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BMJ Open Assessing biomarkers of remission in female patients with anorexia nervosa (REMANO): a protocol for a prospective cohort study with a nested case-control study using clinical, neurocognitive, biological, genetic, epigenetic and neuroimaging markers in a French specialised inpatient unit

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ABSTRACT

Background Anorexia nervosa (AN) is a severe psychiatric disorder associated with frequent relapses and variability in treatment responses. Previous literature suggested that such variability is influenced by premorbid vulnerabilities such as abnormalities of the reward system. Several factors may indicate these vulnerabilities, such as neurocognitive markers (tendency to favour delayed reward, poor cognitive flexibility, abnormal decision process), genetic and epigenetic markers, biological and hormonal markers, and physiological markers. The present study will aim to identify markers that can predict body mass index (BMI) stability 6 months after discharge. The secondary aim of this study will be focused on characterising the biological, genetic, epigenetic and neurocognitive markers of remission in AN.

Methods and analysis One hundred and twenty-five (n=125) female adult inpatients diagnosed with AN will be recruited and evaluated at three different times: at the beginning of hospitalisation, when discharged and 6 months later. Depending on the BMI at the third visit, patients will be split into two groups: stable remission (BMI \geq 18.5 kg/m²) or unstable remission (BMI $<$ 18.5 kg/m²). One hundred (n=100) volunteers will be included as healthy controls.

Each visit will consist in self-reported inventories (measuring depression, anxiety, suicidal thoughts and feelings, eating disorders symptoms, exercise addiction and the presence of comorbidities), neurocognitive tasks (Delay Discounting Task, Trail-Making Test, Brixton Test and Slip-of-action Task), the collection of blood samples, the repeated collection of blood samples around a standard meal and MRI scans at rest and while resolving a delay discounting task.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a prospective cohort study conducted in adult (age \geq 18) women suffering from anorexia nervosa; they will be evaluated at the start and at discharge of an in-hospital treatment with intense refeeding to body mass index (BMI) $>$ 18.5 kg/m², and then again 6 months later. A group of healthy controls matched for sex and age will serve as a reference for all the tests in a nested case-control study.
- ⇒ A multidimensional approach will be used to identify markers that differentiate between stable and unstable remission: self-reported inventories, neurocognitive tasks, blood samples and structural and functional magnetic resonance imaging (MRI).
- ⇒ Limitations include that there is no consensus on the definition of remission and, in the present study, it is based only on BMI.
- ⇒ The group of patients only includes low-weight female adults.
- ⇒ Because of time and financial constraints, only small subgroups will undergo blood sampling around a meal (N=10 patients and 10 controls) or MRI (N=50 patients and 30 controls).

Analyses will mainly consist in comparing patients stabilised 6 months later and patients who relapsed during these 6 months.

Ethics and dissemination Investigators will ask all participants to give written informed consent prior to participation, and all data will be recorded anonymously. The study will be conducted according to ethics recommendations from the Helsinki declaration (World Medical Association, 2013). It was registered on clinicaltrials.gov on 25 August 2020 as 'Remission Factors

in Anorexia Nervosa (REMANO)', with the identifier NCT04560517 (for more details, see <https://clinicaltrials.gov/ct2/show/record/NCT04560517>). The present article is based on the latest protocol version from 29 November 2019. The sponsor, Institut National de la Santé Et de la Recherche Médicale (INSERM, <https://www.inserm.fr>), is an academic institution responsible for the monitoring of the study, with an audit planned on a yearly basis.

The results will be published after final analysis in the form of scientific articles in peer-reviewed journals and may be presented at national and international conferences.

Trial registration number clinicaltrials.gov NCT04560517

INTRODUCTION

Background and rationale

Anorexia nervosa (AN) is a complex psychiatric disorder with 1%–3% prevalence in the general population, and the highest mortality rate of psychiatric disorders.^{1–4} It is mainly characterised by severe and self-induced weight loss, refusal to maintain a minimum weight, body image distortion, and excessive fear of gaining weight.¹

Patients with AN are treated through different therapeutic approaches, such as family interventions,⁵ nutritional interventions, cognitive and behavioural therapy or interpersonal therapy,⁶ but the care provided to patients mainly relies on restoring a healthy body mass index (BMI) and reducing eating and weight symptoms.^{7,8} To this day, there is no consensus regarding the definition of remission in AN.⁹ However, relapses are frequent, as one patient out of two relapses in the year following hospitalisation.^{10–13}

Treatment response has a high variability between patients, and may be influenced by premorbid vulnerabilities,^{14,15} such as neurocognitive inefficiencies¹⁶ underlying AN symptoms. There is therefore a crucial unmet need to improve treatment for AN, through targeting the causes (the involved abnormal mechanisms) more than the consequences (abnormal weight). Investigations are necessary to identify remission markers and improve relapse prevention. Such markers could include:

1. *Neurocognitive markers* could be involved in the tendency of patients with AN to favour delayed reward, with an abnormal increased activity of the striatum and sensitivity to weight restoration.¹⁷ Using the Delay Discounting Task, previous studies showed a higher capacity of patients with AN to delay monetary rewards (4), probably related to the ability in AN to resist the drive to eat and wait in favour of a future weight loss.¹⁸ The use of a monetary paradigm (instead of a reward value of food) has the advantage of not being part of the AN diagnosis, which could help indicate that such abnormalities extend beyond eating-related symptoms.¹⁸

Impaired cognitive flexibility has also been highlighted as a core cognitive specificity of patients with AN^{18–24} and could also be understood as an abnormal decision process where habit-preferences ('stimulus-response') may be favoured compared with goal-directed choices ('action-outcome'),^{25–27} compulsivity being central to

AN.²⁸ There is furthermore direct evidence that the balance between goal-directed and habitual control in humans is dopamine-dependent.²⁹

2. *Genetic variants* in opioid and dopamine signalling are associated with different responsiveness to food rewards³⁰ and several genes (*DRD2*, *BDNF*, *COMT*) are known to be associated with AN.^{31–33} *Epigenetic factors* may also be involved.³⁴ For example, it was reported that genes coding for dopamine and glutamate are more methylated in patients with AN than in controls.³⁵
3. *Biological and hormonal markers*, such as ghrelin, have been showed to be associated with reward sensitivity³⁶ and are involved in the difficulty of patients with AN to perceive the reinforcing role of feeding.³⁷ Ghrelin is a hormone synthesised in the stomach designed to induce energetic deprivation and lead to food ingestion, and signalling for appetite control and energy balance.³⁸ Ghrelin acts via the growth hormone secretagogue receptor (GHSR).³⁹ Another hormone of interest produced in the liver and small intestine, liver-expressed antimicrobial peptide 2 (LEAP2), is an antagonist of GHSR and inhibits the major effects of ghrelin, including food intake.⁴⁰ Previous literature suggests that ghrelin may be increased and positively reinforced in AN, acting as a reward of food restriction and weight loss.^{36,41–45} Both acyl-ghrelin and deacyl-ghrelin may have an active role in the pathophysiology of AN.³⁶ Results of previous studies are heterogeneous regarding the normalisation of ghrelin during weight restoration,^{42,46–49} and few data are available in both the acute phase and during treatment.⁵⁰ Moreover, while the role of ghrelin as a biomarker in AN has been clearly established, its role as a potential indicator of treatment efficacy and recovery has yet to be fully investigated.⁵⁰ Due to the variability of ghrelin throughout the day, it appears necessary to allow dynamic and ecological investigation with multiple measures before and after the meal.
4. *Imaging*, through MRI, fMRI and diffusion tensor imaging (DTI), shows differences in the reward circuitry.⁵¹ For instance, when patients with AN need to make a food choice, compared with controls, there is a higher activity of the dorsal striatum⁵² and a lower capacity from the orbitofrontal cortex to modulate the accumbens.⁵¹

In regard to this literature, it appears that a multidimensional approach is needed to investigate the multiple factors underlying vulnerabilities such as reward abnormalities in AN. Apart from weight restoration, no biological marker to this day can be considered a remission marker, although relapse frequency in AN highlights the need to prioritise such investigations.⁵³

Objectives

The present prospective study primarily aims to identify factors which significantly differ between patients with stable clinical remission of AN (BMI still above

18.5 kg/m² at the 6 month follow-up) and patients with unstable remission (BMI below 18.5 kg/m² at the 6 month follow-up). More specifically, we expect that reward sensitivity, measured through the *Delay Discounting Task*, will be efficient to differentiate between patients with stable and unstable remission, and that stable patients will demonstrate a higher preference score for immediate (vs delayed) reward.

Characterising biological, genetic, epigenetic and brain markers of remission in AN will be the secondary aim of this study. More specifically, we aim to (1) highlight the endophenotypic nature of higher sensitivity to delayed reward in AN, (2) characterise the brain mechanism (through structural MRI, fMRI and DTI), and investigate how it can help differentiate stable from unstable patients, (3) characterise endocrine profiles (fasting and around a standard meal) before and after remission and investigate how it can help differentiate stable from unstable patients, (4) highlight correlations between genetic and epigenetic variants with metabolic markers before and after remission, and investigate how it can help differentiate stable from unstable patients.

METHODS

Trial design

This study is a monocentric prospective cohort study with a nested case–control study. The cohort study consists in comparing patients who are stable (BMI > 18.5 kg/m² 6 months after discharge) versus patients who relapsed during the 6 month follow-up (BMI < 18.5 kg/m²). The design includes a nested case–control study because, since it is not possible to obtain any data prior to the apparition of the disorder, it appeared necessary to include a control group in order to (1) estimate the expected values in the general population, (2) characterise the endophenotypic nature of reward abnormalities. This will help investigate if abnormalities highlighted in patients with AN are also persistent in stabilised patients or similar to individuals without AN.

Assessments occur at the beginning of hospitalisation, at the end of hospitalisation after complete weight recovery (ie, approximately 4 months later), and at follow-up during ambulatory care approximately 6 months after the end of hospitalisation.

Participants

Source population and eligibility criteria

One hundred and twenty-five (n=125) consecutive inpatients diagnosed with AN according to DSM-5 criteria will be recruited at GHU Paris Psychiatrie et Neurosciences, Sainte-Anne Hospital (Clinique des Maladies Mentales et de l'Encéphale) in Paris. All patients will be recruited during a face-to-face interview with a psychiatrist with at least 5 years of experience in eating disorders. Inclusion criteria for patients are follows: (1) female, (2) fluent in French, (3) aged between 18 and 65 years old, (4) diagnosed for AN according to DSM-5 criteria, (5)

BMI < 18.5 kg/m², (6) affiliated to a social security scheme and (7) able to consent.

Patients will be evaluated three times during the protocol: at time 1, at the beginning of hospitalisation (see 2.2.2 for more details); then at time 2, when discharged (around 4 months later, when their BMI is normal, > 18.5) and at time 3, 6 months later (± 15 days), to assign the status 'unstable' or 'stable' clinical remission depending on whether the BMI is below or above 18.5.

One hundred (n=100) volunteers will be included as healthy controls. Inclusion criteria are as follows: (1) female, (2) fluent in French, (3) age between 18 and 65 years old, (4) not corresponding to DSM-5 criteria for AN and (5) BMI between 18.5 and 25 kg/m².

Participants, both patients and controls, will be excluded for the following reasons: (1) lifetime schizophrenia, bipolar disorder or associated acute and unstable medical condition (eg, dyskalemia, cardiac, hepatic or renal dysfunction) which could impact cognitive functions or alter treatment efficacy, (2) physical or mental incapacity to sign an informed consent, (3) liberty-deprived subject (following judicial or administrative decision), (4) refusal to participate, (5) contraindication for fMRI, (6) pregnant or breast-feeding women. Participants lost to follow-up will also be excluded.

Recruitment

Patients

All patients diagnosed with AN in the eating disorder unit of the hospital and meeting the inclusion criteria are considered as potential participants. During patient admission, the psychiatrist in charge of the patient informs the study investigator who will meet and inform the patient during the first week of observation. An information form is given to the patient and, after a thinking delay, the patient can be included in the study and the first visit of the protocol can take place. All patients are informed that the participation to the study is not, in any case, obligatory and that their choice to participate or not participate will have no influence or repercussion on the care provided to them by the medical team.

Healthy participants (control group)

A poster campaign in different universities from the Parisian region (aimed at both students and staff members) and word of mouth around the hospital staff will be used to advertise the study. Potential volunteers can call the study investigator who will, after the individual's consent, use a five-question screening tool (the SCOFF test) to exclude the presence of an eating disorder. The participant decides if they would like to include the MRI and/or the endocrine dosage around a standard meal. Finally, the date of the first visit is decided with the participant, and the consent form and information form are addressed by email.

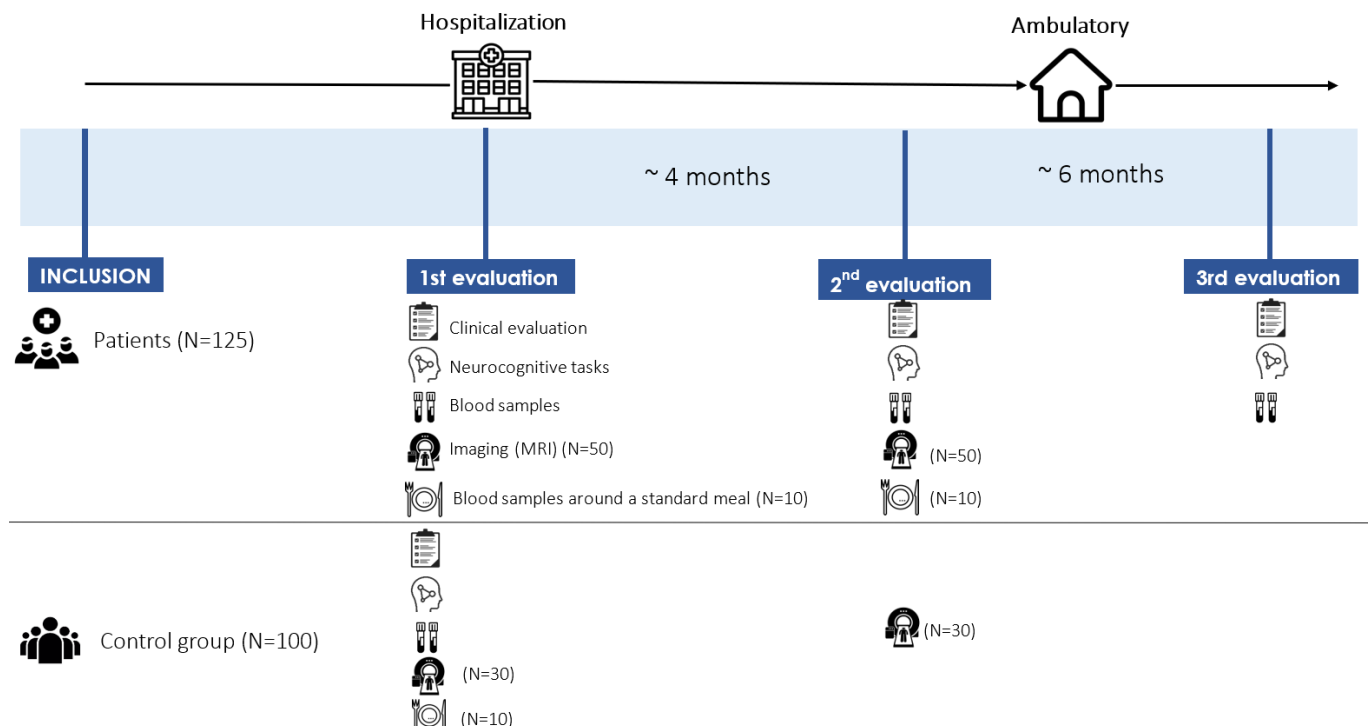


Figure 1 Overview of participants timeline and stages of evaluation.

Procedure

Protocol description

The protocol will include three visits for hospitalised patients (figure 1 and figure 2):

- ▶ **Visit 1:** patients are at the beginning of their hospitalisation ($BMI < 18.5 \text{ kg/m}^2$). Sociodemographic and clinical data will be collected through interview with a psychiatrist and inventories. A blood sample will be collected by a nurse, and participants will be asked to complete four neurocognitive tasks (the *Delay Discounting Task*, the *Brixton Test*, the *Trail-Making Test* and the *Slip-of-action Task*), always in the same order. Forty patients (the first to consent) will be seen for an MRI during which they will complete another *delay discounting task*. Among them, the first 10 patients to consent will be asked for repeated blood samples for endocrine dosage around a standard meal.
- ▶ **Visit 2:** approximately 4 months later, patients are at the end of their hospitalisation when their weight has been restored ($BMI > 18.5 \text{ kg/m}^2$). They will be asked to complete the same inventories and neurocognitive tasks. Those who were seen for an MRI and repeated blood samples around a standard meal will be asked to complete these evaluations a second time.
- ▶ **Visit 3:** 6 months after the end of their hospitalisation, ambulatory patients will be asked to come back to the hospital and will complete the same inventories and neurocognitive tasks.

Participation for subjects included in the control group will consist of a single visit involving the same research interventions as the patients for visit 1. Only the subgroup of 30 subjects participating in the MRI programme will be asked to undertake a second visit, approximately

3 months after visit 1, to repeat the imagery acquisition including the *Delay Discounting Task* inside the MRI.

A compensation of 30 euros will be paid to healthy controls for self-reported inventories, 60 euros for each evaluation including an MRI and 100 euros for repeated blood samples. For patients, while the first two visits take place during their hospitalisation, transportation allowance will be offered for the third visit.

Evaluation

Primary evaluation criteria

The main criterion of evaluation is the *Delay Discounting Task* (DDT) score from the second visit, allowing to predict the distinction between stable and unstable patients 6 months later (during the third visit).

In the DDT, subjects are presented with two options of various amounts of money available at different delays: a smaller amount of money but available within a shorter delay ('Smaller Sooner', SS), or a larger amount of money but available in a longer delay ('Larger Later', LL).

This task allows to measure the subjective value that a person perceives in a given reward depending on the delay. From the different choices, the discount rate k can be calculated. A smaller discount rate indicates a higher perceived value of a given reward and a higher tolerance to waiting. For more details, see online supplemental file S1.

Secondary evaluation criteria

The secondary evaluation criteria are the clinical, neurocognitive, structural imaging, biological, genetic and epigenetic markers of remission in AN detailed below. More specifically, we will compare between patients with

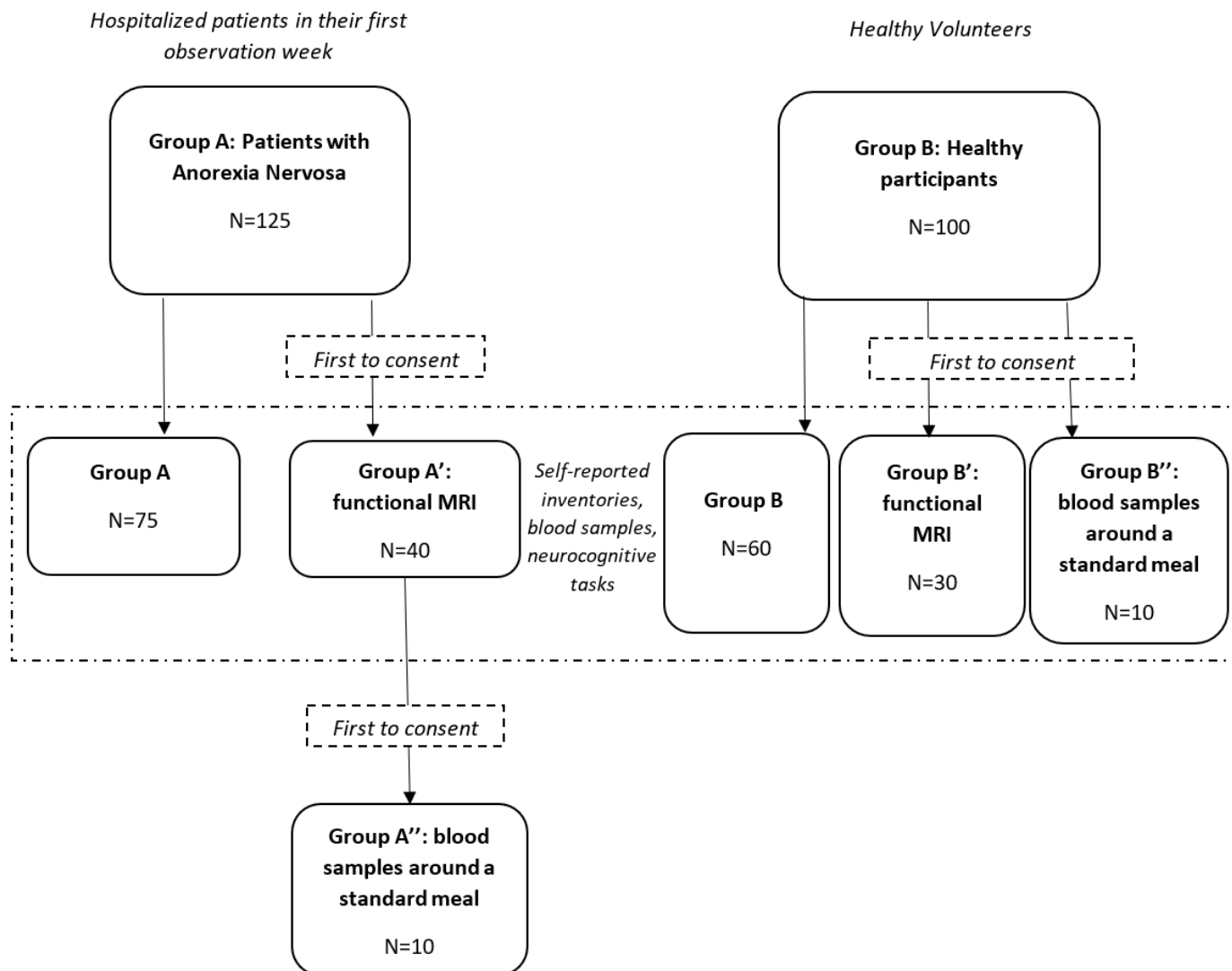


Figure 2 Overview of samples size and recruitment procedure.

stable and unstable remission the data obtained at baseline (visit 1), 4 months later (visit 2) and the evolution of the scores between the two visits.

Clinical markers

Sociodemographic data (age, educational level, working activity and familial history of eating disorder) and clinical data (age of onset of AN) will be assessed at time 1, while clinical traits will be systematically collected at each time of the protocol. This includes BMI, blood pressure and heart rate at rest. Eleven dimensions of eating disorders will be measured by the *Eating Disorder Inventory-2* (EDI-2).⁵⁴ Self-reported inventories will also be used to assess the levels of anxiety and depression (through the *Hospital Anxiety and Depression Scale*, or HADS⁵⁵), of physical activity (through the *Godin Leisure-Time exercise questionnaire*, or GLT⁵⁶) and exercise addiction (through the *Exercise Addiction Inventory*, or EAI⁵⁷), the presence and severity of obsessive-compulsive disorder (through the *Yale-Brown Obsessive Compulsive Scale*, or Y-BOCS^{58 59}), the comorbidity with Asperger syndrome (through the *Ritvo Autism Asperger Diagnostic Scale*, or RAADS⁶⁰) and

the experience of abuse and mistreatment (through the *Childhood Trauma Questionnaire*, or CTQ⁶¹).

Neurocognitive markers

1. Time specificities (capacity to delay reward) will be measured through the DDT, described above. In addition to the primary criterion, the DDT score of stabilised patients at the second visit and the DDT score of healthy patients at the third visit will help demonstrate the endophenotypic character of reward abnormalities.
2. Cognitive flexibility will be measured through the *Brixton test*^{62 63} and the *Trail-Making Test*.^{64 65} The number of errors is measured in the Brixton test, while response time is recorded in the trail making test. Previous research suggests that there exists no practice effect for these tests.^{66 67}
3. Reward-motivated versus habit-driven behavioural choices will be assessed by the *Slip-of-action Task* (SOAT),^{68 69} measuring the tendency to lose sight of a goal (goal/reward motivated choices) due to the activation of habitual responses (habit-driven choices). The SOAT has been previously proven reliable for

healthy participants^{70 71} and in clinical population.^{72–74}

The task will be based on the one used in a previous protocol.²⁵ For more details, see online supplemental file S2.

- Emotional reactivity will be tested through the measure of pupillary response to social, food and body image visual cues.

These cognitive tasks will be performed on computers (with MATLAB) under supervision of a trained neuropsychologist.

Brain imaging

A brain imaging session including DTI, structural and functional MRI will be conducted in the first 50 inpatients and 30 healthy controls to consent. It will take place in the imaging platform of Sainte-Anne hospital, before and after hospitalisation. A 3T MRI Canon scanner will be used with a specific antenna for brain imaging. The analysis will focus on regions of interest such as the striatum (accumbens, caudate and putamen) and the prefrontal cortex, and both anatomical and functional fronto-striatal connectivity will be measured.^{51 52}

For the *functional MRI*, the scanner has a stimulation system (screen and response button) allowing patients to perform a cognitive test (the DDT) while recording their brain activity (BOLD signal). *Structural MRI* will provide quantitative data regarding anatomy (such as brain volumes) and *DTI* will inform us on connectivity between the cortex and the striatum, and between the hypothalamus and the tegmental ventral area.

An adapted DDT compatible with functional MRI has been designed for the study by adapting the task from Van den Bos *et al* to patients with AN.^{75 76} Following a training phase (during which participants explore their preferences between the two options: *small amount, short delay vs large amount, long delay*), the amounts during the test phase will be generated in order to obtain an equiprobability of choices between SS and LL. For more details, see online supplemental file 1.

Genetic and epigenetic markers

A blood sample will be collected before and after hospitalisation to look for genes involved in motivation and reward pathway (dopaminergic receptors DRD1 to DRD5, transporters such as DAT1 and VGLUTs and enzymes such as DBH and COMT) and neurotrophic factors (such as BDNF and NTRK2) and pathways involved in hunger and satiety. Gene sequencing will be performed to characterise rare and common variants, and their frequencies will be compared according to clinical and biological specificities (within sample comparison) and to our sample of already collected patients and healthy controls. Epigenetic evaluation (such as BDNF gene methylation) will take place by analysing the variation differences before and after renutrition and between stabilised and non-stabilised (ie, relapses) patients 6 months after the end of hospitalisation.

Biological markers

In addition to genetic and epigenetic markers, the blood sample will also be used to measure total, acyl and desacyl ghrelin plasma levels at each of the three visits. The evolution will be compared between patients with stable and unstable remission.

Among patients who have been seen for the MRI, those who agree (with maximum n=10 participants) will be asked for repeated blood samples for endocrine dosages (eg, ghrelin, LEAP2, insulin, ...) around a standard meal (salad with vinaigrette, bread roll, fish, carbohydrates, vegetables, sugar-free yoghurt and compote). Samples will be collected around the meal at the following times: -1 hour 30 min, -1 hour, -30 min, -20 min, -10 min, 0 min, +10 min, +20 min, +30 min, +45 min, +1 hour, +1 hour 30 min. A total of 30 mL of blood will be collected in 3 hours (2.5 mL for each sample). The standard meal will take place at 12:00 PM and will be served by a nurse and a doctor. Every 30 min, the patient will be asked to rate their anxiety level, hunger level and satiety level on a scale from 0 to 10. Since we cannot ensure that patients will completely consume the meal, the caloric intake will be quantified with a dietician and a picture of it will be taken before and after.

Data collection and management

Data management

Data will be collected by authorised staff only, and will be conserved on a password-protected computer in the centre. Access to these data will only be reserved to authorised persons directly involved in the study. Participants consent in writing to the statistical treatment and scientific publication of these data in strict anonymity.

Blood samples will only consist in peripheral blood collected by venous puncture or peripheral venous catheter. Punctures will be made on the non-dominant arm. Blood samples will be placed on ice immediately after withdrawal, then centrifuged at 4°C (1000g during 15 min). In addition, plasma samples will be aliquoted and supplemented or not with HCl 0.1N immediately after collection.⁷⁷ Samples will be conserved in a -80°C freezer, in the Centre de Ressources Biologiques of GHU Paris Psychiatry and Neurosciences, in a room with controlled and limited access.

Documents related to the study will be conserved for the legal duration of 15 years and archives will be kept in a locked room under the responsibility of the lead investigator. Data cannot be moved or destructed without the authorisation of the lead investigator.

Confidentiality

Participants will only be identified by their individual identification code. The lead investigator will conserve a participant identification list that will be used only if records need to be identified. Files will be stored on a password-protected computer in accordance with local data protection law and will be handled in strict confidence.

Security, adverse event and protocol deviation

Security

The present study includes minimal risks related to the blood samples (possible pain and/or inflammation as well as a very low risk of infection at the sample-taking location). No risks are associated with the MRI if all contraindications are respected.

Adverse event

An adverse event (AE) is defined as ‘any unfavorable and unintended sign, symptom, or disease temporally associated with study participation that may or may not be related to study procedures, including any adverse change that occurs at any time following consent and before completing study participation’.

AEs are immediately reported by the principal investigator to the promotor of the study, and may lead to a re-evaluation of the benefit–risk balance of the study. AEs are described in the AE form in terms of severity, timing, causes and contributing factors. AEs, if not resolved at the time of discovery, are followed by the study staff during each visit and by phone until it is resolved. Participants are asked about AEs at every study visit.

Protocol deviations

Protocol deviations refer to the fact that one or more procedures described in the study protocol are not followed, either intentionally or unintentionally. All protocol deviations are reported to the promotor on a regular basis, and any major protocol deviation is reported as soon as possible. The reporting of protocol deviation includes a description of the protocol deviation, its causes and consequences on the study and a description of the actions taken to prevent recurrence (for unintentional and unwanted deviations) or a rationale of why such deviation was needed (for intentional deviations).

Statistical methods and analysis

Sample size

According to Decker,¹⁸ the DDT requires 34 participants per condition to be significantly improved. Considering that our final sample will be composed of 50 stable and 50 relapsing patients, our statistical power will allow us to show a significant difference above 0.42. We chose to include slightly more participants than the minimum required, considering both the expected attrition rate (around 20%), and the fact that other evaluation criteria (MRI, genetic and biological) may be more demanding statistically speaking.

Our protocol also requires the recruitment of healthy volunteers to help estimate the expected values in the general population. We therefore chose to recruit 100 healthy volunteers to match the sample size of patients, considering that, apart from those who will be seen for the MRI, control participants are only seen once, thus the attrition rate was not considered. The MRI will in fact be conducted twice among controls, in an attempt

to replicate Decker *et al*'s results and to control the influence of time.¹⁸

Statistical analysis

A p-value equal or inferior to 0.05 will be considered significant for the main criterion (ie, DDT), and a Bonferroni adjustment will be used for other criteria in order to minimise the risk of type I error.

Clinical characteristics will be compared using an analysis of variance) for independent samples, following normality check for all tested variables (using Kolmogorov-Smirnov test with Welch correction and Mann-Whitney-Wilcoxon test). DTT scores will be transformed into logarithmic values ($\log(k)$) and will be analysed following a linear mixed model.

Ethics and dissemination

The study protocol was approved by the Comité de Protection des Personnes (CPP) Sud-Ouest et Outre-Mer II (no. CPP: 19.07.26.54412). Investigators will ask all participants to give written informed consent prior to participation, and all data will be recorded anonymously. The study will be conducted according to ethics recommendations from the Helsinki declaration (World Medical Association, 2013).

The only risk associated with this study is the minimal risk of local infection due to the catheter used for the sampling around a standard meal. MRI sessions are safe; since the risk on fetuses has not been investigated enough, a pregnancy test is taken beforehand to confirm that participants are not pregnant.

All data collected during this trial are the property of the research sponsor and may not be communicated to a third party under any circumstances without the written consent of the sponsor. At the end of the research, the participant has the right to be informed of the overall results of the research, according to the modalities that will be specified during the inclusion interview. Participants will have the possibility of communicating their e-mail address to the investigator who collected their consent in order to obtain the overall results of this research when they become available.

The results will be published after final analysis in the form of scientific articles in peer-reviewed journals and may be presented at national and international conferences. Any publication or communication (oral or written) is decided by mutual agreement between the investigators and the sponsor. Individuals who contribute to the production of the publication will be granted authorship.

CONCLUSION

This project will bring new and important findings through (1) the identification of relevant remission markers that can be used as either diagnostic or prognostic tools in the clinic; (2) a new conceptual framework to apprehend mechanisms involved in the neurobiology of reward to



develop specific and efficient therapeutic approaches and (3) new opportunities to encourage a multidimensional approach of AN, taking also into account the neurobiological, genetic and epigenetic aspects of AN.

This study will lead to characterise discriminant criteria between stabilised and non-stabilised patients (ie, that will relapse in the following months). Having a better knowledge of the clinical, biological, genetic, epigenetic and neurocognitive determinants that underline the mechanisms involved in AN should help to better prevent and treat this psychiatric disease. Therefore, we hope that this project will contribute to facilitate the development of efficient therapeutic strategies such as reinforcing the intensity of ambulatory care, and/or improving cognitive flexibility and reward abnormalities through the training of cognitive skills.

TRIAL STATUS

Recruitment started in April 2021 and should be completed by September 2025.

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