated by first obtaining the indifference points for each individual when they chose the delayed reward (calculated as the difference between the delayed reward on the previous trial, in which they would have chosen 'now' and the delayed reward on the current trial). The timescale and rewards were then normalized, so that they were expressed as a proportion of the maximum value. Subsequently, the area under the curve produced was calculated as

$$AUC = x2 - x1\left[\frac{y1 + y2}{2}\right] \qquad \textit{Eq. 14}$$

where $x_1$ and $x_2$ are adjacent delays and $y_1$ and $y_2$ are the indifference points associated with them (Myerson et al., 2001).

#### *5.2.8.2 Mixed models of outcomes*

The questionnaire outcomes and the blood glutathione levels were analysed using a mixed model, with condition (NAC/Placebo) and order of administration, along with their interaction, as fixed effects, and participant as a random effect. This was specified in R as

$$\text{lmer(y}\sim\text{order} * \text{condition} + (1|\text{participants}))$$

The psychological task outcomes were analysed using a multivariate mixed model, specified as above. The individual results of a mixed model (as above) are also reported

for each task outcome, with the exception of the effects on the Model-Based Score, which is reported as the interaction term reward * transition type * condition from the logistic regression specified in the previous section.

## 5.3 RESULTS

### 5.3.1 Demographics at baseline

The baseline demographics of the participants in this study are shown below in Table 12.

*Table 12: Summary of demographic variables and questionnaire scores of participants.*

| Variable | Mean | Standard deviation | Standard error of the mean |
|---|---|---|---|
| **Age, years** | 23.70 | 4.16 | 0.87 |
| **BMI (kg/m2)** | 22.62 | 2.28 | 0.48 |
| **Estimated verbal IQ** | 115.75 | 4.70 | 0.98 |
| **Cigarettes per day** | 0.20 | 0.58 | 0.12 |
| **EAT-26 at pre-screen** | 10.83 | 5.33 | 0.61 |
| **EPQ Neuroticism** | 8.96 | 4.83 | 1.01 |
| **EPQ Pyschoticism** | 2.35 | 1.47 | 0.31 |
| **EPQ Lie** | 9.04 | 4.07 | 0.85 |
| **EPQ Extraversion** | 13.17 | 5.21 | 1.08 |
| **Self-starvation scale** | 8.61 | 6.02 | 1.25 |
| **HADS – Anxiety** | 4.65 | 3.24 | 0.68 |
| **HADS – Depression** | 1.61 | 2.78 | 0.58 |

*Mean, standard deviation and standard error of the mean for demographic variables and questionnaire scores of participants, measured at baseline (except for EAT-26, which was measured at pre-screening).*

### 5.3.2 Blinding

Blinding was successful: participants were not significantly above chance at guessing the treatment condition: $\chi^2(1) = 0.78$, $p = 0.376$.

### 5.3.3 Questionnaire results

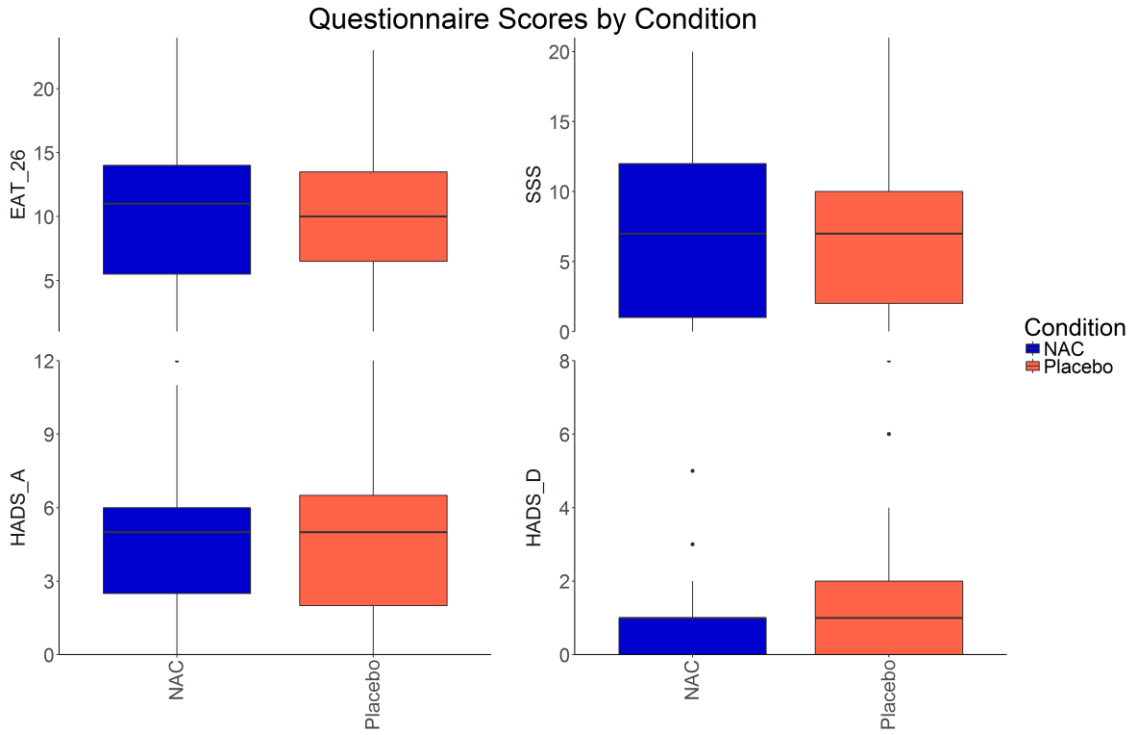
There was no significant main effect of condition (NAC or placebo) during the study visits on any of the questionnaires (see Table 13 and Figure 20).

*Table 13: Results of ANOVA analyses for difference in questionnaire scores after NAC or placebo.*

| **Questionnaire** | ***F* value** | **df** | ***p value*** |
|---|---|---|---|
| **EAT-26** | 1.44 | 1,20.07 | 0.244 |
| **SSS** | 0.07 | 1,20.14 | 0.788 |
| **HADS-Anxiety** | 0.06 | 1,20.12 | 0.809 |
| **HADS-Depression** | 2.67 | 1,20.18 | 0.118 |

*This table displays ANOVA F values, degrees of freedom and p values for the condition main effect of ANOVAs using a mixed model, with the questionnaire scores as outcome values.*

*Figure 20: Questionnaire scores by condition (NAC or placebo).*




*Boxplots for questionnaire scores by condition (NAC or placebo). The median is marked in the centre of the boxplot. Lower and upper hinges correspond to the first and third quartile (25th and 75th percentile), with the upper whisker extending to the largest value no greater than 1.5 times larger than the inter-quartile range from the hinge, with the lower whisker extending from the hinge to the smallest value that is at most 1.5 times the inter-quartile range from the hinge. Outliers beyond these points are plotted individually.*

### 5.3.4 Psychological task results

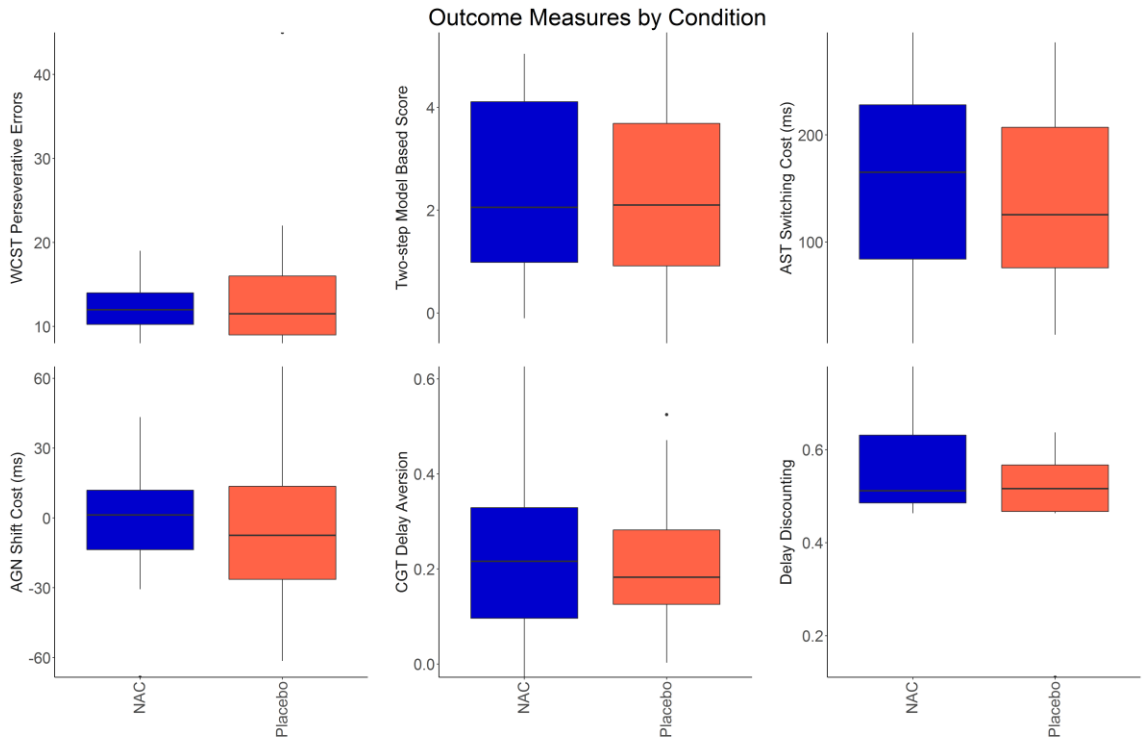
There was no significant main effect of condition in the multivariate analysis of key task outcome measures (Figure 21): $F(6,40) = 0.599$, $p = 0.729$, or on any of the individual ANOVAs performed for each outcome measure (see Table 14). There was also no significant main effect of order, either in the multivariate ANOVA or the individual ANOVAs.

*Table 14: Results of ANOVA analyses for difference in task outcome measures after NAC or placebo.*

| **Psychological task** | **Outcome measure** | ***F* value** | **df** | ***p value*** |
|---|---|---|---|---|
| **WCST** | Perseverative errors | 1.05 | 1,20 | 0.317 |
| **AST** | Switching cost | 1.21 | 1,20 | 0.284 |
| **AGN** | Shifting cost | 0.32 | 1,20 | 0.580 |
| **Two-Step Task** | Model-based index | 0.04 | 1 | 0.841 |
| **CGT** | Delay aversion | 0.01 | 1,20 | 0.905 |
| **DDT** | Area under the curve | 2.41 | 1,20 | 0.136 |

*F, degrees of freedom and p values for the condition main effect of individuals ANOVAs using a mixed model, with each of the psychological task outcome measures as outcome values.*

*Figure 21: Boxplots of outcome measures from psychological tasks by condition (NAC or placebo).*

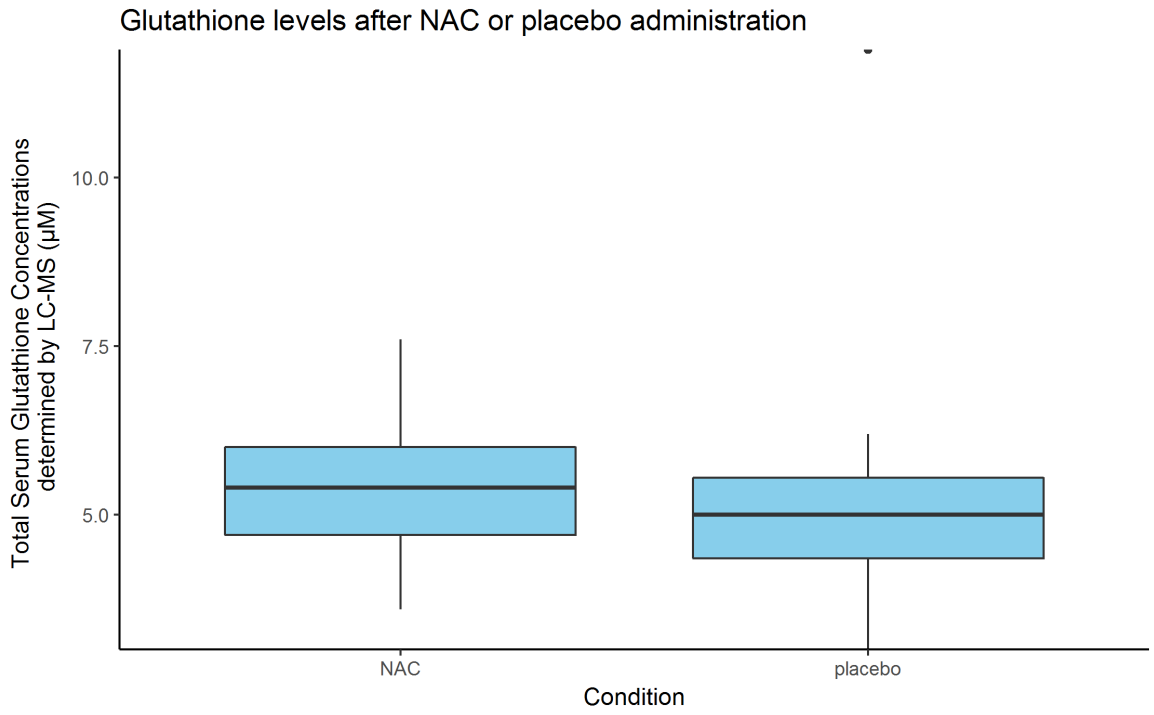



*This displays the median, hinges and whiskers as in Figure 20. There was no difference between NAC and placebo on any of these measures.*

### 5.3.5 Blood glutathione

There was no significant effect of condition on blood plasma glutathione levels: $F(1,13) = 0.037$, $p = 0.851$ (Figure 22).

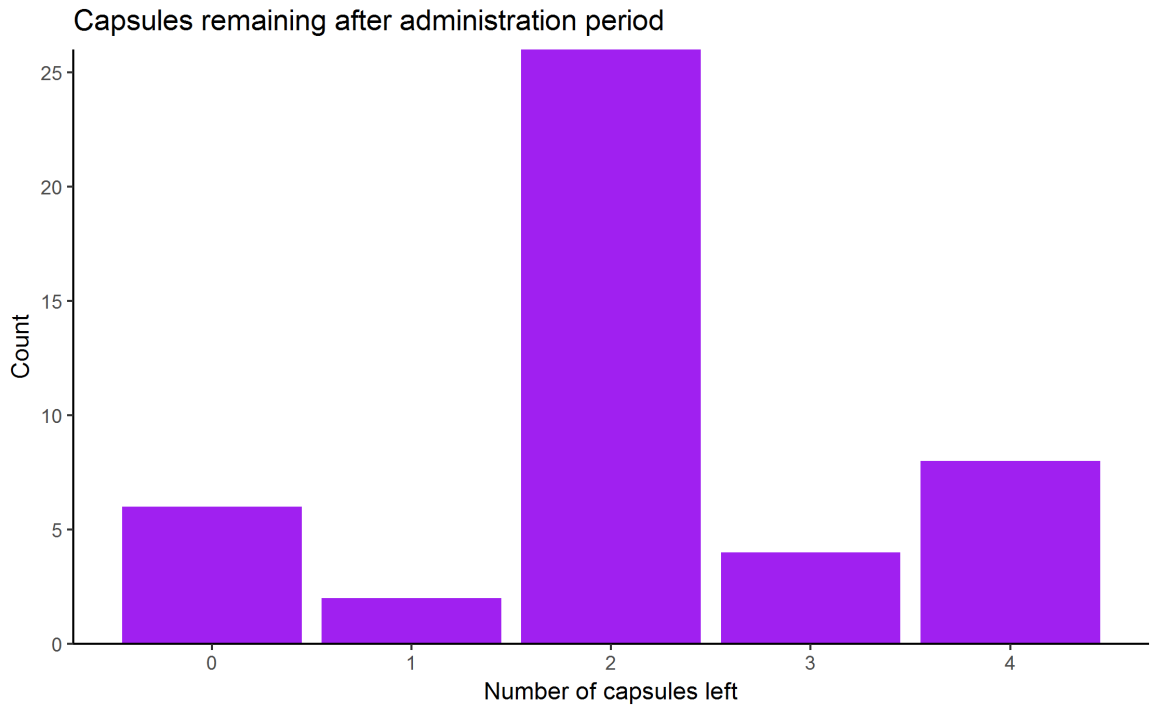
*Figure 22: Total serum concentration of glutathione after 9 days of NAC or placebo administration.*




*There was no significant difference, nor a significant interaction effect with order of administration. The figure displays this data as box-plots, as above.*

This may indicate that there was inadequate compliance with the treatment regime. We recorded how many capsules participants had remaining at the end of the administration period (having given them an excess of two capsules in the supply), and from this it was evident that not all participants completely followed the administration instructions. However, the majority had two capsules left which was as expected (Figure 23).

*Figure 23: Bar plot of capsules remaining after NAC or placebo administration period.*

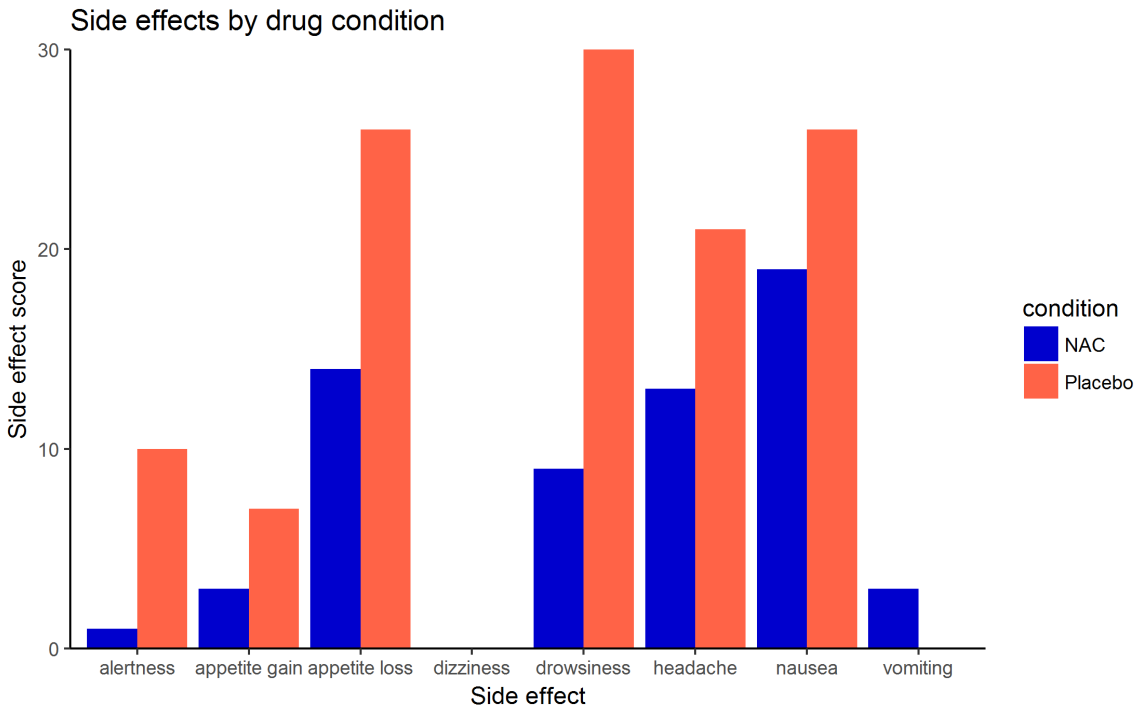



*Note that due to the between-subject design the total frequency is 2 times the number of participants. Each participant should have been left with 2 capsules at the end of each administration period, as is the mode in the graph above, but some noncompliance is also apparent from the non-zero count of the bars for the other numbers of capsules left.*

### 5.3.6 Side effects

There were significantly fewer side effects in the NAC condition than the placebo condition: $\chi^2(1) = 18.48$, $p < .001$. The side effects are displayed in Figure 24.

*Figure 24: Side effects by drug condition (NAC or placebo).*




*Bar graph of cumulative side effect score (where 0 was absent, 1 was mild, 2 was moderate, and 3 was severe) across all participants and all days of administration, by condition (NAC or placebo).*

## 5.4 Discussion

Overall, the results of this study indicate that NAC, in the regime administered, does not modify behaviour on tasks sensitive to compulsive or impulsive responding in high EAT scorers. In this context, it is worth noting that while NAC seems beneficial in disorders characterized by compulsivity, it has not thus far been shown to diminish compulsive behaviour in tasks of psychological performance in either patient groups or healthy controls.

There are a number of possible reasons for these results. One might be that the dose used was too low, but, as discussed above, the dose chosen was comparable to doses used in previous trials of NAC in compulsive disorders. It is also possible that the duration of treatment with NAC was insufficient. In many of the therapeutic trials NAC was given for several weeks with therapeutic effects apparently increasing over time (Oliver et al.,

2015). Additionally, it is also possible that participants were non-compliant, thus confounding our ability to detect findings (e.g. see Figure 23).

It is also possible that NAC may not produce its therapeutic effects specifically by reducing compulsive responding. This is further reinforced by the mixed evidence of benefit from NAC in OCD. NAC may have other actions that account for its therapeutic effects, for example, reduction in oxidative stress, via the actions of glutathione (Deepmala et al., 2015). Indeed, research indicates that compulsive disorders may be associated with oxidative stress (Ersan et al., 2006; Ng et al., 2008), which may also be true of EDs such as AN (Solmi et al., 2015). Potentially, therefore, NAC may still work in EDs but via a different mechanism to the 'anti-compulsive effect' hypothesized in this study.

Another limitation in this study is that the group we selected may not express compulsive and impulsive behaviours as strongly as a group meeting clinical criteria for ED diagnosis. However, this does not seem to be the case. On the WCST, the mean number of errors made was 13.09 (11.0% of trials), which is higher than those who have recovered from AN (11.6, 10.2% of trials) and only slightly lower than those who have current AN (15.1, 11.9% of trials) reported in a large study using the WCST (Tchanturia et al., 2012). This was also much higher than the number reported for HC participants in that study (8.3, 3.8% of trials). It therefore seems unlikely that the participants in this study were not sufficiently compulsive to show an effect of anti-compulsive treatment.

Moreover, a cross-over design was used. This may have introduced practice effects on the psychological tasks, thus confounding our findings. However, there was no main effect of order in the multivariate ANOVA, or in any of the ANOVAs of individual task outcomes. It is also possible that NAC may produce a modest effect on compulsive responding which not large enough to be detected by our study. In a meta-analysis of

studies of EDs using perseverative errors on the WCST, our primary outcome measure, a large effect size of 0.62 was found relative to healthy controls (Roberts et al., 2007). The present study had a power of 0.854 to detect an effect size of 0.55 with $p < 0.05$, and a total sample size of 23. We had a power of 0.75 to detect an 0.50 effect size.

Finally, our blood measure did not suggest that NAC, relative to placebo, increased glutathione levels in the blood. Our findings here are consistent with an acute study of NAC dosing in healthy participants which found no increase in glutathione levels (Burgunder et al., 1989). However, the situation may be different following repeated dosing, particularly in participants with pre-existing with glutathione depletion. For example, De Rosa et al. found that 8 weeks treatment with NAC (8g daily) restored depleted glutathione levels in HIV patients (De Rosa et al., 2000). Therefore it is possible that the failure of NAC to modify compulsivity in the present study was due to an insufficient increase in glutathione levels. However, the dosing regimen we used was able to improve clinical state in a range of compulsive disorders.

This study does confirm that NAC is well-tolerated in this population, with significantly lower side effects reported during NAC administration in this study. This may indicate that even if NAC is not efficacious for every individual with a clinical ED, treatment with it as an adjunct therapy over longer time periods and/or using a higher dose might well be feasible and of potential benefit for some.

Overall, whilst this study found no significant difference in either questionnaire scores or psychological tasks after NAC administration, the results do not rule out potential efficacy of NAC in clinical EDs, due to the limitations outlined above.

# 6 OVERALL DISCUSSION AND CONCLUSIONS

## 6.1 OVERVIEW

This thesis contains the results of three experimental studies which aimed to investigate and characterise the nature of compulsivity in EDs, and to perform a preliminary investigation of a potential pharmacological agent for EDs which may act on compulsivity. A number of methods are used: MRI (specifically, RSFC analyses, task-based fMRI, MRS and structural MRI), computational modelling, pupillometry, cognitive task batteries, and psychopharmacology.

EDs are psychiatric disorders with a high mortality rate (Arcelus et al., 2011; Chesney et al., 2014) and low recovery rate (Herzog et al., 1999). Very little is known about the aetiology of most psychiatric disorders; this is also true for EDs. This thesis takes a transdiagnostic perspective, based on the theory that compulsivity is an endophenotype not only of classical obsessive-compulsive and related disorders, but also of EDs (Godier & Park, 2014; Steinglass & Walsh, 2006).

Within this framework, the specific questions addressed in this thesis are:

1) What is the neural basis of compulsivity in EDs?
2) Is the cognitive inflexibility found in EDs a result of difficulty adjusting learning rates, and, if so, is this is related to NA functioning?
3) Does NAC, a dietary supplement of therapeutic benefit in some compulsive disorders, reduce compulsive and impulsive responding in cognitive tasks in a group at risk of clinical EDs?

## 6.2 SUMMARY OF FINDINGS

The first study, presented in Chapter 3, was a multimodal MRI investigation of the neural differences between participants who had recovered from AN, and control participants. The results of this study indicated that there might be significant differences in the parietal cortex, across both fMRI modalities used (RSFC and task-based fMRI). Additionally, these may be linked to compulsivity; the contrast which showed between-group differences in the precuneus in the task-based fMRI analysis was the difference between extra-dimensional and intra-dimensional shifting, which is complementary to the oft-found behavioural deficits displayed by ED patients in set-shifting (Roberts et al., 2010; Tchanturia et al., 2012). Furthermore, RSFC analyses found differences between groups in subcortical-parietal connectivity, and cingulate-cuneal connectivity. Additionally, the slope of correlation between performance on the WCST (a set-shifting task) was reduced in the RA group for the connectivity between striatal and frontal regions, indicating less influence of this connectivity in the production of perseverative errors; but increased between striatal areas and parietal/occipital regions. These results together point to a pattern of compulsivity, or more specifically cognitive inflexibility, being linked to parietal functioning and connectivity in ED groups. This hypothesis reflects recent calls for parietal areas to be included in the network of regions which are thought to contribute to compulsive behaviour (Göttlich et al., 2014).

However, no differences in fronto-striatal connectivity were found between groups in the RSFC connectivity analysis; fronto-striatal connectivity has been repeatedly linked to compulsive behaviour, particularly in OCD (Fineberg et al., 2010; Vaghi et al., 2016; van den Heuvel et al., 2010). This may be for a number of reasons. Firstly, it may be that the apparently compulsive behaviour in EDs does not have the same neural underpinnings. Whilst our study might suggest this, the lack of evidence to reject the null

hypothesis is not equivalent to evidence in support of the null. Secondly, it may be that those who have recovered from AN exhibit much less compulsivity, and thus might not be expected to share neural differences with those who are currently unwell with other compulsive disorders. However, this seems unlikely, as cognitive flexibility in particular (e.g. set-shifting difficulty, reversal learning problems, adaptive learning issues) has been found in those who have recovered from AN, and proposed as an endophenotype, which indicates that it is likely to be a trait factor rather than a state factor of current illness (Holliday et al., 2005; Tchanturia et al., 2012). However, cognitive flexibility deficits have been found to be smaller in groups who have recovered from AN (Tchanturia et al., 2012); hence, a larger sample size might be necessary to detect a difference.

The second study, presented in Chapter 4 of this thesis, is a further investigation of the nature of cognitive flexibility. The aim of this study was to examine whether ED groups show deficits in their ability to adjust their learning rate based on changing environmental contingencies, as has been shown in non-psychiatric populations (Behrens et al., 2007; Pulcu & Browning, 2017). Contrary to our expectations, the participants who had recovered from AN (RA group) seemed to have a greater difference in learning rates between volatile and stable blocks; which we hypothesise is caused by an increased learning rate in the first block specifically. Whilst the task structure does not allow us to disentangle the effects of volatility from the effects of the first block, there was no effect of group in any other block of the task, or when examining volatile and stable outcomes alone. However, this group effect may be due to heightened uncertainty in the RA group at the start of a novel task, causing a higher learning rate. Whilst we did not observe the learning rates decreasing during the first block, as might be expected in this case, this could be explained if the effect on learning rates of a novel task is either heightened or protracted in those who have recovered from AN.

Analysis of the learning rates in the first block indicated that all of the learning rates therein, except the learning rate to losses in the control group, were significantly different to the 'ideal' learning rate (derived from a BIO model). This allows us to conclude that it is likely that the elevated learning rates in the RA group in this block (which were significantly different to those of controls, with the currently-symptomatic group not showing a significant difference to controls but being elevated numerically) are sub-optimal. It is possible that these learning rates might cause negative outcomes over time (due to inappropriately high learning rates, and 'overreaction' to events that go against those predicted) if these results are generalisable to other situations; whilst we found no differences in the 'money won' from this task, this task was relatively short (240 trials), and designed to examine learning rate differences rather than the relatively crude variable of 'money won'.

Additionally, we collected pupillometry data for this task. The results from this indicated that the EA group might have reduced pupil dilation to rewarding outcomes when that outcome was 'stable'. It is possible that this reflects differences in noradrenaline, which would warrant further investigation.

The final study of this DPhil thesis, presented in Chapter 5, was an investigation into the glutathione-precursor NAC. The aim was to investigate whether sub-acute NAC dosing could reduce impulsive or compulsive responding in cognitive tasks in a group of participants at risk of clinical EDs, and to investigate whether this drug might be a worthy avenue of research in EDs. There was no significant difference between NAC and placebo on any of the compulsive or impulsive tasks used, and equally there was no significant difference on questionnaire measures of ED symptom scores, or anxiety or depression scores. Whilst this finding is discouraging, there were a number of limitations of this study. Firstly, the participants were not current ED sufferers, which may have reduced the

effect size of the drug, making it undetectable given our sample size. However, as mentioned in chapter 5, their scores on a measure of cognitive flexibility (the WCST) did indicate that they had elevated compulsivity, intermediate between those with current and former AN in a large study (Tchanturia et al., 2012). Another possible explanation for this is that the dose was too low, though it was comparable to other studies; or that the actual dose received was too low given the fact that compliance was not perfect. The cross-over design of this study may also not have been ideal because of the potential for either extended effects of NAC (although there was a wash-out period of 7 days) or learning effects due to the repeated performance of the tasks.

Another explanation which deserves investigation is whether NAC acts by another mechanism to reduce symptoms in those with compulsive disorders. At the end of chapter 5 we suggest that reduction in oxidative stress may be responsible (Deepmala et al., 2015), which might also explain the fact that benefit has been observed in non-compulsive disorders from NAC (Berk et al., 2008).

## 6.3 SUGGESTIONS FOR FUTURE EXPERIMENTS

This thesis is, by nature, largely exploratory. Therefore, a number of the findings in this thesis are subject to future confirmation and replication, and a number of experiments could be proposed that might meet this purpose. Equally, some of the findings in this thesis are unexpected, and new experiments ought to be designed to investigate these further.

The results of Chapter 3 indicate that there may be a difference in parietal functioning and connectivity in those who have recovered from AN. However, this study was cross-sectional, and in those who have recovered; therefore it is possible that the differences observed are a result of 'scarring' from the illness. An improvement on this

study would be to analyse MRI data from a longitudinal cohort of participants, with some prior to the onset of an ED, some with a current ED, and some who have recovered. This analysis could be performed either using a 'big-data' resource such as the UK Biobank, or by collecting participants thought to be at risk for EDs. (e.g. those with a first-degree relative with an ED). The benefits of recruiting a new cohort are that tasks can be used and sequences specified depending on the questions of interest, but the costs of longitudinal studies are large, and the degree of conversion from 'at-risk' status would be relatively low. Thus, the Biobank resource might be a useful way to perform this analysis and see if the results from this thesis replicate, before recruiting a cohort.

Additionally, future studies using the method of RSFC in EDs could use the precuneus or other parietal regions as seeds, in order to fully investigate the nature of parietal connectivity differences in EDs. To substantiate the claim that the frontostriatal model of compulsivity could be extended to include the parietal cortex, other studies should be performed using participants with other compulsive disorders.

Finally, whilst we aimed to investigate the neural bases of compulsivity in EDs, we did not include a group that was selected as a 'compulsive control', i.e. participants with no ED but with high compulsivity. In future studies, an OCD group or a group scoring highly on behavioural measures of compulsivity (e.g. habit-formation tasks) might be used.

In Chapter 4, we found that there was a greater adjustment of learning rates between volatile and stable blocks in the RA group, perhaps due to increased learning rates in the first block in the RA group. This was unexpected. To further investigate this effect, it is necessary to disentangle the effects of volatility and the novelty of the task. A modification of the task used in chapter 4 that randomised the order of all blocks, such

that the first block does not always have a ‘volatile’ structure for both outcomes, should allow this to be empirically tested. Alternatively, one could use repeated testing of participants on the task during a session, or pre-training, such that any effects resulting from it being a ‘novel task’ are reduced.

To investigate whether this effect might be due to the fact that participants are performing a novel task, a new experiment might include a number of tasks which are not hypothesised to show differences between participants with and without EDs. These tasks could be pre-trained to different extents, and one could examine whether performance changes systematically as a function of exposure to the task. Equally, one could take a computational modelling approach, that explicitly attempts to model familiarity with a task (e.g. by including a parameter for novelty in the learning model of the task which can influence learning rates), and examining whether there is any systematic variation in that between ED groups.

As mentioned in the discussion of Chapter 4, one of the flaws in the task design is that ‘stable’ associations are fixed at a probability of 0.5, which also introduces a high level of noise. In future studies, the ‘noise’ associated with stimuli could be manipulated, or it could be held constant and matched between volatile and stable blocks.

Additionally, the functioning of NA in EDs (which is thought to be reduced, see Section 4.1) could be probed by pharmacologically increasing NA transmission using a selective NA uptake inhibitor such as atomoxetine, and then examining the effects on cognitive flexibility.

Chapter 5 investigated the use of NAC. Further research with this dietary supplement should focus on establishing whether it has any effect on compulsive and impulsive responding, using participants who are selected specifically due to high

compulsivity. Additionally, a higher number of participants should be used to enhance the ability to detect smaller effect sizes, and a longer duration of NAC administration might also be necessary.

To investigate the use of NAC in EDs, Phase 2 clinical work could be performed in this group to investigate whether it is likely to have any effect on ED symptoms. The cohort recruited should ideally have a current ED, rather than just being symptomatic. As this drug is used as a dietary supplement, and has been tested in humans previously (and as the work presented in Chapter 5 indicates that it was well-tolerated and the side-effect profile did not differ from that of controls), Phase 1 work would not be necessary. If found to improve ED symptoms, multiple doses should be trialled to find the minimum effective dose.

## 6.4 CONCLUSIONS

In conclusion, the work presented in this thesis indicates that there are differences between ED groups and control participants in a number of neurobiological aspects, some of which may relate to compulsivity; parietal response to set-shifting, subcortical-parietal connectivity, and heightened adjustment of learning rates potentially relating to heightened learning rates at the start of a task. These findings are not as congruent with the literature on compulsivity or the hypotheses of this thesis as might be hoped, but nevertheless point to a number of potential avenues for further research. In particular, the inclusion of parietal connectivity in the fronto-striatal model of compulsive responding could be investigated in other compulsive disorders, to examine whether it is specific to EDs.

Furthermore, the use of a computational approach allows the broad construct of 'cognitive flexibility' to be deconstructed and quantified, with consideration for the

underlying computations that the brain might perform whilst solving problems that require flexibility. This type of approach should be used in future research in compulsivity in order to increase precision of both hypotheses and results.

The potential increase in learning rates in response to performing a novel task might lead to difficulty in novel environments in ED participants, and might lead to overreaction to one-off events in novel environments, which could lead to negative consequences and thus perhaps avoidance. This finding should be confirmed using the other experiments suggested in Section 6.3, and if true, should be studied in more ecologically-valid contexts to determine what effects it might have on psychosocial functioning.

Finally, the functioning of NA in EDs seems to warrant further investigation in light of the pupillometry findings in this thesis, and research linking NA to cognitive flexibility in general, and set-shifting performance in particular.

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