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ADIE to prevent development of anxiety disorders in autism

Submission date	Recruitment status
23/10/2017	No longer recruiting
Registration date	**Overall study status**
25/10/2017	Completed
Last Edited	**Condition category**
18/08/2022	Mental and Behavioural Disorders

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Autism Spectrum Conditions (ASCs) affect 2% of the population and are characterized by lifelong difficulties in social functioning with restricted patterns of behaviour and interests. People with ASCs are vulnerable to anxiety; at least 1 in 4 develops a co-morbid anxiety disorder, which may be resistant to typical drug therapy and psychological approaches. Interoception is the ability to sense internal changes in the body such as heart rate. Some of our recent work has shown anxiety can be increased if there is a discrepancy between how well patients feel they can interpret signals, such as their heartbeat, from their body and how well they are actually able to do this. It was found that helping people to be more aware of their ability, and to increase their ability to interpret signals from the body, helps reduce and may prevent anxiety symptoms. There is a need to try out and compare a new treatment, Aligning Dimensions of Interoceptive Experience (ADIE), teaching ASC patients these skills against the current treatment. The aim of this study is to test the efficacy of ADIE on anxiety symptoms and to check anxiety disorder diagnosis, medication and function one year later using state-of-the-art neuroimaging (images of the brain) to investigate the brain's physiological response to ADIE, also guiding ways to optimise the therapy.

Who can participate?
Adults aged 18 and older who have a confirmed ASC diagnosis.

What does the study involve?
Participants are asked to fill out a set of questionnaires to ask about symptoms they might have (e.g. anxiety, depression) and about the way in which they experience emotion and signals from their body. Another questionnaire asks questions about interests and thought patterns. Participants are randomly allocated to one of two therapy groups, receiving either an existing therapy to improve recognition of emotion from the way people say things, called prosody, or the new ADIE therapy. They will then receive training according to the group they have been assigned to. Both types of therapy are accompanied by tasks which assess prosody (matching phrases to emotional faces or words), interoception (monitoring their own heartbeat), empathy (the ability to feel for others) and joint hypermobility (how bendy their joints are). Assessment sessions takes 1-2 hours, training sessions take around 30 minutes. There are three assessment sessions and six training sessions that areheld over the course of 3-4 weeks. At the end of the

study participants are debriefed and asked about their experience and have the opportunity to ask any questions.

What are the possible benefits and risks of participating?
Participants may benefit from participating in the training as this may reduce or prevent any anxiety symptoms they may experience. This research could result in new ways of treating and preventing anxiety in people with autism spectrum conditions. There are no risks to taking part. Information from the study will be protected and anonymous so that people will not have access to the information about who took part or find out results of any one individual.

Where is the study run from?
Brighton and Sussex Medical School (UK)

When is the study starting and how long is it expected to run for?
January 2017 to March 2021 (updated 11/01/2021, previously: December 2019)

Who is funding the study?
MQ: Transforming Mental Health (UK)

Who is the main contact?
Professor Hugo Critchley
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Study website
https://www.mqmentalhealth.org/research/profiles/breaking-the-link-between-autism-and-anxiety

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
33694

Study information

Scientific Title
Aligning Dimensions of Interoceptive Experience (ADIE) to prevent development of anxiety disorders in autism

Acronym
ADIE

Study objectives
Current hypothesis as of 11/01/2021:

Reducing the mismatch between objective and subjective dimensions of interoceptive experience will lead to decreased trait anxiety via an increased ability to regulate, predict, and interpret interoceptive signals.

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Previous hypothesis:

After training to align dimensions of interoception in individuals with high-functioning autism, trait anxiety will be reduced and the development of anxiety disorders in autistic individuals will be prevented.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Health Research Authority (HRA), 31/03/2017, ref: 17/WM/0125

Study design
Randomised; Interventional; Design type: Treatment, Prevention, Psychological & Behavioural

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Specialty: Mental Health, Primary sub-specialty: Developmental disorders - Autism; UKCRC code/ Disease: Mental Health/ Disorders of psychological development

Interventions
Current interventions as of 11/01/2021:

The first training therapy session involves a brief introduction to the intervention and reassurance that many people find the tasks challenging. Information leaflets and business-card-style summary cards will be handed out that include reassuring content pointing out that everyone has their strengths and weaknesses, and suggestions for dealing with anxiety outside the sessions. The leaflets and cards can be found in the appendix. All participants complete between 1-3 training sessions per week, with the constraint that all sessions are performed within a 2-month period.

ADIE Intervention
In the active interoceptive training group, each training session entails two blocks, between which participants undergo a self-paced exercise that aims to enhance heartbeat perception. During the pre- and post-exercise block, each participant first completes the heartbeat tracking task (counting heartbeats in a specified time-frame, to determine the ratio of reported to actual heartbeats as a measure of interoceptive accuracy) and, for each trial, notes their confidence in their answer on a VAS scale and is given accurate feedback ("that is correct" for exact reporting of heartbeats, or "that is incorrect, your actual number of heartbeats were n") about the number of heartbeats occurring in the respective amount of time. All participants start training with the duration of the first heartbeat tracking trial as 10 seconds. If participants are accurate in counting their heartbeats (+/- 2 heartbeats), the next trial progresses incrementally in 5 second increases, up to a maximum of 50 seconds. If participants are inaccurate (>+/- 3 heartbeats), the trial stays the same length if at 10 seconds or decreases 5 seconds. This is to avoid frustration and build confidence.

Twenty trials of the heartbeat discrimination task then follow (where tones are played in sync or out of sync with the participants' heartbeats. Participants report synchronicity judgements, and correct judgements serve as a measure of interoceptive accuracy). After each trial, participants record their confidence in their answer and then receive feedback about whether synchronicity judgement of the tones (on- or off-beat) is correct ("That is correct" or "That is incorrect, that was actually in/out of sync").

Exercise manipulation: In between these task blocks, each participant is required to exercise for 1 -2 minutes to the point where their heartbeats become noticeably elevated, but to stop before discomfort occurs. Suggested methods are star jumps or jogging on the spot, but other methods are accepted as long as they succeed in elevating heart rate.

Prosody control intervention
In the active control prosody training therapy, participants receive a computer-based training protocol to enhance prosodic emotion recognition. The individual sessions increase in difficulty

as outlined below. After each individual trial, participants receive computer-generated feedback about whether they were right or wrong.

Session one. The initial session is comprised of four randomized training blocks totalling 100 trials. The first two blocks use only the six basic emotions whereas the second two blocks use only complex emotions. A two-choice training paradigm is employed. As with baseline, participants are presented with a series of audios alongside two visual emotion choices. Each block ends with the pairing together of same valence emotions in order to increase the difficulty of the tasks and to begin the gradual enhancement of participant sensitivity to tonal differences.
Session two. The second session utilises a two-choice training approach, this time combining basic and complex emotions into the same trials. Two blocks of 38 trials are employed. The first block consisted of opposing valence presentations, whereas the second block utilises same valence presentations.
Session three. Session three introduces graded intensities of basic emotions (such as happy vs happy mild). The first block consisted of 48 randomised repeated trials of different intensity pairings, and the second block of 50 trials integrates these with the complex emotions. Once again a two-choice training procedure is employed.
Session four. The fourth session incorporates three-choice training to increase the difficulty of the tasks. The first block comprised of 50 trials. Choices included the target emotion, an emotion of the same valence as the target emotion and an emotion of the opposing valence to the target emotion. To increase the difficulty further, the second block of 38 trials only offered same valence choices
Session five. Session five consists of two blocks of 50 trials and utilises four-choice training. Block one utilises only adult voices and block two utilised only children's voices. The four-choice formula in training sessions once again utilises the format of presenting the target emotion alongside two choices of the same valence and one of the opposing valence.
Session six. The final training session replicates session five, however, this time, presentations of children and adults are mixed within the same blocks and different stimuli are used. This session essentially integrates all learning from the previous five sessions.

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Previous interventions:

Participants are allocated to either the treatment or control arm using a 1:1 ratio and permuted block randomisation by the Clinical Trials Unit (CTU). After participant recruitment, the research assistant contacts the CTU to find out the allocation. To double-blind the clinical trial, neither the research assistant administering the treatment and control nor the participant are informed of which training regime is expected to deliver a therapeutic benefit.

The first of the three study phases is a double blind superiority randomised controlled trial comparing ADIE therapy to an active control therapy (prosody recognition training). Each group recruits 60 participants with ASCs (autism spectrum conditions).

Prosody therapy (Control group):
Participants receive an initial assessment where they are asked to complete some computer tasks. The computer tasks require application of finger sensors to measure their pulse. They receive three therapy sessions per week for three weeks. These focus on elements of speech such as intonation and rhythm. They are played phrases which are spoken in ways which convey different emotions (e.g. happy, sad, fearful etc.). The aim of this therapy is to help them better

identify the emotion underlying the way in which things are said. They match phrases to different emotional faces and words, feedback is provided to help them improve their perception of emotion from the way people say things.

ADIE therapy (Active group):
Participants are asked to complete some computer tasks. The computer tasks require application of finger sensors to measure their pulse. They then receive three therapy sessions per week for three weeks. These focus on the participant's ability to read signals from inside their body (what we call interoception) with feedback and guidance. They are asked to monitor their own heartbeat, but without physically feeling for it (i.e. just by sensing it internally). These tasks of interoception ask them to count how many heartbeats they feel during a period of time or decide if they think a rhythmic beep is in time or out of time with their own heartbeat. Participants are given feedback on how they have done in order to help them become more accurate in their awareness of their own heartbeats.

Participants undergo baseline (T0) testing of interoceptive abilities and affective (anxiety and depression) symptomatology, and are retested (after body awareness training and equivalent training in the active control group) and follow up after one year, to assess the impact of body-awareness training on potential reductions in anxiety, and indices of improved psychosocial functioning. A subset of ASC individuals from the ADIE therapy group undergo pre-post neuroimaging. Three week long therapist-guided training programme (three treatment sessions per week) focus on interoception with immediate feedback and guidance, in combination with established biofeedback techniques.

The effectiveness of ADIE therapy to a similar training protocol targeting ASC-relevant exteroceptive processing is compared, rather than using a sham feedback training control group (which we anticipate can enhance anxiety) or comparing the ADIE therapy group to a treatment-as-usual group.

Follow-up assessments are carried out by separate research assistant who was not involved in the delivery of the therapy.

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 11/01/2021:

Spielberger STAI trait anxiety at 3 months

Previous primary outcome measure:

Trait and state anxiety is measured using the STAI trait anxiety score State-Trait Anxiety Inventory determined from the STAI (State-Trait Anxiety Inventory questionnaire) at 3 months.

Secondary outcome measures
1. Anxiety is measured using the STAI state and trait anxiety scores at 1 year
2. Generalized anxiety is measured using the GAD7 score at three months and one year
3. Generalised anxiety is measured using the diagnosis criteria (MINI) met for generalized anxiety disorder at 1 year

4. Use of anxiolytic medication is measured using patient interviews at one year
5. Recovery is measured using the MINI criteria for anxiety disorder and the Spielberger trait anxiety score at three months and one year
6. Relapse is measured using the diagnostic criteria of the MINI generalised or social anxiety disorder with Spielberger trait anxiety score at one year
7. Trait Interoceptive prediction error on behavioural tests of interoceptive ability (error measured from z-score of heartbeat detection score accuracy -subjective (questionnaire and confidence) ratings of interoceptive 'sensibility' at 3 months and 1 year
8. Metacognitive interoceptive awareness measured from performance confidence correspondence (ROC curve analyses) at 3 months and 1 year
9. Clinical predictors of therapy response on ASD-related measures, i.e., cognitive, verbal and performance IQ, and ADI-R scores on dimensions of 1) social interaction, 2) communication and language and 3) repetitive stereotyped interests and behaviours predict magnitude of change in Spielberger anxiety score at 3 months and 1 year
10. Functional neural datasets is measured using SPM (Statistical Parametric Mapping) at 3 months and their relation to symptom response to treatment
11. Established efficacy of implementable software solution (beta testing–comparison against laboratory training methods therapist-measured ratings of ease-of-use) at 1 year
12. Participant’s capacity to control the occurrence of mindwandering and contents of their experience is measured using a 0-back-1-back-task and MDES (Multi-Dimensional Experience Sampling) at 3 months and 1 year

Overall study start date
01/01/2017

Completion date
31/03/2021

Eligibility

Key inclusion criteria
1. ADI-R confirmed ASC diagnosis
2. Aged 18 and over
3. Normal or corrected-to-normal vision
4. Fluent English speakers

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 120; UK Sample Size: 120

Total final enrolment
121

Key exclusion criteria
1. Age below 18 years
2. Past head injury or neurological disorders
3. History of major medical or psychiatric disorder (other than anxiety and co-morbid depression)
4. Cognitive impairment
5. History of substance or alcohol dependence
6. Heart disease
7. Obesity (body mass index > 30kg/m2)
8. Hypertension (>140/90 mm Hg)
9. Pregnancy
10. Asthma/respiratory illness
11. Migraines
12. Claustrophobia or other MRI exclusions
13. Upper age limit of 65

Date of first enrolment
10/07/2017

Date of final enrolment
01/03/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Brighton and Sussex Medical School
University of Sussex
Trafford Centre
Falmer
Brighton
United Kingdom
BN1 9RR

Sponsor information

Organisation
Sussex Partnership NHS Foundation Trust

Sponsor details
Assessment and Treatment Centre
Chapel Street
Chicester
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Arundel Road
Worthing
England
United Kingdom
PO19 1BX

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05fmrjg27

Funder(s)

Funder type
Government

Funder Name
MQ: Transforming Mental Health

Alternative Name(s)
Mental Health Research, MQ: Transforming Mental Health, MQ

Funding Body Type
Government organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Research findings will be presented at conferences and in publications. The aim is to submit findings for publication within 6 months of data acquisition. All publications will be open access. Findings will be to presented back to patients, at local Mood and Anxiety research Sussex (MARS) engagement events, at Sussex Partnership Trust Research and Developmental annual conference and to local third sector organisation meeting ASSERT Brighton and Hove.

Target journals for publication are British Journal of Psychiatry, Biological Psychiatry, and Brain. Another target is publication in a practice-based journal to broaden awareness of ADIE therapy if the trial is successful (e.g. Journal of Consulting and Clinical Psychology; Behaviour Therapy and Journal of Engagement and Involvement).
Within the technology development part of the project a market analyses and pathways to introduce into practice will be defined if the approach is established to be effective. There is planning for an Impact event for year 3 to launch this application to the healthcare sector.
The findings shall be disseminated at three to four key scientific conferences: International Congress of the Royal College of Psychiatrists in year 1; European Congress (EPA) year 2; Biological Psychiatry and or Social for Neurosciences (USA) Year 3.

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository Health, physiological, medical and performance data will be obtained from participants in the research and stored for the purposes of analysis and recording. During informed consent, all participants will be made aware of the methods used for handling personal data, the justification for requesting/obtaining their data, the duration of data use and storage and the guarantees concerning the rightful use of data. The basic principle regarding data storage throughout this project is that data will be anonymised (removal of all personal identifiers and held for a minimum of 5 years from the time of collection). The research team and the Institute abide by the Data Protection Act (1998) and will ensure all research is conducted according to EU legislation and the forthcoming EU Regulation on Data Protection. Data will be held on password protected computers or locked filing cabinets within university premises. Participant identifiers will be removed from all databases, and anonymised data will be used in all cases of dissemination. A copy of the participant identifier key will be stored in hard copy from within a single locked filing cabinet accessible by the PI, lead Co-I and CTU manager. An electronic record of this anonymisation key will be stored in encrypted password protected form on the Co-I's computer. The participant's identifier numbers will be used for all written forms, scanning data and physiological recording files. Data storage will conform to EU data protection legislation within firewalled, virus screened hardware on University of NHS premises. The length of storage will in part be determined by the nature of data; the National Research Ethics Service (NRES) advise long term storage of neuroimaging data.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V5	16/08/2017	25/10/2017	No	Yes
Results article		01/08/2021	18/08/2021	Yes	No
Protocol file			18/08/2022	No	No
HRA research summary			28/06/2023	No	No