Neuroanatomical Differences Associated with Anorexia Nervosa and Masking Behaviour in Autistic Individuals

Sponsor	University of Aberdeen
Funder	Eating Disorders and Autism Collaborative (EDAC); UK Research and Innovation (UKRI)
Chief Investigator	Dr Michelle Sader
Sponsor number	2-081-24
Version Number and Date	Version 2, 20th May 2025

PROTOCOL APPROVAL

Neuroanatomical Differences Associated with Anorexia Nervosa and Masking Behaviour in Autistic Individuals

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

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LIST OF ABBREVIATIONS

AN	Anorexia Nervosa
AQ	Autism Quotient
ASRS	Adult Attention Deficit Hyperactivity Disorder Self-Report Scale
CAT-Q	Camouflaging Autistic Traits Questionnaire
CI	Chief Investigator
CSOG	Clinical Studies Oversight Group
ED	Eating Disorder
EDAC	Eating Disorder and Autism Collaborative
EDE-Q	Eating Disorder Examination Questionnaire
EDS	Eating Disorders Service
HADS	Hospital Anxiety and Depression Scale
ITQ	International Trauma questionnaire
LSAS	Leibowitz Social Anxiety Scale
MQ	Monotropism Questionnaire
MRI	Magnetic resonance imaging
REC	Research Ethics Committee
ROI	Region of Interest
R&D	Research and Development
UKRI	UK Research and Innovation
WSAS	Work and Social Adjustment Scale

PROTOCOL SUMMARY

CONSIDERED FOR ENTRY	Autistic individuals (either self-diagnosed or clinically diagnosed) as controls and Autistic individuals with a restrictive eating disorder (ED) such as anorexia nervosa (AN). Participants will be aged 25-45.
TRIAL ENTRY	Autistic individuals with and without AN will be screened for eligibility. Either online or written informed consent will be sought prior to the study.
MAIN AIMS OF STUDY	The main aim of the study is to determine whether there are neuroanatomical or functional differences between Autistic individuals relative to Autistic individuals with AN, and whether Autistic individuals with AN exhibit higher masking behaviour than Autistic individuals without AN.
CO-ORDINATION	**Local and Overall:** overseen by the Chief Investigator
FUNDER	EDAC; UKRI

ABSTRACT OF PROPOSED INVESTIGATION

Autism is a neurodevelopmental condition and presents as a distinct neurotype, characterised by a wide range of social and behavioural differences, including divergences in cognitive thinking and methods of communication [1]. Autism shares significant behavioural features with restrictive eating disorders (EDs) such as anorexia nervosa (AN). Those with AN exhibit significantly elevated levels of Autistic characteristics, ranging between 2%-53% [2-4]. Importantly, a characteristic shown by some Autistic people is the presence of masking, a term describing a strategy used by Autistic people, whether conscious or unconscious, to 'blend in' with neurotypical peers [5]. While initially overlooked, it is now well-known that masking behaviour can produce detrimental effects on Autistic individuals' mental health. The presence of masking behaviour has been associated with increased levels of physical and mental exhaustion [6,7], anxiety/depression [8], and importantly, an increased presence of EDs [5].

The Eating Disorder and Autism Collaborative (EDAC) [9] used an arts-based method called Photovoice to capture the experiences of Autistic individuals with lived/living experience of an ED. Participants commented on the how an ED can serve as a means to mask or camouflage within a neurotypical world (e.g., an Autistic person may use restrictive eating or excessive exercise as a means with which to 'fit in' with their peers). Magnetic resonance imaging (MRI) research can assist in understanding which regions of the brain are associated with masking behaviour, and whether there are differences in brain function/structure in Autistic individuals with versus without an ED.

This research aims to use a combination of brain imaging techniques and administration of scientifically validated questionnaires to investigate the relationship between autism, restrictive EDs, and masking. A 3T MRI scan will be used to investigate neuroanatomical and functional differences in Autistic individuals with AN (n=25) relative to healthy Autistic individuals (n=25), with questionnaires used to evaluate levels of Autistic characteristics, ED traits, as well as masking and social camouflage. Findings from this research aim to provide evidence towards the complexities of ED development and maintenance in Autistic individuals.

BACKGROUND

Autism shares significant behavioural features with restrictive eating disorders (EDs), such as AN. Anorexia Nervosa (AN) is a severe and life-threatening eating disorder (ED) characterised by pathological fears of weight gain, a distorted body image, and extremely low body weight in relation to individual age and sex [1]. In Autistic people, masking has been associated with increased presentation of restrictive eating habits [5,7] and has been associated with poorer mental health. The presence of masking behaviour has been associated with increased levels of physical and mental exhaustion [6,7], anxiety, and depression [8].

Structural magnetic resonance imaging (MRI) research reports similarities in brain structure between those with AN and Autistic individuals, reporting differential structure of the amygdala [10,11], cerebellum [12,13], insula [14,15], cingulate cortex [14-16], as well as orbitofrontal and frontal cortex [15,16] in both groups. Shared differences extend to neuroanatomical parameters essential for brain development and connectivity [17], such as cortical thickness and surface area [18,19]. Further, there are no studies investigation structural correlates with masking behaviour, or distinct aspects of social camouflage such as masking, assimilation and compensation [20]. Further research is necessary to disentangle the complex relationship between Autistic characteristics and symptomatology associated with restrictive EDs.

We believe that by further understanding the brain structure and function associated with ED symptomatology and masking behaviour in Autistic individuals can assist with the development of novel or tailored interventions for EDs in this community.

STUDY AIMS AND OBJECTIVES

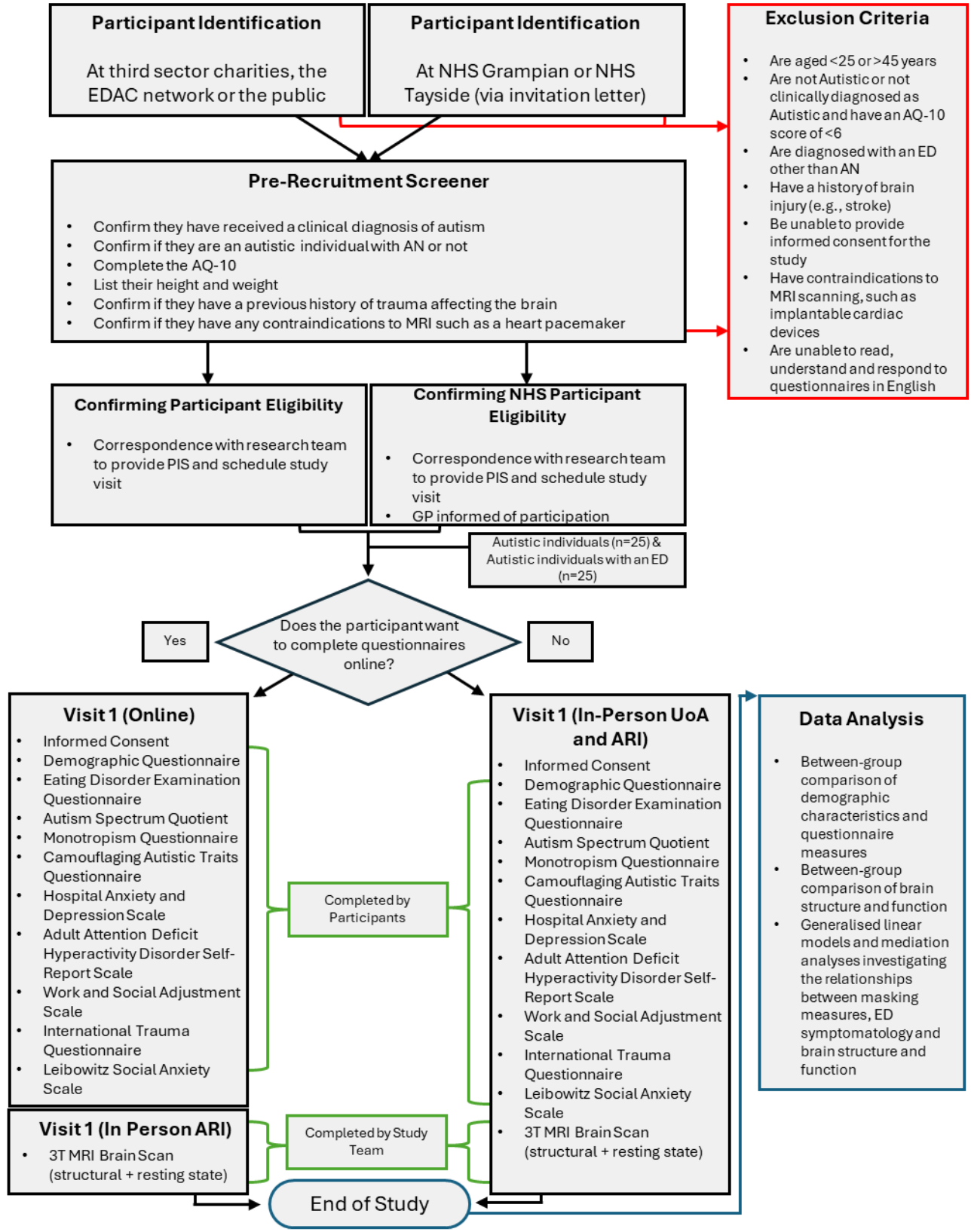
The main aims of the study are:

1) To examine whether Autistic individuals with AN exhibit differences in brain structure or function relative to Autistic individuals without AN.
2) To determine whether Autistic individuals with AN exhibit higher masking behaviour than Autistic individuals without AN.
3) To determine if there are associations between the levels of masking, ED symptomatology and brain structure in Autistic individuals.

Primary Objective

The primary objective of this study is to determine the relationship between masking, ED symptomatology and brain structure in Autistic individuals.

STUDY DESIGN



Abbreviations: AQ – Autism Spectrum Quotient; ARI – Aberdeen Royal Infirmary; ED – Eating Disorder; EDAC – Eating Disorders and Autism Collaborative;

STUDY POPULATION

The target population for this study includes 25 healthy Autistic individuals and 25 Autistic individuals with AN (aged 25-45). This study will be focusing on an adult sample to ensure individuals are able to articulate longstanding experiences of masking and social camouflage. Participants must also have no contraindications to MRI and have no history of trauma affecting the brain.

INCLUSION CRITERIA

Study Phase 1

- Healthy Autistic Individuals (Autistic Controls) must:
  - Be aged 25-45 years
  - Be Autistic (clinically diagnosed and/or have an AQ-10 score of ≥6)
  - Be able to provide informed consent for the study
  - Be able to read, understand and respond to questionnaires in English
  - Have no history of an ED
  - Willing to have an MRI scan in Aberdeen
- Autistic Individuals with AN (Autistic individuals with AN) must:
  - Be aged 25-45 years
  - Be Autistic (clinically diagnosed and/or have an AQ-10 score of ≥6)
  - Be able to provide informed consent to the study
  - Be able to read, understand and respond to questionnaires in English
  - Have a diagnosis of AN or a BMI of <18.5
  - Willing to have an MRI scan in Aberdeen

EXCLUSION CRITERIA

- Individuals are not eligible for the study if they:
  - Are aged <25 or >45 years
  - Are not Autistic or not clinically diagnosed as Autistic and have an AQ-10 score of <6
  - Are diagnosed with an ED other than AN
  - Have a history of brain injury (e.g., stroke)
  - Be unable to provide informed consent for the study
  - Have contraindications to MRI scanning, such has implantable cardiac devices
  - Are unable to read, understand and respond to questionnaires in English
  - As participants will need to consent to the study and complete questionnaires by themselves, individuals with intellectual disability will be excluded from this study

The Autism Spectrum Quotient (AQ-10) is a short questionnaire that primary care practitioners can use to test if a person should be referred for an autism assessment. We will use this as a screening tool to confirm the presence of Autistic traits in addition to the presence of a clinical diagnosis.

PARTICIPANT SELECTION AND ENROLMENT

IDENTIFYING PARTICIPANTS FOR ELIGIBILITY

Individuals will be considered an Autistic control if they meet study eligibility criteria and have no previous or current history of an ED and have no contraindications to MRI. Potential participants will be considered an Autistic individual with an ED if they meet study eligibility criteria and have a current diagnosis of AN and have no contraindications to MRI. Clinical members of the Eating Disorders Services (EDS) at NHS Grampian will assist with recruitment by identifying patients who are Autistic and have AN. This will involve review of medical records by the direct care team.

Once potential participants have been identified, a pre-recruitment screening survey will ask all participants to:

1) Confirm they have received a clinical diagnosis of autism,
2) Confirm if they are an Autistic individual with AN or not
3) Complete the AQ-10
4) List their height and weight
5) Confirm if they have a previous history of trauma affecting the brain
6) Confirm if they have any contraindications to MRI such as a heart pace-maker.

For both groups, potentially eligible participants will be given a standard participant information sheet, and a simplified pictorial participant information sheet. If eligible to participate, all participants will also be given an MRI Information Pack to familiarise themselves with the on-site location and process associated with an MRI scan.

Participant who meets the inclusion criteria will be then asked whether they would prefer to receive their consent form and questionnaires electronically or complete them in-person just before their MRI scan. All participants will provide informed consent before completing the questionnaires and having their MRI scan. The MRI scan will be scheduled with the participant at their convenience. If the participant misses their study visit, they will be contacted by the research team to reschedule their scan. If 1) participants complete the pre-recruitment screener and are not eligible to participate or 2) participants are deemed eligible but the recruitment limit of n=50 has been reached, they will be informed that they will not be able to take part, and will be thanked for their time and interest. With permission, all participants' GPs will be informed of their participation.

Autistic Controls:

Autistic controls will be recruited by advertising the study to third sector charities such as Autism & Neurodiversity North Scotland (A-ND) and Scottish Women's Autism Network (SWAN) and by bulk email to the University of Aberdeen's Neurodiversity Network facilitated by leads of this network, and to members of the Eating Disorders and Autism Collaborative (EDAC) Research network who have previously notified their interest to participate in future autism-related research. Autistic controls who self-report an autism diagnosis will be confirmed as eligible to participate upon completion of the AQ-10 with a cut-off score of ≥6. All potential participants will complete the pre-recruitment screening survey to determine eligibility for the study.

Recruitment via Third Sector Charities & The EDAC Network:
Individuals from third sector charities and the EDAC network who have previously flagged that they would like to be contacted for future research will receive a participant invitation letter. Contact information of the research team will be included with the invitation letter to reach out to the research team if they have any questions. Individuals will also receive the participant information sheet (PIS) and a link to a participant pre-recruitment screening survey to determine study eligibility. If participants are deemed eligible to participate, they will receive the participant eligibility confirmation letter. Once individuals confirm their participation, the research team will correspond with the participant to schedule their study visit and MRI scan, and the participant will receive the MRI Information Pack.

Recruitment via Third Sector Charities & the public:
Autistic controls will also be recruited by advertising the study to the public through adverts, flyers, press releases and on social media. Recruitment via this approach will also include those from third sector charities who have not previously flagged that they would like to be contacted for future research. All advertising material will contain a QR code and a link which will redirect participants to the pre-recruitment screener to determine eligibility to participate in the study. If participants are deemed eligible to participate, they will receive the participant eligibility confirmation letter, and the participant information sheet (PIS). Once individuals have read the PIS and confirm their participation, the research team will correspond with the participant to schedule their study visit and MRI scan and the participant will receive the MRI information pack.

Autistic Individuals with AN:

Autistic Individuals with AN will be recruited through the EDS team within NHS Grampian, North East Eating Disorder Support (NEEDS), BEAT Eating Disorders, Autism & Neurodiversity North Scotland (A-ND) and Scottish Women's Autism Network (SWAN) and by advertising the study to the public through adverts, flyers, press releases and on social media, and through members of the Eating Disorders and Autism Collaborative (EDAC) Research network who have previously notified their interest to participate in future eating disorder and autism related research.

Recruitment via Third Sector Charities & The EDAC Network:
Individuals from third sector charities and the EDAC network who have previously flagged that they would like to be contacted for future research will receive a participant invitation letter. Contact information of the research team will be included with the invitation letter to reach out to the research team if they have any questions. Individuals will also receive the PIS and a link to a participant pre-recruitment screening survey to determine study eligibility. If

participants are deemed eligible to participate, they will receive the participant eligibility confirmation letter. Once individuals confirm their participation, the research team will correspond with the participant to schedule their study visit and MRI scan and the participant will receive the MRI Information Pack.

Recruitment via Third Sector Charities & the public:
Autistic patients will also be recruited by advertising the study to the public through adverts, flyers, press releases and on social media. Recruitment via this approach will also include those from third sector charities who have not previously flagged that they would like to be contacted for future research. All advertising material will contain a QR code and a link which will redirect participants to the pre-recruitment screener to determine eligibility to participate in the study. If participants are deemed eligible to participate, they will receive the participant eligibility confirmation letter, and the participant information sheet (PIS). Once individuals have read the PIS and confirm their participation, the research team will correspond with the participant to schedule their study visit and MRI scan and the participant will receive the MRI information pack.

Recruitment via NHS Grampian:
Clinicians in NHS Grampian who may be in contact with potentially eligible participants will be informed about the study and we will include posters for the study in public areas of the NHS and EDS. Potential participants will be identified by their clinical care team who will give them an electronic version of the participant invitation letter and the PIS at a routine clinical appointment. The information sheet will include researchers' contact details to allow potential participants to contact the study team for further information or to indicate that they wish to participate in the study. Upon contacting the research team, individuals will receive a link to a participant pre-recruitment screening survey to determine study eligibility. If participants are deemed eligible to participate, they will receive the participant eligibility confirmation letter, and the participant information sheet (PIS) once more. Once individuals have read the PIS and confirm their participation, the research team will inform their GP of their participation, and correspond with the participant to schedule their study visit and MRI scan. The participant will also receive the MRI information pack.

CONSENTING PARTICIPANTS

Written and verbal explanation of the study will be provided. It will be clearly stated that the individual is free to withdraw from the study at any time for any reason without any prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will have 2 weeks to consider taking part after receiving the participant eligibility confirmation letter. Participants will receive a follow-up email after one week of inactivity after the research team confirms their eligibility to take part in the research, to inform them that we will no longer consider them as an individual taking part in the study after a further week of inactivity. Under the condition with which participants withdraw from the study at this stage, all information collected through the screening form will be deleted.

Written informed consent will be recorded with an electronic signature for those who choose to complete the questionnaires online or be recorded in-person in the Research MRI Centre in Aberdeen Royal Infirmary, if the individual chooses an in-person phase 1 session, by a researcher who has been trained to take informed consent. In both in-person and online settings, a copy of the completed consent form will be provided to the participant. Participants

will receive a total of 3 follow-up emails for each week of inactivity under the following conditions: 1) Participants opting to complete questionnaires in an online format who have yet to complete questionnaires; 2) Participants who completed questionnaires online who are asked to schedule their on-site visit for their MRI scan; 3) Participants who opt to complete questionnaires during their in-person visit to receive their MRI scan, who are asked to schedule their on-site visit. Under the condition with which participants withdraw from the study at this stage, all information collected through the screening form will be deleted.

INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Only eligible individuals (following our pre-defined inclusion/exclusion criteria) will continue with the rest of the study procedures. Participants who are not eligible will not be recruited into the study. Individuals will complete a pre-recruitment screening survey. The link to this screening survey will be sent to potential participants who have expressed an interest in taking part in the study, and will be completed by all potential participants. If 1) participants complete the pre-recruitment screener and are not eligible to participate or 2) participants are deemed eligible but the recruitment limit of n=50 has been reached, they will be informed that they will not be able to take part, and will be thanked for their time and interest. Non-eligible individuals will also be made aware that the data they have provided and their contact details will be deleted.

WITHDRAWAL PROCEDURES

Participants are free to withdraw at any time during the study without having to give a reason. Should this occur, additional participants will be recruited until the required study target number is achieved. Data collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on the participant.

STUDY ASSESSMENTS

Questionnaires (either online or in-person): To be completed by all participants.

- A demographic questionnaire that will be used to collect information on gender, age, height and weight, education level, employment status, time since and quality of autism diagnosis, co-occurring physical, mental health or psychological conditions, co-occurring EDs and duration of ED illness, as well as current medication status.
- The Eating Disorder Examination Questionnaire (EDE-Q; [21]) will be used to evaluate the presence, frequency and severity of eating disorder symptoms.
- The 10-item Autism Spectrum Quotient (AQ-10; [22]) will be used to examine Autistic characteristics. The AQ-10 will also be used to screen for ingenuine participants.
- Presence and levels of monotropism or selective interests will be evaluated using the Monotropism Questionnaire (MQ; [23]).

- The presence and level of masking behaviour will be measured using the Camouflaging Autistic Traits Questionnaire (CAT-Q; [20]). The CAT-Q contains three subscales that will be used in the proposed research: compensation (identifying means to circumvent social and communication differences associated with autism), assimilation (strategies implemented by Autistic individuals to 'fit in') and masking (hiding of the Autistic identity to conform with non-Autistic peers) [20].

Additional questionnaires will be used to evaluate levels of mental health and wellbeing between.

- Levels of depression and anxiety will be assessed using the Hospital Anxiety and Depression Scale (HADS; [24]).
- Levels of co-occurring ADHD will be assessed using the Adult Attention Deficit Hyperactivity Disorder Self Report Scale (ASRS-v1.1; [25])
- Levels of work and social adjustment will be assessed using the Work and Social Adjustment Scale (WSAS; [26]).
- The International Trauma Questionnaire (ITQ; [27]) will be used to assess levels of psychological trauma.
- Levels of social anxiety will be assessed using the Leibowitz Social Anxiety Scale (LSAS; [28]).

Including informed consent, this is expected to take no longer than 2 hours and 10 minutes. Questionnaires can be completed in-person, or online via Qualtrics. Material within the online version and paper, in-person version are identical.

MRI Assessment (in-person): The MRI scan will be conducted by a trained radiologist. Participants will be asked to lie in the MRI scanner while we collect 3D T1- and T2-weighted images, as well as resting state functional connectivity and diffusion tensor images.

This will last approximately 45 minutes. The total amount of time spent on this study will be no longer than 3 hours.

Post-Research Activities: Participants will receive the debrief sheet and will be compensated for their participation in this study in the form of a £30 Amazon or Love2Shop voucher, depending on their preference. After participation, individuals will also be asked to complete an optional anonymous feedback survey delivered via link on their experience participating in the study.

POTENTIAL RISKS AND HAZARDS

The described research involves the recruitment of Autistic individuals with and without AN.

Risk of incidental findings from MRI scans: The MRI scans taken for this research project are not the same as those that would be needed for clinical diagnostic purposes. However, in

the event that the radiologist collecting the scan notices something of medical relevance, a CSOG clinician will inform the participant and their GP if the participant wishes for the research team to do this. A University clinician will then arrange for subsequent or further investigation/treatment, if needed.

Risk of participant distress brought on by questionnaires: There is a chance participants may become distressed due to the nature of the questionnaire material, but this is unlikely since the questionnaires do not ask the individuals to recall specific events.

- To mitigate risks of distress participants will be able to complete the questionnaires in an environment they are comfortable and familiar with if they choose.
- The research team will provide information within the participant information sheet to direct participants to appropriate support services.

Risk of participant distress due to the MRI environment: Autistic individuals may find the MRI scanning environment distressing due to the loud noise and bright lights associated with an MRI scan, as well as the style of interaction with the radiographers. Participants may find the MRI particularly distressing if they are prone to claustrophobia. To minimise possible distress, we will:

- Ask participants if they have specific sensory sensitivities before their scan appointment is made so that adequate preparations can be made.
- Provide participants with foam ear plugs as well as ear defenders. Participants will also be given the option of listening to their preferred music or sounds during the scan.
- Dim the lights of the scanner room to provide a more comfortable environment for participants
- Provide participants with an additional MRI information booklet and video recordings to familiarise them with the scanning location and the MRI process, as well as one-on-one meetings with researchers to discuss the science and steps behind MRI if wanted.
- Encourage participants to inform the research team in advance of their preferences for the level of interaction and physical contact during the scan. The research team and radiographers will work together to create procedures to minimise distress while maintaining participant safety.
- Give the participant a call button to hold during their scan to alert the radiographers. Participants who express significant discomfort due to claustrophobia will be withdrawn from the study.

Risks associated with use of MRI: Magnetic resonance imaging is a safe, non-invasive procedure and there are no known side effects to receiving an MRI scan. However, if there is any indication or potential with which an individual may be pregnant, they will not be considered eligible for the study. This information will be collected on the MRI safety screener before an individual receives their scan.

SAMPLE SIZE

Sample size calculations are not appropriate for pilot studies. Our sample size of 25 for each group will ensure a spread of measurements to effectively estimate effect sizes and aid planning for future studies.

DATA COLLECTION

All research activities, methods of data collection and analysis associated with the proposed project will be conducted in accordance with the UK data protection laws.

All online data collection for this project will be conducted using Qualtrics (https://www.qualtrics.com/en-gb), a secure online survey platform. Qualtrics will facilitate efficient data gathering, enabling participants to complete the questionnaires remotely with a variety of accessibility options and at their own convenience. If participants opt to complete questionnaires during their in-person visit, all data will be provided on paper, and will be transposed to an Excel spreadsheet securely stored on University of Aberdeen servers via a University OneDrive folder. Electronic consent forms will also be securely stored on a separate excel spreadsheet on a University OneDrive folder. The paper copies of both questionnaires and informed consent will be retained and stored securely in locked cabinets within room F04 of the Lilian Sutton Building, made only accessible to the research team. Subject logs will also be retained as an Excel spreadsheet and stored on a separate secure University OneDrive folder. MRI scans will also be stored on a secure OneDrive folder, with statistics from scans transposed to an Excel spreadsheet. Once participant MRI scans have been linked to participant questionnaire responses and their consent, research data will contain ID numbers for each participant which will be pseudoanonymised. The index linking pseudoanonymised IDs to participants' names will be stored in a separate, secure excel spreadsheet within a University of Aberdeen OneDrive folder, made only accessible to the PI (Dr Michellle Sader).

Data generated from this study will be kept for a minimum of 10 years and Dr Michelle Sader will act as custodian for the data. Contact details, upon provision of consent by participants, will be kept up to 5 years for the purposes of conducting future ethically-approved research. Otherwise they will be deleted at the end of the study. All data in electronic form will be retained and archived in secure University of Aberdeen servers. All data in physical or paper form will be retained in archived in a secure locked drawer associated with this study within Room F04 of the Lilian Sutton Building at the University of Aberdeen. Only the named members of the research team (see Study Management and Oversight) will be able to access this data.

The sponsor is responsible for ensuring that study data is archived appropriately. Documents will be archived in line with the Sponsor's standard operating procedures.

DATA PROTECTION

All data collected through Qualtrics will be securely stored on servers compliant with the UK data protection laws and other international privacy standards, ensuring robust protection of personal information. Qualtrics adheres to strict data privacy policies, including data encryption, de-identification and anonymisation, both in transit and at rest. Qualtrics also has role-based access controls and ensures that only authorised members of the research team involved in the project will have access to the data to effectively safeguard participant data.

A member of the clinical care team will access medical records for the purposes of reviewing medical data relevant to participant eligibility, including age, date of birth, diagnosis of AN, diagnosis of Autism, and history of trauma affecting the brain. This information will only be seen by members of the individual's direct care team.

The chief investigator (CI) and study staff involved with this project will comply with the requirements of the UK Data Protection Laws. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the participant information sheet.

The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

PROPOSED ANALYSES

Methods of analysis will include assessment of demographic characteristics, brain structure and functional connectivity patterns, as well as calculation of generalised linear models between characteristics of masking and brain structure, as well as between characteristics of masking and symptoms of eating disorders. Pre-processing of MRI scans will utilise the FreeSurfer and fMRIprep software packages for brain structure and function respectively. Regions of interests (ROIs) will be derived from normalisation to the standard Desikan Killiany atlas. All statistical analyses will be conducted using the R Software.

To achieve aim 1, structural differences of brain regions, both global and specific ROIs, will be reported as mean ± standard deviation (in mm^3) for each ROI between groups. For functional differences an independent component analysis approach will be used via the CONN toolbox on the statistical parametric mapping (SPM) software package, reported in Z-scores for incorporated components, and means ± standard deviations of component loadings. Neuroimaging-based findings will also be accompanied by determining any group-based differences across demographic and questionnaire-derived information.

To achieve aim 2, mean differences on scores derived from the CAT-Q will be compared across groups and will be reported as mean ± standard deviation.

To achieve aim 3, linear models will be used to evaluate associations between brain structure and function and domains of social camouflage (particularly masking behaviour), as well as associations between levels of masking and the presence of reported anxiety, depression, work and social adjustment and trauma. A 3-path mediation model will also assess whether ROI-based brain structure mediates the relationship between masking behaviour and ED symptomatology within the entire sample.

The statistical analysis will be conducted by the Chief Investigator (CI; Dr Michelle Sader), and an Autistic peer researcher and PhD student (Caitlin Parsons). The statistical plan was developed by the CI and Dr Gordon Waiter.

MISSING DATA

Where appropriate, missing data will be imputed to minimise the loss of data. Depending on the type of data missing, either simple imputation, multiple imputation will be used to minimise data loss.

EARLY STOPPING

No interim analysis is planned to inform early stopping.

STUDY MANAGEMENT AND OVERSIGHT

The CI will run the study on a day-to-day basis. The study management committee will include Dr Michelle Sader (CI), Dr Gordon Waiter (Reader in biomedical imaging, University of Aberdeen), Dr Sam Aitcheson (Clinical Psychologist, NHS Grampian), Dr Madge Jackson (Psychologist, University of Aberdeen) and two Autistic peer researchers (Caitlin Parsons, Ellen Maloney). External oversight will include a meeting with EDAC, who has provided the funding for this research.

The CI will be responsible for checking the CRFs for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the study.

INSPECTION OF RECORDS

The chief investigator (CI), PI and all institutions involved in the study shall permit study related monitoring, audits, and research ethical committee (REC) review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

GOOD CLINICAL PRACTICE

Ethical conduct of the study

The study will be conducted in accordance with the principles of good clinical practice.

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate NHS research ethics committee (REC) and appropriate NHS research and development (R&D) approval(s) will be obtained prior to commencement of the study.

Confidentiality

All results, questionnaires, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area within the Lilian Sutton Building, University of Aberdeen, with access limited to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The chief investigator (CI) and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

The CI and study staff involved with this study will comply with the requirements of the UK data protection lawswith regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

INSURANCE AND INDEMNITY

The University of Aberdeen is sponsoring the study.

The University of Aberdeen holds and maintains policies of indemnity. These policies cover principals, partners, directors, employees and students of the University.

STUDY CONDUCT RESPONSIBILITIES

Protocol Amendments, Deviations, and Breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the case reporting form, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the

Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of good clinical practice is suspected, this will be reported to the Sponsor immediately using the form "Breach Report Form".

Study Record Retention

Archiving of study documents will be carried out as per University of Aberdeen guidelines. The sponsor standard operating procedure will be followed. Study documents will be archived in the Health Sciences Building archive.

The sponsor is responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of study. Upon participants consenting their contact details will be kept for 5 years for the purposes of conducting future ethically approved research.

End of Study

The end of study is defined as the final participant's visit. The Sponsor and the CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. A summary report of the study will be provided to the Sponsor and appropriate REC within 1 year of the end of the study.

REPORTING, PUBLICATION AND NOTIFICATION OF RESULTS

Authorship Policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analyzed and tabulated, and a clinical study report will be prepared.

Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of the results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

PEER REVIEW

Peer review of the initial study approach was performed by 3 peer reviewers. The final version of this study was reviewed by 2 external peer reviewers and 1 internal peer reviewer, who were Autistic individuals with lived or living experience of an ED. The specifics of the study protocol was reviewed by 3 internal peer reviewers with relevant expertise.

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