Caption for supplementary material

Appendix I: Amendments to the Trial Protocol. This file includes a list of changes made to the Trial Protocol, all of which have been reviewed and approved by the relevant ethical committees.

Appendix II: Trial Protocol (V1). This file entails the original Trial Protocol, which was registered before start of recruitment.

Appendix III: Supplementary Material. This file includes details on all trial procedures, details of the complete case analysis, analysis with post-randomization clustering by therapist, and multiple imputation approach with tables, details on the construction of secondary outcome 'Recovery', data plots for secondary outcome measures, and a table with baseline characteristics before and after initial attrition.

Appendix

I. Amendments to Trial Protocol

All amendments are dated and listed below, and were approved by the Research Ethics Committees and Sponsor.

1 Protocol V1

The original Trial Protocol is found below

2 Protocol V2

Amendment 01, approved on 15.05.2017 before recruitment start, resulting in Protocol V2

1. Left-handed individuals will be included to increase sample size and simplify recruitment. The inclusion criterion to be right-handed was stated to make all participants eligible for fMRI scanning. However, only 40 out of 120 participants will participate in the scanning part of the study, hence it is not necessary to exclude all left-handed individuals.
2. Individuals with active anxiety disorders are now to be included. The main objective of the study is to test whether state and trait anxiety decreases with ADIE therapy. Therefore it will be necessary to recruit participants with active anxiety disorders to test whether state anxiety can be reduced. Including individuals with anxiety disorders also provides a larger recruitment pool, since anxiety disorders are fairly common in ASCs.
3. The following questionnaires will be added:
    a) Multidimensional Assessment of Interoceptive Awareness (MAIA); to test for the participant's awareness of bodily and emotional sensations and their ability to regulate them. MAIA will provide a measure of whether these abilities improve after exposure to ADIE therapy.
    b) UCLA Loneliness Scale; to assess feelings of loneliness pre and post therapy. The active therapy condition can lead to decreased social anxiety and thus decreased feelings of loneliness, while the control condition can increase social understanding and thereby diminish loneliness.
    c) Body Perception Questionnaire (BPQ); the questionnaire consists of several sections, however, for the current study only the awareness section is of interested. It tests for the ability to perceive bodily signals and will show whether this ability improves after therapy.
    d) Positive Affect and Negative Affect Scales (PANAS); to measure subjective distress and positive engagement and record changes after therapeutic intervention.
    e) Patient Health Questionnaire (PHQ-9); to test for symptoms of depression and negative mood. Depressive symptoms might be alleviated by ADIE therapy.
4. Recruitment will now also include advertisement on social media, specifically in online autism support groups. Posters and leaflets will be posted on Facebook groups to reach more potential participants.

3 Protocol V3

Amendment 02, approved on 09.05.2018, after recruitment start, resulting in Protocol V3

1. The eligibility criteria currently exclude individuals with co-morbid psychiatric disorders other than anxiety and depression. We wish to amend these criteria to allow individuals who have received a diagnosis of another psychiatric condition in the study. Given that the main outcome of our study is to test whether anxiety can be reduced with ADIE therapy in individuals with autism spectrum conditions, we believe that we can statistically account for most co-morbidities. We will still exclude individuals with psychiatric disorders that entail psychotic experiences, such as schizophrenia, borderline personality disorder, bipolar disorder, or major depression. Individuals with these diagnoses will only be excluded if they experience psychotic episodes. We hope to make our ADIE therapy available to a wider range of individuals with autism spectrum conditions by amending this specific exclusion criterion.
2. In agreement with our PPI group, we wish to add an information leaflet specifically tailored for each study group to provide them with additional knowledge and reassurance. We acknowledge that starting a new treatment and gaining new insight into task performance can be challenging. We aim to reduce stress that is related to this by handing our participants a leaflet in their first training session and go through its content with them. They will be able to ask any questions they might have and raise any concerns. We provide the leaflet in two versions that participants can choose from, one with a normal and one with a dyslexia-friendly font.
3. Our study has recently been featured in a brief BBC Stories video. We wish to send this video out to potential participants to give them a better idea about our study. This might also reduce anxiety that often precedes the first study session by giving participants an impression of what might happen and who they will meet. As this video is freely available, we do not need explicit consent from the producers. However, we have attached an email conversation with one of the producers confirming that we are allowed to use the video for recruitment purposes. The video can be viewed here: http://www.bbc.com/future/story/20180423-how-a-s

4. We wish to improve recruitment through clinicians at the Neurobehavioural Clinic led by Professor Critchley. We have thus formulated a letter that we wish to send out to potential participants two weeks after they have received their diagnosis. This added delay might reduce being overwhelmed after a long diagnostic interview and make patients more comfortable with getting a research invitation.
5. We wish to increase our recruitment numbers and open the study to more individuals. In order to do so, we wish to set up a training site at the University of London, School of Advanced Studies. We will ask our participants in the London area to come to Brighton for their two assessment sessions, but conduct the six training session locally in London to reduce travel time for out participants. Our aim is to broaden our recruitment pool while not burdening our vulnerable patient group with added expenditure of time.

We have updated our PIS to include all the proposed changes and to include an up-to-date timetable of the study. The changes only refer to timing issues to keep all sessions below two hours as we wish to not burden our participants with too long sessions.

4 Protocol V4

Amendment 03, approved on 09.08.2019, after recruitment start, resulting in the final Protocol V4

1. We have received feedback from a number of study participants about the usage of our leaflets. Many said that having a concise, smaller version of the key messages would be helpful in order to carry it with them at all times. We have thus, in collaboration with our PPI group, developed a business-card-sized card with the key message of the respective therapy participants receive. Participants who are yet to start or who are currently receiving training will be provided with the cards and encouraged to personalize it according to their needs. We aim to send the cards out via post to those participants who have finished the training but have not yet completed their 3 months follow up assessment with a brief explanation.
   We seek permission to contact clinicians, provide them with information about the study, and refer patients to us. Mental health clinicians working in the host site (Sussex Partnership NHS Foundation Trust) will be asked to identify any potential participants for this study. We will be approaching clinicians working in primary care setting (GP practices) and mental health services, including Assessment and Treatment Services (ATS), Assertive Outreach Teams (AOT), Recovery Services, Community Mental Health Teams (CMHTs) and Inpatient Mental Health Services. The clinicians will be the first to approach the potential participant regarding this research study, and will be encouraged to pass on a Participant Information Sheet (PIS) to any potential participants. If the potential participant is interested in taking part in this study they can either contact the research team directly themselves, or the clinician can make a referral (after the potential participant has given their verbal consent for this). Clinician Online Referrals will be available via Qualtrics, a safe online screening software.

II. Trial Protocol (V1)

Aligning Dimensions of Interoceptive Experience

(ADIE)

RESEARCH PROTOCOL

V1: 14.03.2017

ISRCTN	**14848787**	
Study Title:	**Aligning Dimensions of Interoceptive Experience (ADIE) to prevent the development of anxiety disorders in autism**	
Study Acronym:	**ADIE**	
Principal Investigator**:**	Professor Hugo Critchley[a,b,c]	**h.critchley@bsms.ac.uk**
Research Team:	Professor Sarah Garfinkel[a,b,e]	**s.garfinkel@bsms.ac.uk**
	Dr Clara Strauss[b]	**c.y.strauss@sussex.ac.uk**
	Dr Yoko Nagai[a]	**y.nagai@bsms.ac.uk**
	Anna-Marie Jones[a,d]	**a.jones4@brighton.ac.uk**
	Dr Lisa Quadt[a,b,c]	**l.quadt@bsms.ac.uk**
Study Sponsor**:**	**Sussex Partnership NHS Foundation Trust**	

[a] *Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex, Brighton, UK*
[b] *Sussex Partnership NHS Foundation Trust, Brighton, UK*
[c] *University of Sussex, Brighton, UK*
[d] *University of Brighton, Brighton, UK*

1 Abstract

Background

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. We have 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. We would like to try out and compare a new treatment, Aligning Dimensions of Interoceptive Experience (ADIE), teaching ASC patients these skills against the current treatment.

Methods/Design

This is a randomized controlled trial (RCT), combining neuroimaging methods, psychological/behavioural assessments and body-centred therapy. Participants will be 120 autistic adults recruited via Sussex Partnership Foundation Trust (SPFT). The study involves 2 separate assessment phases with 6 therapy sessions in between, and follow up assessments at 3 months and 12 months post therapy.

We will conduct a clinical trial, alongside an active control intervention, testing the efficacy of ADIE on anxiety symptoms, with secondary outcomes including anxiety disorder diagnosis, medication and function one year later.

Discussion

The neurodevelopmental ‘organic’ nature of ASCs means doctors don’t always accept psychological interventions as being affective treatment. To challenge this misconception, we will use state-of-the-art neuroimaging investigate the brain’s physiological response to ADIE, also guiding ways to optimise the therapy.

2 Keywords

Autism Spectrum Conditions; Anxiety; Interoception; Neuroimaging; Intervention: randomized controlled trial

3 List of abbreviations

ADIE	Aligning Dimensions of Interoceptive Experience
ADI-R	Autism Diagnostic Interview-Revised
AQ	Autism Quotient
ASC	Autism Spectrum Condition
CISC	Clinical Imagining Sciences Centre
CTU	Clinical Trials Unit
EQ	Empathy Quotient
EU	European Union
FMRI	Functional Magnetic Resonance Imaging
GAD-7	Generalized Anxiety Disorder 7 item Questionnaire
LEAF	Lived Experience Advisory Forum
MINI	Mini International Neuropsychiatric Interview
NART	National Adult Reading Test
PAG	Periaqueductal Grey Matter
PANAS	Positive and Negative Affect Scale
PHQ-9	Patient Health Questionnaire
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
RVF	Research Variables Form
SPFT	Sussex Partnership NHS Foundation Trust
STAI	Spielberger Trait-State Anxiety Inventory
TAS-20	Toronto Alexithymia Scale
VAS	Visual Analog Scale

4 Background

There are distinct psychological dimensions to the perception of internal bodily sensations, including arousal states such as fast heart rate, a process known as interoception.[1] We have developed a theoretical model proposing that anxiety is linked to the degree of divergence of subjective and objective dimensions of interoception, i.e., how subjectively sensitive we feel we are to bodily changes vs how accurately we actually perceive them.[2] We have shown this divergence (what we call interoceptive trait prediction error) is a powerful predictor of anxiety symptoms in people with a diagnosis of Autism Spectrum Conditions (ASCs).[3] Emotional experiences are shaped by interoceptive signals concerning the internal state of the body.[4,5] Anxiety symptoms are particularly linked to states of cardiovascular arousal and their perception.[2-4,6,7] We demonstrated that autistic individuals express deficits in tests of interoceptive accuracy; i.e. they are impaired in their ability to accurately detect internal bodily signals,[3] notably their own heart beating at rest. Moreover, on other measures, individuals with ASCs display heightened subjective beliefs about how sensitive they are to bodily signals.[3] This discrepancy between their objective performance and subjective experience is a 'interoceptive trait prediction error', explaining nearly 50% of the variance in anxiety in people with ASCs.[3] This accords with theoretical work linking anxiety to an altered interoceptive prediction signal.[8,9]

The demonstrated success of this ADIEs treatment for ASC will enrich options for a vulnerable 2% of the population.[10] The same approach may help anxiety management within non-ASC populations. Anxiety disorders affect 69.1 million European Union (EU) citizens at an annual cost to the EU of €74.4 billion.[11] Thus, this new effective psychological therapy for anxiety has potential for much broader impact in managing risk of anxiety of disorders. ASCs are neurodevelopmental conditions characterized by lifelong difficulties in social and emotional functioning alongside restricted stereotyped patterns of behaviour, interests and activities.[12] The majority of people with ASCs are classifiable as high functioning (i.e. without a general intellectual impairment).[10-12] Anxiety disorders are the most common co-morbidity experienced by between 23-60% of people with ASC.[13,14] Psychological interventions, notably cognitive behavioural therapy, can be effective for anxiety treatment in ASC.[15] yet barriers, and even pessimism, exists in treating an 'organic' neurodevelopmental condition, and there is often a desire among patients and carers for ASC tailored treatments. Moreover, some interventions are typically only available once deterioration is established.

We consequently developed and piloted a (bio)feedback based training therapy aimed at mitigating anxiety symptoms through 'aligning' dimensions of interoceptive experience (ADIE) to reduce interoceptive trait prediction error.

4.1 Research question

This trial pursues the question of whether an interoception-based, (bio)feedback training therapy can significantly reduce anxiety symptomatology in autistic adults, compared with an active control training therapy based on enhancing prosodic emotional recognition.

5 Patient and Public Involvement (PPI)

5.1 Past PPI

Our involvement plan is premised on an ethos of coproduction. LEAF (Lived Experience Advisory Forum) members with direct experience of high functioning autism or experience as caregivers have been consulted in the design of this study and have already given advice that will be used in our ethics application, around noise in the scanner and the acceptability and presentation of the research to this client group.

5.2 Future PPI

The LEAF members will continue to use their expertise to optimise preparation of service-user friendly materials pre ethics, advise on enablers and disablers to recruitment and support the preparation of lay summaries for participants and the wider general public. They will also pay attention to any issues of mission creep arising from the potential commercial applications of this research. We have funding support for a grade 5 coordinator of service-user involvement. Over the project's course, we have costed for 4 service user involvement meetings and 30 hours of additional consultation with experts-by-experience and a PPI coordinator.

6 Methods/Design

6.1 Type of study

This is a randomised controlled trial comparing ADIE therapy to an active control therapy (prosodic recognition training).

6.2 Participants

Participants will be 120 autistic adults between the ages of 18-65 years without intellectual disabilities.

6.2.1 Inclusion/exclusion criteria

Inclusion criteria:
All potential participants will have ADI-R confirmed ASC diagnosis. They must be right-handed, aged 18 and over, have normal or corrected-to-normal vision, and be fluent English speakers.

Exclusion criteria:

Age below 18 years, past head injury or neurological disorders, history of major medical or psychiatric disorder, epilepsy, cognitive impairment, history of substance or alcohol dependence, heart disease, obesity (body mass index > 30kg/m2), hypertension (>140/90 mm Hg), pregnancy, asthma/respiratory illness, migraines, claustrophobia or other MRI exclusions.

6.3 Aims & Objectives

Primary objective
To compare a new treatment involving training people to become more aware of bodily responses as a means of raising awareness of emotions with prosody treatment. The aim of this new treatment is to reduce risk of developing anxiety disorders, and bring down overall anxiety levels in autistic adults.

Secondary objectives
To use brain imaging to investigate other indicators of well-being, with an aim to enhancing personalised therapy for optimum success rates. This is currently a rapidly growing area of neuroscience.

Specific Aim 1: Conduct a clinical trial of ADIE therapy in people with ASC

Approach: Use therapist guided techniques, incorporating state-of-the-art cardiac biofeedback, with assessments at baseline (T0), following training (T1) and one-year follow up (T2).

Hypothesis 1: Reduced trait anxiety and reduced psychosocial difficulties will be observed at T1 and T2 in the ADIE group.

Hypothesis 2: Reduced interoceptive trait prediction error will relate directly to decreases in anxiety and psychosocial difficulties at T1 and T2.
ADIE therapy focuses on aligning people's beliefs about their ability to interpret signals from their body (such as their heart beat) with how well they actually can

interpret signals from their body. We believe that this therapy can thereby reduce anxiety.
The efficacy of the therapy over time will be assessed pre and post ADIE training, in relation to baseline levels of trait and state anxiety and remittance of symptoms relative to an active control group of individuals with ASC undergoing training on an 'exteroceptive skill' (voice prosody recognition).

Specific Aim 2: Identify mechanisms of action to predict outcome

Approach: Bodily arousal (autonomic signatures of cardiac reactivity) and neurocircuitry will be characterised using a combination of an emotional task, physiological measures and fMRI scans in a subset of ASC individuals at baseline and following body-awareness training (N=40, 80 scans in total). The task is an established means from our research group to access brain systems relevant to anxiety and its link to bodily arousal. This work builds on leading expertise and track record on the neuroscience of interoception and anxiety.

Hypothesis 3: Psychophysiological reactivity will be attenuated following ADIE therapy, indicating more effective regulation of emotional arousal. Within brain, functional connectivity between anterior insular cortex (mapping physiological arousal, dorsolateral prefrontal cortex and periaqueductal grey matter (PAG) will mirror behavioural improvement in measures of adaptive interoceptive 'integration' pre-post training. This will be associated with a decreased tendency to develop an anxiety disorder.

6.4 Recruitment and consent methods

Participants will be identified from current and former patients of Sussex Partnership Neurobehavioural Clinic (specialist service for diagnostic evaluation of potential ASCs). We will recruit adult people of all genders (18 yrs+) with established diagnoses of an ASC. Participants will also be recruited from 3rd sector organisations. All potential participants will undergo screening on the Mini International Neuropsychiatric Interview (MINI).

6.4.1 Recruitment and consent

Participants will be introduced to the project by one or more of the following pathways:
a) Posters displayed in clinics and in voluntary organisations or support groups such as Autism Sussex and ASSERT (Brighton and Hove)
b) Leaflets displayed in clinics
c) Letters/leaflets sent with appointment notifications
d) Introduction by managing clinicians
e) Sussex Partnership Recruitment Databases. Created by Sussex Partnership NHS

Foundation trust to bring together participants who are interested in participating in research, the network supports a database of potential volunteers. For other studies, we have corresponding ethical approvals for similar recruitment strategies. Sussex Partnership Foundation NHS trust is committed to service-user involvement. People interested in the study will be invited to contact the research team by email or telephone, or access the study website. Depending on their chosen route, they will be given a brief explanation by the research assistant and, if they remain interested, they will be sent a participant information sheet (PIS) and given a further telephone appointment or face-to-face appointment. The participant will be able to read about the study and is encouraged to ask others their opinion. At the follow up interview with the research assistant, the participant will be given full opportunity to ask any questions about the study and procedures in accordance with the ethics approval. The consent terms will be read to the participant. If they confirm that they will be interested to continue, a screening interview will be conducted over the telephone to establish eligibility, or participants can undergo screening online via Qualtrics.
There will be no explicit or implicit coercion of participants to participate. We anticipate and encourage potential participants with ASC to be supported by an appropriate adult in their decision to participate in the study. Fully informed consent will be obtained by the researcher at the first and subsequent appointments. For the subset of participants from the active group recruited to the imaging study at the time of imaging, a separate PIS and Consent is used.

6.5 Assessment process

This trial includes several phases. In a Baseline Assessment (T0), participants will fill out a battery of self-report measures on anxiety, mood, emotional regulation, bodily sensation perception, and general affect. They will also undergo two standardized interoception tasks to assess baseline interoceptive abilities, the heartbeat counting[16], and the heartbeat discrimination task[17]. They will also complete a behavioural task to assess baseline prosodic emotion recognition. 40 out of the 60 participants who were allocated to the ADIE treatment group also undergo fMRI scanning with a task to establish cardiac modulation of fear processing[6], a mind-wandering task, and an interoception task[4]. After the 6 therapy training sessions in the randomly allocated group, participants undergo a Final Assessment (T1), where all measures of T0 will be repeated.

Assessment	Carried out by	What the assessment is for	How is the assessment carried out	At what stage is the assessment carried out	Copy of assessment is in Appendix Y/N
Baseline	Researcher	Baseline measures	Self-report either in session or online, all tasks in session	Before training starts, after informed consent is provided	Y
Final	Researcher	Final measures	Self-report either in session or online, all tasks in session	After training has ended	Y
3 months follow up	Independent	Follow-up measures	Online via Qualtrics	3 months after final assessment	Y
1 year follow up	Researcher	Follow-up measures	Self-report either in session or online, all tasks in session	1 year after final assessment	Y

6.5.1 Baseline Assessment

Self-report measures

- Demographic Information
- Toronto Alexithymia Scale (TAS-20)[18]
- Autism Quotient (AQ)[19]
- Empathy Quotient (EQ)[20]
- Spielberger State-Trait Anxiety Inventory (STAI)[21]
- General Anxiety Disorder (GAD-7)[22]
- Patient Health Questionnaire (PHQ-9)[23]

Interoception Tasks

Heartbeat tracking and discrimination tasks will be used to determine objective interoceptive accuracy (i.e. accuracy in detecting internal bodily sensations). Participants were seated at a table with a VAS-sheet in front of them to mark confidence with their dominant hand. Their non-dominant arm and hand were placed on a pillow (participants were given the option not to use the pillow if their sensory sensitivities interfered), and a Nonin Pulseoximeter placed on their index finger. They were asked to keep still during the trials, but were free to move in between.

In the heartbeat discrimination task, participants are required to judge whether a series of ten auditory tones are synchronous with his/her heartbeat; this procedure is repeated 26 times to form 26 trials. Each participant is provided with the following instructions: 'You will hear ten tones. Please can you tell me if the tones are in or out of sync with your heartbeat'. Each trial consists of 10 tones presented at 440 Hz and having 100 ms duration, triggered by the participant's heartbeat. Under the synchronous condition, tones are generated at the beginning of the rising edge of the pulse pressure wave. Under the asynchronous condition, a delay of 300 ms is inserted,

adjusting for the average delay (~250 ms) between the R-wave and the arrival of the pressure wave at the finger. This setup delivered tones around 250 ms or 550 ms after the R-wave, which correspond to maximum and minimum synchronicity judgements respectively.

At the end of each trial, the participants responded by stating whether the series of tones were either synchronous or asynchronous with her/his heartbeats. In both conditions, the tones were presented at the same rate (i.e. either on the heartbeat or time-shifted), hence participants could not use the tempo of tones or other knowledge about their heart rate to guide responses: phase synchrony of tones and heartbeats served as the only informative cue.

In the heartbeat tracking task, participants will be given the following instructions: 'Without manually checking, can you silently count each heartbeat you feel in your body from the time you hear "start" to when you hear "stop"'. This task will be repeated six times to form six trials, using time-windows of 25, 30, 35, 40, 45 and 50 s, presented in randomized order. For each trial, an accuracy score is calculated using the following formula: 1 − (|nbeatsreal− nbeatsreported|)/((nbeatsreal+nbeatsreported)/2). An average of the resulting accuracy scores over the 6 trials yields an average value for each participant.

As a control task, participants will be given a time tracking task that is identical to the heartbeat tracking task, but with the following instructions: "In this task, please can you silently count seconds from the time you hear start to when you hear stop".

At the end of each trial (N = 26 for heartbeat discrimination and N = 6 for heartbeat/time tracking), the participant immediately rates his/her confidence in their perceived accuracy of response. This confidence judgement will be made using paper/pencil marked on a continuous visual analogue scale (VAS) that was 10 cm long. One end is marked "Total guess/No heartbeat awareness" while the other end is labelled "Complete confidence/Full perception of heartbeat/time".

A measure of interoceptive sensibility (i.e. self-perceived dispositional tendency to be internally self-focused and interoceptively cognisant) pertaining to self-perceived heartbeat detection will be derived from the mean confidence during both heartbeat discrimination and heartbeat tracking tasks (i.e. averaged over experimental trials to produce a global measure of mean confidence). A measure of interoceptive awareness (i.e. metacognitive awareness of interoceptive accuracy) will be quantified using receiver operating characteristic (ROC) curve analysis of the extent to which confidence predicted accuracy during the heartbeat discrimination task.

Prosody task

Participants were first instructed to put on over-the-ear headphones and were presented with on screen instructions explaining that they would hear audio clips of different phrases and that they should "*focus on the tone of voice as much as possible*". After each audio clip, they were presented with different emotion options in the form of facial expressions, words or faces with words. Their task was to decide which of the emotions best matched the tone of voice in the clip that they had just heard. Once it was clear that participants fully understood the task, they then progressed to the main experiment. This comprised 114 trials, where the voice was played while the four different emotion options were presented simultaneously on the screen. Depending on trial type, these were either in the form of face only, text only or face/text combined, all four options remained on screen until the user responded. Emotions included feature the six basic emotions; *happy, sad, disgusted, surprised, angry, afraid.* These were presented in two levels of intensity - regular and mild. In addition, thirteen complex emotions were also included; *bored, kind, jealous, unfriendly, hurt, disappointed, interested, joking, ashamed, proud, excited, frustrated* and *worried.* The audio clips were content neutral to ensure that emotion may only be detected through prosodic cues. Any audio clips deemed to include semantic content were removed and omitted from the study. Three different trial types were utilised; matching voices to faces (face-only), matching voices to emotion descriptors (text-only) and matching voices to faces and emotion descriptors combined (face with text) (Fig. 1). Each domain was further divided into positive and negative valence. In total 114 trials were completed (38 face-only, 38, text-only and 38 face with text). Each of the 19 verbally expressed emotions were presented twice for each domain but remained novel. The presentations were randomised and no trials were repeated. Out of 114 trials, 72 were of a negative valence (24 out of each trial type).

6.5.2 Training therapy

See section 6.7

6.5.3 Final Assessment

After the last training therapy session, participants are invited to a Final Assessment during which they repeat all measurements of the Baseline Assessment outlines in section 6.5.1

6.5.4 3 months follow up

Participants will be contacted via Email by the researcher and asked to fill out a brief Online Survey via the platform Qualtrics for some repeat measures taken at T0 and T1. This survey entails 2 self-report measures:

- STAI
- GAD-7

6.5.5 1 year follow up

Participants will be contacted via Email by the researcher and asked to come back to their study site for a follow up assessment, which entails all measurements taken at T0 and T1.

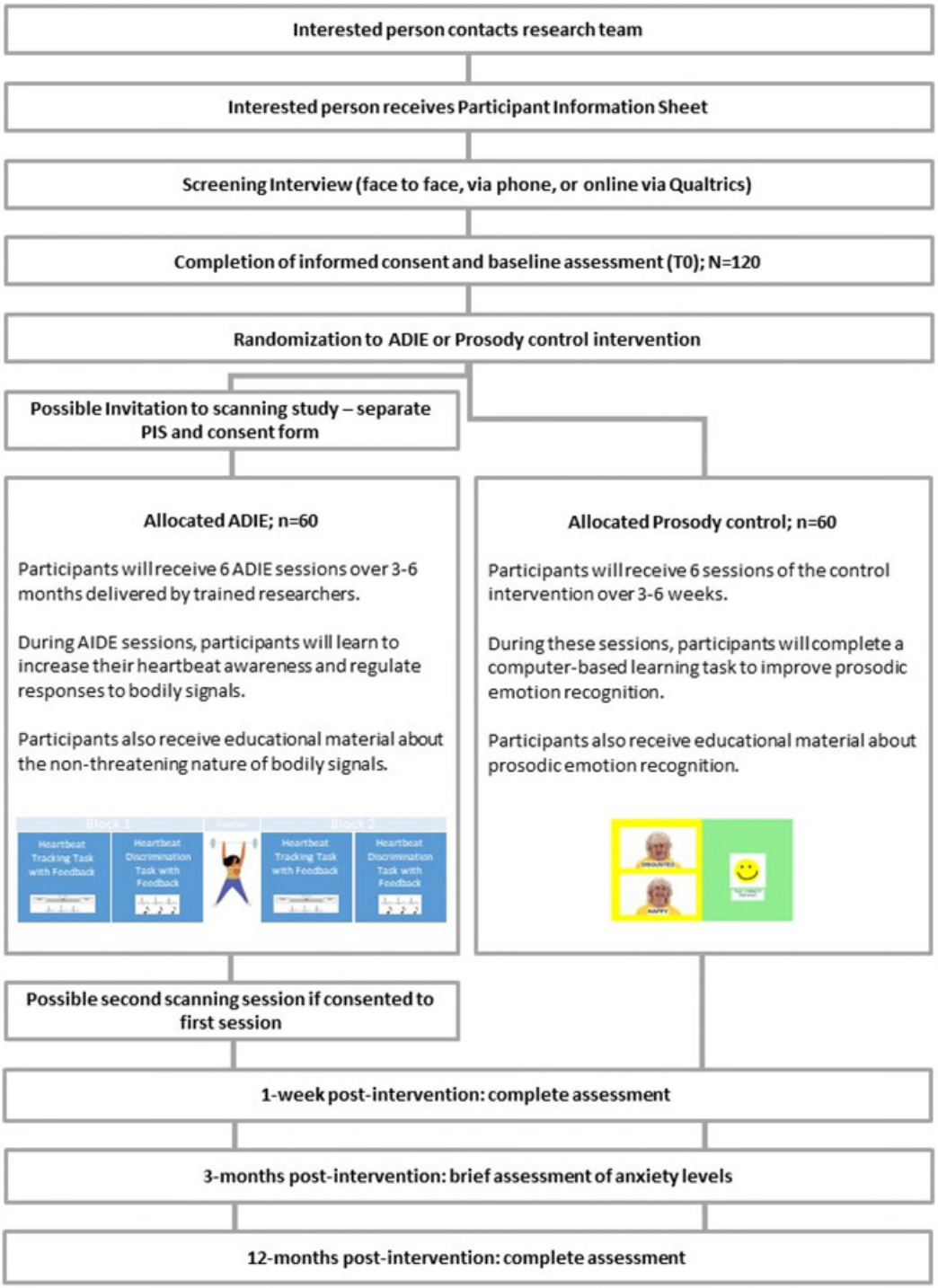
6.6 Randomisation process & allocation concealment

Participants will be allocated to either the treatment or control arm using a 1:1 ratio and permuted block randomisation by the Brighton and Sussex Clinical Trials Unit (CTU). After participant recruitment, the research assistant will contact the Brighton and Sussex CTU to find out the allocation. To double-blind the clinical trial, neither the research assistant administering the treatment and control nor the participant will be informed of which training regime is expected to deliver a therapeutic benefit. Follow-up assessments will be carried out by a separate research assistant who was not involved in the delivery of the therapy.

6.7 Procedure

6.7.1 Schematic procedure

Fig.1 Consolidated Standards of Reporting Trials (CONSORT) diagram of study design



6.7.2 Time Table Example (without brain scans)

Week	Day	Session	Content	Time
1	1	Baseline Assessment	• Consent Form • Questionnaires • Computer Task 1 • Questionnaires • Computer Task 2 • Questionnaires	• 10 minutes • 15 minutes • 30 minutes • 15 minutes • 15 minutes • 15 minutes Total ~2 hours
	2	Training Session 1	• ADIE or prosody therapy	• 15-30 minutes
	3	Training Session 2	• Training	• 15-30 minutes
2	4	Training Session 3	• Training	• 15-30 minutes
	5	Training Session 4	• Training	• 15-30 minutes
3	6	Training Session 5	• Training	• 15-30 minutes
	7	Training Session 6	• Therapy	• 15-30 minutes
	8	Final Assessment	• Questionnaires • Computer Task 1 • Questionnaires • Computer Task 2 • Questionnaires	• 15 minutes • 30 minutes • 15 minutes • 15 minutes • 15 minutes Total ~2 hours
After 3 months		3 months follow-up	• 2 Online Questionnaires	• 15 minutes
After 1 year		1 year follow-up	• Questionnaires • Computer Task 1 • Questionnaires • Computer Task 2 • Questionnaires	• 15 minutes • 30 minutes • 15 minutes • 15 minutes • 15 minutes Total ~2 hours

6.8 Therapy protocols

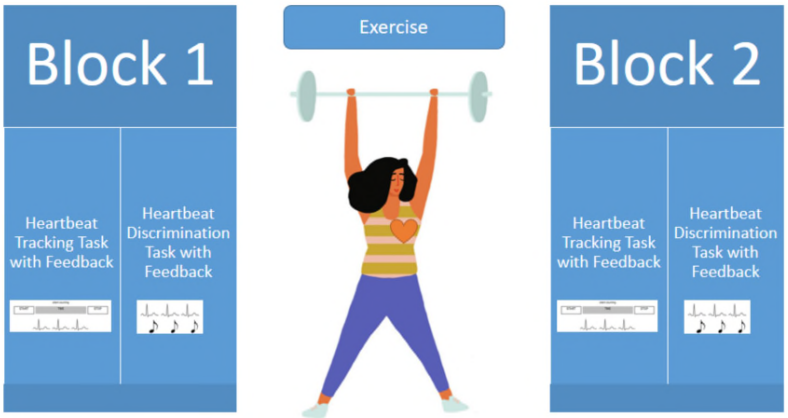
The first training therapy session involves a brief introduction to the intervention and reassurance that many people find the tasks challenging. All participants complete between 1-3 training sessions per week, with the constraint that all sessions are performed within a 2-month period.

6.8.1 Intervention procedure

In the active interoceptive training group, each training session entails two blocks, between which participants undergo a self-paced physical activity 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 our out of sync with the participants' heart beats. 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 synch").

Activity manipulation: In between these task blocks, each participant is required to engage in a physical activity 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.



6.8.2 Control / comparison procedure

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.

6.9 Primary & Secondary Outcome Measures

6.9.1 Primary Outcome measure

STAI trait anxiety score at 3 months

6.9.2 Secondary Outcome measures

a) STAI state and trait anxiety scores at 1 year
b) GAD7 score at 3 months and 1 year
c) Diagnosis criteria (MINI) met for generalized anxiety disorder at 1 year.
d) Use of anxiolytic medication at 1 year.
e) Recovery at 3 months and 1 year No longer fulfilling MINI criteria for anxiety disorder with 6 point drop in Spielberger trait anxiety score (<55)
f) Relapse at 1 year. Fulfilling of diagnostic criteria on MINI of generalized or social anxiety disorder with Spielberger trait anxiety score of 55 or greater
g) 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
h) Metacognitive interoceptive awareness measured from performance confidence correspondence (ROC curve analyses) at 3 months and 1 year.
i) Functional neural datasets at 3 months and their relation to symptom response to treatment
j) Established efficacy of implementable software solution (beta testing–comparison against laboratory training methods; therapist-measured ratings of ease-of-use)
k) Emotional state at T1 (TAS-20, PANAS, PHQ-9)

6.9.3 Details on Self-Report Outcome Measures

1. Spielberger State-Trait Anxiety Inventory (STAI)[21]

The STAI is a commonly used measure of trait and state anxiety, comprising 20 items for assessing trait anxiety and 20 for state anxiety. State anxiety items include: “I am tense; I am worried” and “I feel calm; I feel secure.” Trait anxiety items include: “I worry too much over something that really doesn’t matter” and “I am content; I am a steady person.” All items are rated on a 4-point scale from 1-4 (e.g., from “Almost Never” to “Almost Always”). Higher scores indicate greater anxiety. Internal consistency coefficients for the scale have ranged from .86 to .95; test-retest reliability coefficients have ranged from .65 to .75 over a 2-month interval.[24]

2. Generalized Anxiety Disorder 7 item scale (GAD-7)[22]

The GAD-7 is a commonly used measure of generalized anxiety symptoms in psychiatric and other populations and various settings. The questionnaire consists of 7 items asking about symptoms indicative of generalized anxiety over the last 2 weeks and consists of items such as “Trouble relaxing”, “Not being able to stop or control worrying”. All items are rated on a 4-point scale from 0-3 (e.g., “Not at all”, “Nearly Every Day). Higher scores

indicate higher anxiety levels. Internal consistency (α=.92) and test-retest reliability (ICC=0.83) are high, indicating good validity.[25]

3. Patient Health Questionnaire 9 item scale (PHQ-9)[23]

The PHQ-9 is the module of the Patient Health Questionnaire for depression and scores 9 DSM-IV criteria for major depressive disorder on a 4-point scale from 0-3 (e.g., "Not at all", "Nearly every day"). Scores up to 5 represent mild symptoms, 10 represent moderate, 15 moderately sever and 20 severe depression. The questionnaire has shown to have good reliability and validity.

4. Autism Quotient (AQ)[19]

The AQ was developed to fill a gap in short, self-administered screening tools for autistic traits. 50 items are scores on a 4-point item scale ("Definitely Agree", "Slightly agree", "Slightly disagree", "Definitely Disagree"), although scores are binary (0 or 1). A higher score indicates a higher chance of presence of Autism, and a score above 32 strongly indicates the presence of Autism. Test-retest coefficient is 0.7, and internal consistency high across different samples.[19]

5. Empathy Quotient (EQ)[20]

The EQ consists of 40 items measuring cognitive and affective empathy, and sympathy on a 4-point item scale ("Definitely Agree", "Slightly agree", "Slightly disagree", "Definitely Disagree"), although scores are binary (0 or 1). The questionnaire also has 20 filler items that are all scores 0. Higher scores indicate higher empathy.

6. Toronto Alexithymia Scale (TAS-20)[18]

Alexithymia describes a condition in which individuals have difficulty identifying and describing their own emotions. The TAS-20 assesses Alexithymia over 20 items, such as "It is difficult for me to find the right words for my feelings" or "It is difficult for me to reveal my innermost feelings, even to close friends" that are scored on a 5-point scale ("Strongly agree" to "Strongly disagree"). The cut-off score that indicates alexithymia has been set at 60. The TAS also includes three sub scores, including Difficulty Describing Feelings, Difficulty Identifying Feelings, and Externally-Oriented Thinking.

6.9.4 Details on Interoceptive Outcome Measures

1. Interoceptive Accuracy

For the HBT task, for each trial, an accuracy score is calculated using the following formula: $1 - (|\text{nbeatsreal} - \text{nbeatsreported}|)/((\text{nbeatsreal}+\text{nbeatsreported})/2)$. An average of the resulting accuracy scores over the 6 trials yields an average value for each participant. For the HBD task, *d-prime* (*d'*) was used as the accuracy index following signal detection theory, calculated as the standardised difference between the mean of the signal-to-noise distribution, compared against the standard deviation of signal-to-noise distribution.

2. Interoceptive Awareness

Interoceptive awareness is a metacognitive measure derived from confidence-accuracy correspondence.[2] For HBD interoceptive awareness was quantified using receiver operating characteristics (ROC) curve analysis for confidence-accuracy correspondence. ROC analysis indexes the strength of correspondence between confidence (measured by VAS) and a binary state variable, i.e. correct or incorrect asynchrony judgements during heartbeat discrimination. Confidence judgements were divided by hit rate, the proportion of correct trials on which confidence was high, and the false alarm rate, the proportion of incorrect trials on which confidence was high. The ROC curve then gives a measure of the extent to which confidence reflects accuracy, independent of the participant's propensity to report high confidence.

3. Interoceptive Trait Prediction Error (ITPE)[2]

ITPE describes the discrepancy between objective performance of interoceptive heartbeat detection tasks and subjective belief about one's own ability to perceive bodily signals, i.e., interoceptive sensibility, measured on the BPQ.[2] ITPE will be separately computed for the tracking and discrimination task, using standardized z-values of

accuracy scores and BPQ scores. Positive ITPE values represent an overestimation and negative ITPE values represent an underestimation of one's interoceptive abilities.

7 Data Management & Analysis

7.1 Summary of the Types of Data

Demographic information and self-report questionnaires will be completed via electronic forms in session or Qualtrics to aid data entry. Eligibility assessments will be completed using a separate paper-based or electronic case record form. Following collection, data will be entered into Stata for analysis.

7.2 Research Variables Form (RVF)

Type of data	Variable name	Outcomes/units	Source/Any Instructions
Inclusion	Aged 18-65	Yes/No	Self-report
Inclusion	ASC diagnosis	Yes/No	Self-report
Inclusion	Fluent in speaking and reading English	Yes/No	Self-report
Inclusion	Normal/corrected vision	Yes/No	Self-report
Inclusion	Healthy hearing	Yes/No	Self-report
Exclusion	Brain injury	Yes/No	Self-report
Exclusion	Blood pressure medication	Yes/No	Self-report
Exclusion	Pregnancy	Yes/No	Self-report
Exclusion	Psychiatric diagnoses	Yes/No	Self-report
Exclusion	Neurological/neurodegenerative disorder	Yes/No	Self-report
Screening	MINI Anxiety Disorder	Yes/No	MINI Section N GAD
Consent	Has the participant given consent freely	Yes/No	Consent form
Demographics	Age	Years	Qualtrics survey/ Self-report
Demographics	Gender Identification	M/F/Other/	Qualtrics survey/ Self-report
Demographics	Gender assigned at birth	M/F/Other	Qualtrics survey/ Self-report
Demographics	Gender ID fit to asab	Yes/No	Qualtrics survey/ Self-report
Demographics	Height	Cm/inch	Qualtrics survey/ Self-report
Demographics	Weight	Stone/kg	Qualtrics survey/ Self-report
Demographics	Nationality	Text	Qualtrics survey/ Self-report
Demographics	First language	Yes/No/Text	Qualtrics survey/ Self-report

Demographics	Educational achievement	Selection list	Qualtrics survey/ Self-report
Demographics	Perceived physical fitness	Selection list	Qualtrics survey/ Self-report
Demographics	Medication use	Text	Qualtrics survey/ Self-report
Demographics	Handedness	Right/Left/ Ambidextrous	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	TAS-20	Score for each item, subscores and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	AQ	Score for each item and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	EQ	Score for each item, and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	STAI State Anxiety	Score for each item, and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	STAI Trait Anxiety	Score for each item, and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	GAD-7	Score for each item and total score	Qualtrics survey/ Self-report
Validated Questionnaire (Likert scale)	PHQ-9	Score for each item and total score	Qualtrics survey/ Self-report
Neuroimaging Data	fMRI/resting state	Blood oxygen level dependent (BOLD) signal	n/a
Neuroimaging Data	Structural	Structural and diffusion data	n/a
Non-Validated Questionnaire	SQ – post block	Score for each item	In-scanner response
Non-Validated Questionnaire	SQ – post scan	Score for each item	Self-report
Experimental Data	Prosody Task	Scores accuracy	Computer-based task
Experimental Data	Heartbeat Task	Scores for interoceptive accuracy, awareness and sensibility	Behavioural task
Assessment Data	NART	Total score and subscores	Self-report

7.3 Sample size & Power calculations

The sample size was calculated based on experimental data.[3] These showed that the mean anxiety levels in individuals with Autism was 52.65 (sd = 12.03). We hypothesize that interoceptive trait prediction error will

reduce anxiety levels measured on the Spielberger State and Trait Anxiety Inventory (STAI). A clinical meaningful difference would be 7.65 points following treatment. So with a threshold of significance set at 5% for a two-sided test, power set at 90% and a 1:1 allocation ratio, a sample size of 53 participants is needed per arm (total study size, N = 100) to detect a difference in means of 7.65 between the treatment group and the control group (s.d. = 12.03) based on a t-test. Recruitment will be increased to 120 to allow for ~ 10% drop out. The sample size (N=40) within the neuroimaging study is informed by (i.e. exceeds) permits across group regressions analyses of individual differences in baseline measures and treatment response express as change in default mode network resting state connectivity and task-related activation differences in amygdala during emotional processing in ASC participants.[3,6,26,27]

7.4 Planned data analysis

ADIE treatment response: All participant characteristics, baseline scores and outcome measures will be summarized using descriptive statistics: frequency counts and proportions for categorical data; mean, median, s.d., min and max for continuous data. All analyses will be conducted on an intention-to-treat basis, which means that all participants will be analysed as per their randomization. The treatment effect size for the bodily awareness training in comparison to the active control will be estimated for the primary outcome using a mixed model followed by contrasts. This will include time (T1 & T2) and treatment group as factors. The baseline anxiety score will be included as a covariate. Random effects for individuals and a treatment group by time interaction will be included. All analyses will be carried out in STATA v13. Estimated parameters will be reported with corresponding 95% confidence intervals and standard errors. Standardized effect sizes (Cohen's d) will be calculated using the unstandardized effect size divided by the baseline pooled standard deviation. Secondary continuous outcomes will be estimated in the same way binary and outcomes will be analysed using chi-squared tests.

Neuroimaging correlates of interoceptive prediction error signalling within right insular cortex and connectivity between insula and dorsal cingulate with amygdala and PAG following therapy. We will use established neuroimaging methods including SPM (www.fil.ion.ucl.ac.uk/SPM) to process and analyse functional neural datasets, testing for brain predictors of treatment efficacy.
1) Resting state conductivity patterns pre-treatment
2) Task evoked responses to emotion challenges, interoceptive judgment / heartbeat detection.

7.5 Data handling: collection, entering, coding and checking process

Members of the research team will conduct the data collection. The data will be entered into a Stata file as it is collected. From the pool of data collected during this study, the analysis for each data set will be led by the researcher for whom it is their area of expertise. The other members of the research team will supervise the processing of the data.

Quantitative questionnaire data will be collected using Qualtrics (an online questionnaire programme) or electronic questionnaires, so that data can be automatically downloaded.

All members of the research team that are involved in the collection and management of data will be given the necessary training on how to use and administer the clinical measures used in this study. Training will involve a meeting with a member of the team who is experienced in using the particular clinical measure to discuss the questions and instructions. Next, the individual will be required to observe an experienced member of the team using the clinical measure, and then for them to be supervised using the clinical measure. If after this training process there are still problems in their use of the clinical measure, any of the training steps may be repeated until a member of the research who is experienced in using the measure, is confident in the individual's ability to use the measure.

7.6 Missing data policy

Attrition rate, i.e., withdrawal from follow-up will be reported overall and by intervention group. Missing values of participants for each variable, and reasons for withdrawal will be summarized for each treatment group at each time point.

7.7 Data custodian and data ownership

Name of data custodian: Professor Hugo Critchley

Name of data owner: University of Sussex

7.8 Data quality and Standards

The research team adhere to the good practice and standards principles which are set out in the Sussex Partnership Policy for Data Protection, Security and Confidentiality 2013. This policy reflects the recommendations from current legislation, including The Caldicott Report (1997), the British Standard (ISO IEC 27002) for Information Security, the Data Protection Act, 1998 and the Sussex Partnership Foundation Trust Research Policy 2012.

All research will be carried out under the above standards and will be reviewed by an NHS Ethics Committee and given approval by the R&D Department under the NHS Research Governance Framework 2005.

All members of the research team involved in consenting participants and collecting data will have completed Information Governance Training, and have their Good Clinical Practice certification. The collecting and analysis of the data will be supervised by the more senior researchers within the team: specifically Professor Hugo Critchley, and Dr Sarah Garfinkel. The management of the data will be a regular item at the research team meetings.

7.9 Data security

Participant names will not be used at any point during the collection of research data. With regards to data collection, participants will be identified using a unique numerical code. A separate file will be kept electronically linking participants names and personal details to the codes; this file will be kept in a password protected file that only members of the research team will have access to.

The quantitative data collected using computers (i.e. assessment data collected using Qualtrics) will be downloaded from the secure online Qualtrics database as soon as it is complete. All of the data collected on computers will be anonymous and non-identifiable, and protected by a password (i.e. a password will be required to download the Qualtrics data, and a password will be required to access the data collected from computerised tasks). The data that is downloaded electronically, along with any other electronic data (i.e. the Stata file with questionnaire scores) will be anonymised, and kept locally in a password-protected file, on a password-protected computer. Only members of the research team will know the passwords, and will therefore be able to access the electronic data. The password-protected computers that data will be stored on will be situated in the Department of Neuroscience at Brighton and Sussex Medical School.

Data acquired during scanning will contain a non-identifiable Clinical Imaging Sciences Centre (CISC) identification number, in addition to the participant's gender and date of birth. This is standard clinical practice for scanning data acquired from participants and patients undergoing MRI scanning at CISC. Identifiable personal data collected during the CISC consent process is stored alongside the CISC ID number in the participant's file, in a locked cabinet, accessible only to authorised CISC staff. Scanning data is initially stored in a database on the scanner, before being transferred by a member of the CISC radiography team to the CISC archive database. Data is retained on the scanner database for approximately three weeks before being deleted. Data is retained on the CISC archive database for ten years. Access to the CISC archive database is restricted to authorized individuals, via their secure password-protected University of Sussex computer account.

7.10 Data sharing

Anonymised data may be shared outside of the research team for research purposes only. Only anonymised data will be shared. This will be make explicit to participants on the study consent form. The participants' personal details will not be shared with anyone outside of the research team.

The number of participants recruited, and how they are recruited will need to be recorded and shared with both the Sussex Partnership NHS Foundation Trust research and development department, and the National Institute

for Health Research. The number of participants recruited will need to be shared to inform recruitment targets for both institutions. None of the personal details of the participants will be shared.

8 Ethical considerations

The researchers involved in this programme of work adhere to the 1996 version of the Declaration of Helsinki, as referred to in the Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, Schedule 1 parts 1.2 and 2.6: The health of our patients will be our first consideration; we shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.

8.1 Informed consent:

Consent to take part in this study will be informed. All participants will be given the PIS for at least 24 hours before meeting with a member of the research team to discuss consent. Furthermore participants will have the opportunity to ask questions about the research study before signing a consent form. The combination of the PIS and the chance to ask questions to a member of the research team will mean that any consent given will be fully informed.

8.2 Right to withdraw:

All participants will be told both verbally during the consent meeting, and within the PIS that they can withdraw from the research study at any point, with giving any explanation, and without their medical care or legal rights being affected. Participants will be asked to sign an item on the consent form that confirms their right to withdraw and that they are not obligated to provide a reason for leaving the study. Participants will also be given the option to withdraw from certain aspects of the study i.e. not complete all of the assessments.

8.3 Confidentiality:

All of the data collected within the research study will be kept confidential and personal information will not be released outside of the research team. Participants will be identified during data collection using a unique participant identification code (ID code). A separate document will be kept that links participants identifiable information to their ID code – this document will be kept securely in an electronic format, in line with the data storage and security policies set out in this protocol (see section 7.6). Confidentiality will only be broken if participants disclose any information that would put themselves or another at risk. Participants will be made aware of this confidentiality clause in the PIS and in the consent form. If information of this nature is shared by the participant, then Sussex Partnership NHS Foundation Trust risk procedures will be followed.

8.4 Risk procedures:

If information is shared that presents risk to the participant or someone else, Trust risk procedures will be followed.

In the first instance, any issues of risk will be reported to the researcher currently 'on-duty'. If the issue of risk requires action, this will be taken to the principal investigator (HC). All researchers have experience leading on research studies with vulnerable populations. HC is a research Psychiatrist, with extensive experience working with people experiencing mental health difficulties. Both HC and SG have extensive experience running studies that involve scanning people with mental health problems.

If the issue cannot be resolved within the research team, the participant's care coordinator and/or GP, and any other relevant authorities, will be contacted and made aware of the risk. In emergency situations, the emergency services will be contacted.

8.5 Risk to research staff:

There are not believed to be any likely risks to members of the research team in conducting this study. Risk procedures will be put in place in the event of any adverse events. When meeting with participants at the

University of Sussex, appointments will be restricted to office hours, so that other members of staff will be available in the building. Furthermore, the 24 hour security staff based at the University can be contacted using both university phones (which are available in most offices), or personal mobiles (which researchers will be instructed to keep on their person at all times).

Where referrals are made by third parties, the referrer will be asked to note any risk associated with the participant. Where there are notable risks or violence issues, the research team may choose to decline the referral, or plans can be made to ensure safety for all throughout the research process. Where participants self-refer to the study, the research team will request their permission to contact their care coordinator, in order to screen for any risk issues. If they do not consent to this, the research team will decline the referral.

Where participants are unable to travel to the University independently, a member of the research team may collect and drive the person to their appointment. The researcher will not enter the participant's home; and Trust's Lone Working Policy will be followed. Another member of the research team will be made aware of where the participant is being picked up from, at what time they should be picking the participant up, and what time they are expected to arrive at the university. The researcher will be expected to call their colleague at agreed times to confirm they have arrived at the participants home, and that they have arrived at the university. This travel option will only be offered to participants where the risk assessment indicates this is appropriate. Also, the researcher will seek additional insurance coverage from their car insurer provider to cover both the researcher and participant during these journeys.

8.6 Anonymity:

The names of participants will not be used in the collection and storing of data. Participants will be assigned a unique participant identification code (ID code) that will be used in the place of a name. A separate file, that will be password protected, will detail all of the participants' personal information (e.g. names, addresses, phone numbers) and the number/pseudonym they have been assigned. See section 7.11 for details of data security.

8.7 Potential for distress:

It is unlikely that participants will experience significant distress when completing the computer tasks and questionnaires. Previous research has found that participants enjoy the opportunity to reflect on their mental health, and can find it therapeutic (Notley et al., 2015). The measures and tasks included in this study (or similar versions) have been used in a number of previous research studies, and some are used frequently within clinical practice. However some of the questionnaires – such as those relating to mental health symptoms – contain questions that are potentially sensitive. These questionnaires will be undertaken in the presence of the researcher so that participant reactions can be monitored and managed appropriately. Participants will be informed in the PIS that some questions may be difficult and/or personal, and have the option not to participate, or to decline to answer questions that make them feel uncomfortable.

In relation to the neuroimaging component of the study, at CISC in Sussex, we have an established track record of longitudinal and interventional neuroimaging studies in neuropsychiatric patients, emotional instability and neurodevelopmental conditions. We are expert in supporting patient participants, and are attentive to issues such as discomfort in the scanner from noise or claustrophobia (a concern of our consulted service user panel).

In the event that a participant does become distressed, the SPFT policy for managing distress and risk will be followed. Participants will be offered the opportunity to take a break. Participants will be reminded of their right to withdraw, and where there is evidence of significant distress, participants will be explicitly offered the opportunity to withdraw from a specific aspect of the study (i.e. not complete a particular assessment), or withdraw from the study as a whole.

9 Discussion of practical and operational issues

Adverse events: The Good Clinical Practice guidelines will be followed in the event of any adverse events during the study. The procedure that will followed is outlined here:

1. If any adverse event occurs this will be taken firstly to the Researcher that is 'on-duty' i.e. the researcher currently involved in the data collection

2. The adverse event will then be rated on a 5 point scale for severity and a separate 5 point scale for relevance to the study
3. If the event is deemed to be severe, then this will be taken to the Principal Investigator (HC).
4. If there is a cause for concern (i.e. an adverse event was rated as both severe and relevant to the study) this would then be taken to the sponsor (Sussex Partnership NHS Foundation Trust)
5. The sponsor will then make a decision as to whether the adverse event needs further investigation, and whether the study needs to be stopped
6. The outcome of any investigation will then determine the future of the study (e.g. whether the study is able to resume again, and if so, when it can resume)

Any severe and relevant adverse events that occur during the research will also be reported to the ethics committee, in line with NHS ethics protocol. Additionally, the participants' care coordinator and/or GP will be informed about the adverse event. Emergency services will also be contacted where needed.

The Principal Investigator will take responsibility for informing the sponsor of any adverse events. The sponsor will be informed via email – all emails related to this will be marked as urgent.

Managing risk: In the event there are risk-related issues brought to the attention of the research team (i.e. when a clinician makes a study referral), the study protocol will be adapted to manage these in a safe way. Where the risk is too high and involvement in the research study may put the participant at any further risk, they will not be recruited to participate.

10 Projected outputs and Dissemination

The findings from this research project will be published in high quality peer-review academic journals. We will specifically target journals with large impact factors that reach an international audience, and where the readership will have an interest in mental health and clinical psychology. We will also seek to present the findings at conferences where both academics and clinicians will be present.

The research team will also make use of the local community engagement events that attract service users, carers, clinicians and researchers alike. For example, a member of the research team will present the findings during the Sussex Partnership NHS Foundation Trust Research Network conference.

Importantly, we will ensure the findings are disseminated to the relevant stakeholders. Plain English summaries of the results will be sent to all of the participants involved in the project, as well as everyone who referred a participant into the study. This plain English summary will also be included in the quarterly Sussex Partnership NHS Foundation Trust Research and Development magazine, and the Brighton and Sussex Medical School InPulse magazine – both of these publications attract a significant readership comprise of academic and non-academic persons.

11 Amendments

The following sections have been amended from the original protocol:

6.2.1. Inclusion/exclusion criteria

Inclusion criteria:
All potential participants will have ADI-R confirmed ASC diagnosis. They must be aged 18 and over, have normal or corrected-to-normal vision, and be fluent English speakers.

Exclusion criteria:
Age below 18 years, past organic brain injury, epilepsy, history of psychotic experiences, cognitive impairment, history of substance or alcohol dependence, heart disease, obesity (body mass index > 30kg/m2), hypertension (>140/90 mm Hg), pregnancy, asthma/respiratory illness, migraines.

6.4.1. Recruitment and consent

Participants will be introduced to the project by one or more of the following pathways:
a) Posters displayed in clinics and in voluntary organisations or support groups such as Autism Sussex and ASSERT (Brighton and Hove)

b) Leaflets displayed in clinics
c) Letters/leaflets sent with appointment notifications
d) Introduction by managing clinicians
e) Sussex Partnership Recruitment Databases Created by Sussex Partnership NHS Foundation trust to bring together participants who are interested in participating in research, the network supports a database of potential volunteers.

For other studies, we have corresponding ethical approvals for similar recruitment strategies. Sussex Partnership Foundation NHS trust is committed to service-user involvement. People interested in the study will be invited to contact the research team by email or telephone, or access the study website. Depending on their chosen route, they will be given a brief explanation by the research assistant and, if they remain interested, they will be sent a participant information sheet (PIS) and given a further telephone appointment or face-to-face appointment. The participant will be able to read about the study and is encouraged to ask others their opinion. At the follow up interview with the research assistant, the participant will be given full opportunity to ask any questions about the study and procedures in accordance with the ethics approval. The consent terms will be read to the participant. If they confirm that they will be interested to continue, a screening interview will be conducted over the telephone to establish eligibility, or participants can undergo screening online via Qualtrics.
There will be no explicit or implicit coercion of participants to participate. We anticipate and encourage potential participants with ASC to be supported by an appropriate adult in their decision to participate in the study. Fully informed consent will be obtained by the researcher at the first and subsequent appointments. For the subset of participants from the active group recruited to the imaging study at the time of imaging, a separate PIS and Consent is used.

6.5.1. Baseline Assessment

Self-report measures

- Demographic Information
- Porges Body Perception Questionnaire Awareness Section (BPQ)[28]
- Toronto Alexithymia Scale (TAS-20)[18]
- Autism Quotient (AQ)[19]
- Empathy Quotient (EQ)[20]
- Spielberger State-Trait Anxiety Inventory (STAI)[29]
- General Anxiety Disorder (GAD-7)[22]
- Multidimensional Assessment of Interoceptive Awareness (MAIA)[30]
- Positive and Negative Affect Scale (PANAS)[31]
- Patient Health Questionnaire (PHQ-9)[23]

(rest of the section stayed the same)

6.5.2. 1-week post-intervention assessment
After the last training therapy session, participants are invited to an assessment during which they repeat all measurements of the Baseline Assessment outlines in section 6.5.1

6.5.4. 3-months post-intervention assessment
Participants will be contacted via Email by the researcher and asked to fill out a brief Online Survey via the platform Qualtrics for some repeat measures taken at T0 and T1. This survey entails 3 self-report measures:

- BPQ
- STAI
- GAD-7
-

6.9.2. Secondary Outcome measures

a. STAI state and trait anxiety scores at 1 year
b. GAD7 score at 3 months and 1 year
c. Diagnosis criteria (MINI) met for generalized anxiety disorder at 1 year.
d. Use of anxiolytic medication at 1 year.
e. Recovery at 3 months and 1 year No longer fulfilling MINI criteria for anxiety disorder with 6-point drop in Spielberger trait anxiety score (≤55)
f. Improvement at 3 months and 1 year with 6-point drop in Spielberger trait anxiety score regardless of overall score

g. Relapse at 1 year. Fulfilling of diagnostic criteria on MINI of generalized or social anxiety disorder with Spielberger trait anxiety score of 55 or greater
h. 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'[2] at 3 months and 1 year
i. Metacognitive interoceptive awareness measured from performance confidence correspondence (ROC curve analyses[2]) at 3 months and 1 year.
j. Emotional state at T1 (TAS-20, PANAS, PHQ-9)
k. Functional neural datasets at 3 months and their relation to symptom response to treatment
l. Established efficacy of implementable software solution (beta testing–comparison against laboratory training methods; therapist-measured ratings of ease-of-use)

6.9.3. Details on Outcome Measures

Spielberger State-Trait Anxiety Inventory (STAI)

The STAI is a commonly used measure of trait and state anxiety, comprising 20 items for assessing trait anxiety and 20 for state anxiety. State anxiety items include: “I am tense; I am worried” and “I feel calm; I feel secure.” Trait anxiety items include: “I worry too much over something that really doesn’t matter” and “I am content; I am a steady person.” All items are rated on a 4-point scale from 1-4 (e.g., from “Almost Never” to “Almost Always”). Higher scores indicate greater anxiety. Internal consistency coefficients for the scale have ranged from .86 to .95; test-retest reliability coefficients have ranged from .65 to .75 over a 2-month interval.[24]

Generalized Anxiety Disorder 7 item scale (GAD-7)

The GAD-7 is a commonly used measure of generalized anxiety symptoms in psychiatric and other populations and various settings. The questionnaire consists of 7 items asking about symptoms indicative of generalized anxiety over the last 2 weeks and consists of items such as “Trouble relaxing”, “Not being able to stop or control worrying”. All items are rated on a 4-point scale from 0-3 (e.g., “Not at all”, “Nearly Every Day). Higher scores indicate higher anxiety levels. Internal consistency (α=.92) and test-retest reliability (ICC=0.83) are high, indicating good validity.[25]

Patient Health Questionnaire 9 item scale (PHQ-9)

The PHQ-9 is the module of the Patient Health Questionnaire for depression and scores 9 DSM-IV criteria for major depressive disorder on a 4-point scale from 0-3 (e.g., “Not at all”, “Nearly every day”). Scores up to 5 represent mild symptoms, 10 represent moderate, 15 moderately sever and 20 severe depression. The questionnaire has shown to have good reliability and validity.[23]

Autism Quotient (AQ)

The AQ was developed to fill a gap in short, self-administered screening tools for autistic traits. 50 items are scores on a 4-point item scale (“Definitely Agree”, “Slightly agree”, “Slightly disagree”, “Definitely Disagree”), although scores are binary (0 or 1). A higher score indicates a higher chance of presence of Autism, and a score above 32 strongly indicates the presence of Autism. Test-retest coefficient is 0.7, and internal consistency high across different samples.[19]

Empathy Quotient (EQ)

The EQ consists of 40 items measuring cognitive and affective empathy, and sympathy on a 4-point item scale (“Definitely Agree”, “Slightly agree”, “Slightly disagree”, “Definitely Disagree”), although scores are binary (0 or 1). The questionnaire also has 20 filler items that are all scores 0. Higher scores indicate higher empathy.

Positive and Negative Affect Scale (PANAS)

On 20 items for each positive and negative affect, participants are asked to rate to what extent they felt a certain way (e.g. “interested”, “excited, “enthusiastic” for positive affect, “distressed”, “guilty”, “hostile” for negative affect) during the past week on a scale from 1-5. The scale was developed to measure positive and negative affect

as two prominent dimensions of mood, and have proven good psychometric properties over several samples and settings.[32]

Multidimensional Assessment of Interoceptive Awareness (MAIA)

The MAIA assesses awareness of bodily sensations along 8 sub scores without calculating a total score. The MAIA includes 4 items for "Noticing: Awareness of uncomfortable or comfortable, and neutral bodily sensations", 3 items for "Not-Distracting: Tendency to ignore or distract oneself from sensations of pain and discomfort", 3 items for "Not-Worrying: Tendency not to worry or experience emotional distress with sensations of pain or discomfort", 7 items for "Attention Regulation: Ability to sustain and control attention to body sensations", 5 items for "Emotional Awareness: Awareness of the connection between body sensations and emotional states", 4 items for "Self-Regulation: Ability to regulate distress by attention to body sensations", 3 items for "Body Listening: Active listening to the body for insight", and 3 items for "Trusting: Experience of one's body as safe and trustworthy".[30] Items are statements like "I notice when I am uncomfortable in my body", and participants are asked to rate how often statements apply to them generally in daily life on a scale from 0-5 (0=Never, 5=Always) and averaged individually.

Body Perception Questionnaire, Awareness Section (BPQ)

The BPQ has five sub-sections, of which we chose the Awareness section, in which participants are asked to image how aware they are on their body processes and rate on a 5-point (1=Never, 5=Always) scale "During most situations I am aware of:" from a 45 item list of different bodily sensations, such as "An urge to urinate", "Goose bumps", "How fast I am breathing".

Toronto Alexithymia Scale (TAS-20)

Alexithymia describes a condition in which individuals have difficulty identifying and describing their own emotions. The TAS-20 assesses Alexithymia over 20 items, such as "It is difficult for me to find the right words for my feelings" or "It is difficult for me to reveal my innermost feelings, even to close friends" that are scored on a 5-point scale ("Strongly agree" to "Strongly disagree"). The cut-off score that indicates alexithymia has been set at 60. The TAS also includes three sub scores, including Difficulty Describing Feelings, Difficulty Identifying Feelings, and Externally-Oriented Thinking.

Interoceptive Trait Prediction Error (ITPE)

ITPE describes the discrepancy between objective performance of interoceptive heartbeat detection tasks and subjective belief about one's own ability to perceive bodily signals, i.e., interoceptive sensibility, measured on the BPQ. ITPE will be separately computed for the tracking and discrimination task, using standardized z-values of accuracy scores and BPQ scores. Positive ITPE values represent an overestimation and negative ITPE values represent an underestimation of one's interoceptive abilities.

Appendices
Appendix 1: Information Leaflets and Cards handed to Participants
ADIE Intervention group:

FRONT

brighton and sussex medical school

Sussex Partnership NHS
NHS Foundation Trust

Aligning Dimensions of Interoceptive Experience (ADIE)

Information about heart beat and anxiety

Information Leaflet Version 1 01 February 2018

BACK

Further help & information

- If you are struggling with your mental health, talk with your **GP**
- **Online helpline and information:**
  http://www.autism.org.uk/helpline
- **Information on anxiety and tips to manage it:**
  http://www.moodjuice.scot.nhs.uk/anxiety.asp
- **Online live-chat:**
  https://www.anxietyuk.org.uk/get-help/anxiety-uk-national-infoline-service/live-chat/

Information Leaflet Version 1 01 February 2018

How is anxiety related to body sensations?

When anxious, you can get into a **Cycle of Anxiety:**

Trigger
e.g., feeling one's heart beat

Anxious thought
e.g., 'Something is wrong with my heart'

Worry
e.g., 'This could be dan-

Body response *
e.g., faster heart beat, sweating, faster breathing

Catastrophizing
e.g., 'I'm having a heart attack!'

*On the next page you find tips that might help to break the cycle!

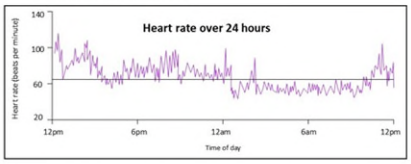
Information Leaflet Version 1 01 February 2018

Heart beat facts and managing anxiety

Some people feel their heart beat all the time, some only sometimes, some don't feel it at all—**all of this is normal.**

The speed of your heart beat varies over the day

> This is **normal** and **healthy!**



Reminding yourself of these things might help to break the cycle of anxiety:

> A heart beat is a **non-threatening** body sensation
> It is **normal** to feel your heart beat
> Take **deep and even breaths** to slow your heart down

Improving your interoceptive skills helps you to see your heart beat for what it is:
A healthy body sensation and not a threat

Information Leaflet Version 1 01 February 2018

FRONT

brighton and sussex medical school

MQ Transforming mental health through research

Feeling anxious?

- Notice -

- Normalize -

- Regulate -

Information Card Version 1 01 July 2019

BACK

- Notice -

⇒ **Localise your heartbeat**

- Normalize -

⇒ **"This is just my heart"**

- Regulate -

⇒ **Breathe deeply**

⇒ **Shift attention**

Prosody Intervention Group:

FRONT

brighton and sussex medical school

Sussex Partnership NHS
NHS Foundation Trust

Aligning Dimensions of Interoceptive Experience (ADIE)

Information about prosody and emotion understanding

Information Leaflet Version 1 01 February 2018

BACK

Further help & information

- If you are struggling with your mental health, talk with your **GP**
- **Online helpline and information:**
  http://www.autism.org.uk/helpline
- **Information on anxiety and tips to manage it:**
  http://www.moodjuice.scot.nhs.uk/anxiety.asp
- **Online live-chat:**
  https://www.anxietyuk.org.uk/get-help/anxiety-uk-national-infoline-service/live-chat/

Information Leaflet Version 1 01 February 2018

Prosody and understanding Emotions

- Prosody is the tone of voice used in spoken language
- Emotions can be expressed in different ways
  > One way is through tone of voice
- Recognising and interpreting emotions in tone of voice needs two things:

WHAT is said? **Content**	HOW is it said? **Prosody**
How long have you been here?	
How long have you been here?	

Information Leaflet Version 1 01 February 2018

Why it can be hard to understand emotions

- Emotion understanding is very complex and has many components:

⇒ This is why it can be very hard to understand and interpret emotions

Prosody is just one part of being able to understand emotions. It is normal to have strengths in some parts and difficulty with others.

Information Leaflet Version 1 01 February 2018

FRONT

brighton and sussex medical school

MQ Transforming mental health through research

It can be hard to understand emotions

- Notice -

- Normalize -

- Regulate -

Information Card Version 1 01 July 2019

BACK

- Notice -

⇒ **"I don't quite understand"**

- Normalize -

⇒ **"That's okay, it can be hard"**

- Regulate -

⇒ **Ask for clarification**

⇒ **Remind yourself of your strengths**

12 Competing Interests

The research team have no competing interests to declare.

13 Authors' contributions

This protocol was written by Clare Brown (Research Assistant). All of the members of the research have approved the submitted version of the protocol. PPI consultants and representatives of the sponsor have also reviewed the protocol and provided feedback.

14 Acknowledgements

The research team would like to thank the MQ Mental Health Charity Awarding body for funding this trial.

15 References (Trial Protocol only)

1. Garfinkel SN, Critchley HD. Interoception, emotion and brain: new insights link internal physiology to social behaviour. Commentary on:: "Anterior insular cortex mediates bodily sensibility and social anxiety" by Terasawa et al. (2012). *Soc Cogn Affect Neurosci* 2013; **8**(3): 231-4.
2. Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol Psychol* 2015; **104**: 65-74.
3. Garfinkel SN, Tiley C, O'Keeffe S, Harrison NA, Seth AK, Critchley HD. Discrepancies between dimensions of interoception in autism: Implications for emotion and anxiety. *Biological psychology* 2016; **114**: 117-26.
4. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nature neuroscience* 2004; **7**(2): 189-95.
5. Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 2003; **13**(4): 500-5.
6. Garfinkel SN, Minati L, Gray MA, Seth AK, Dolan RJ, Critchley HD. Fear from the heart: sensitivity to fear stimuli depends on individual heartbeats. *J Neurosci* 2014; **34**(19): 6573-82.
7. Carnevali L, Makovac E, Schumann A, et al. From body to mind (and vice versa) via heart rate variability. PSYCHOSOMATIC MEDICINE; 2019; Vancouver, Canada: LIPPINCOTT WILLIAMS & WILKINS; 2019. p. A184-A5.
8. Seth AK. Interoceptive inference, emotion, and the embodied self. *Trends Cogn Sci* 2013; **17**(11): 565-73.
9. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry* 2006; **60**(4): 383-7.
10. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Blumberg SJ. Estimated Prevalence of Autism and Other Developmental Disabilities Following Questionnaire Changes in the 2014 National Health Interview Survey. *Natl Health Stat Report* 2015; (87): 1-20.
11. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012; **19**(1): 155-62.
12. Frith U. Autism-are we any closer to explaining the enigma? *Psychologist* 2014; **27**(10): 744-5.
13. Joshi G, Wozniak J, Petty C, et al. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *Journal of Autism and Developmental Disorders* 2013; **43**(6): 1314-25.
14. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample; 2008.
15. Nadeau J, Sulkowski ML, Ung D, et al. Treatment of comorbid anxiety and autism spectrum disorders. *Neuropsychiatry (London)* 2011; **1**(6): 567-78.
16. Schandry R. Heart beat perception and emotional experience. *Psychophysiology* 1981; **18**(4): 483-8.
17. Whitehead WE, Drescher VM, Heiman P, Blackwell B. Relation of heart rate control to heartbeat perception. *Biofeedback and Self-Regulation* 1977; **2**(4): 371-92.
18. Bagby RM, Parker JD, Taylor GJ. The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research* 1994; **38**(1): 23-32.
19. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. *Journal of autism and developmental disorders* 2001; **31**(1): 5-17.
20. Baron-Cohen S, Wheelwright S. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *J Autism Dev Disord* 2004; **34**(2): 163-75.
21. Spielberger CD. State-Trait anxiety inventory. *The Corsini encyclopedia of psychology* 2010: 1-.
22. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**(10): 1092-7.
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine* 2001; **16**(9): 606-13.

24. Spielberger CD. State-trait anxiety inventory for adults. APA PsycTests; 1983.
25. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Löwe B. Anxiety Disorders in Primary Care: Prevalence, Impairment, Comorbidity, and Detection. *Annals of Internal Medicine* 2007; **146**(5): 317-25.
26. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *The Journal of physiology* 2000; **523 Pt 1**(1): 259-70.
27. Critchley HD, Rotshtein P, Nagai Y, O'Doherty J, Mathias CJ, Dolan RJ. Activity in the human brain predicting differential heart rate responses to emotional facial expressions. *Neuroimage* 2005; **24**(3): 751-62.
28. Porges S. Body perception questionnaire. *Laboratory of Developmental Assessment, University of Maryland* 1993.
29. Spielberger CD. State-Trait Anxiety Inventory. In: Weiner IB, Craighead WE, eds. The Corsini Encyclopedia of Psychology; 2010: 1-.
30. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS One* 2012; **7**(11): e48230.
31. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988; **54**(6): 1063-70.
32. Bakhshipour R, Dezhkam M. A CONFIRMATORY FACTOR ANALYSIS OF THE POSITIVE AFFECT AND NEGATIVE AFFECT SCALES (PANAS). *JOURNAL OF PSYCHOLOGY* 2006; **9**(4 (36)): 351-65.

III. Supplementary Material

1 Details on Procedure

1.1 Baseline Assessment (T0)

Eligible participants were invited for a baseline assessment taking place on University ground either at University College London or University of Sussex in a dedicated research facility. The following self-report measures were taken either at baseline assessment or, depending on individual preference and presence of learning disabilities like dyslexia, completed at home by the participant using the Online Platform Qualtrics.

1.1.1 Self-report Measures

- Demographic Information
- Porges Body Perception Questionnaire Awareness Section (BPQ) [1]
- Toronto Alexithymia Scale (TAS-20) [2]
- Autism Quotient (AQ) [3]
- Spielberger State-Trait Anxiety Inventory (STAI) [4]
- General Anxiety Disorder (GAD-7)
- Multidimensional Assessment of Interoceptive Awareness (MAIA) [5]
- Positive and Negative Affect Scale (PANAS) [6]
- Patient Health Questionnaire (PHQ-9) [7]

Participants also completed two standard heartbeat detection tasks, and a baseline prosody task without any feedback performance on either experimental task:

1.1.2 Interoception Tasks

Heartbeat tracking and discrimination tasks were be used to determine performance accuracy (i.e. accuracy in detecting internal bodily sensations). Participants were seated at a table with a Visual Analogue Scale-sheet in front of them to mark confidence with their dominant hand. Their non-dominant forearm and hand were placed on a pillow (participants were allowed not to use the pillow, or a soft item of their own, if their sensory sensitivities interfered), and a Nonin Pulseoximeter placed on their index finger. They were asked to keep still during the trials, but were free to move in between. All participants were tested first on the heartbeat tracking and control task, then on the heartbeat discrimination task.

In the heartbeat tracking task, participants were given the following instructions: ‘Without manually checking, can you silently count each heartbeat you feel in your body from the time you hear “start” to when you hear “stop”’. This task was repeated six times to form six trials, using time-windows of 25, 30, 35, 40, 45 and 50 s, presented in randomized order. For each trial, responses of reported heartbeats were recorded by the researcher.

As a control task, participants were given a time tracking task that is identical to the heartbeat tracking task, but with the following instructions: “In this task, please can you silently count seconds from the time you hear start to when you hear stop”.

In the heartbeat discrimination task, participants were required to judge whether a series of ten auditory tones were synchronous with their heartbeat; this procedure is repeated 26 times to form 26 trials. Each participant was provided with the following instructions: ‘You will hear ten tones. Please can you tell me if the tones are in or out of sync with your heartbeat’. Each trial consisted of 10 tones presented at 440 Hz and having 100 ms duration, triggered by the participant’s heartbeat. Under the synchronous condition, tones were generated at the beginning of the rising edge of the pulse pressure wave. Under the asynchronous condition, a delay of 300 ms was inserted, adjusting for the average delay (~250 ms) between the R-wave and the arrival of the pressure wave at the finger. This setup delivered tones around 250 ms or 550 ms after the R-wave, which corresponded to maximum and minimum synchronicity judgements respectively.

At the end of each trial, the participants responded by stating whether the series of tones were either synchronous or asynchronous with their heartbeats. In both conditions, the tones were presented at the same rate (i.e. either on the heartbeat or time-shifted), hence participants could not use the tempo of tones or other knowledge about their heart rate to guide responses: phase synchrony of tones and heartbeats served as the only informative cue. Responses were recorded on the experiment laptop by the researcher.

At the end of each trial (N = 26 for heartbeat discrimination and N = 6 for heartbeat/time tracking), the participant immediately rated their confidence in their perceived accuracy of response. This confidence judgement was made using paper/pencil marked on a continuous visual analogue scale (VAS) that was 10 cm long. One end was marked "Total guess/No heartbeat awareness" while the other end was labelled "Complete confidence/Full perception of heartbeat/time".

1.1.3 Prosody Task

Participants were first instructed to put on over-the-ear headphones and were presented with on screen instructions explaining that they would hear audio clips of different phrases and that they should "*focus on the tone of voice as much as possible*". After each audio clip, they were presented with different emotion options in the form of facial expressions, words or faces with words. Their task was to decide which of the emotions best matched the tone of voice in the clip that they had just heard. Once it was clear that participants fully understood the task, they then progressed to the main experiment. This comprised 114 trials, where the voice was played while the four different emotion options were presented simultaneously on the screen. Depending on trial type, these were either in the form of face only, text only or face/text combined, all four options remained on screen until the user responded. Emotions included feature the six basic emotions; *happy, sad, disgusted, surprised, angry, afraid*. These were presented in two levels of intensity - regular and mild. In addition, thirteen complex emotions were also included; *bored, kind, jealous, unfriendly, hurt, disappointed, interested, joking, ashamed, proud, excited, frustrated* and *worried.* The audio clips were content neutral to ensure that emotion may only be detected through prosodic cues. Any audio clips deemed to include semantic content were removed and omitted from the study. Three different trial types were utilised; matching voices to faces (face-only), matching voices to emotion descriptors (text-only) and matching voices to faces and emotion descriptors combined (face with text). Each domain was further divided into positive and negative valence. In total 114 trials were completed (38 face-only, 38, text-only and 38 face with text). Each of the 19 verbally expressed emotions were presented twice for each domain but remained novel. The presentations were randomised and no trials were repeated. Out of 114 trials, 72 were of a negative valence (24 out of each trial type).

1.2 Interventions

Approximately one week after baseline assessment, participants were invited to their first session of their allocated intervention, of which they were informed at the end of the baseline assessment. The first session involved a brief introduction to the intervention, and hand-outs with basic information about the intervention (Fig. 1 & 2). All participants completed between 1-3 sessions per week, with the constraint that all sessions need to be completed within a 2-month period.

1.2.1 ADIE Intervention

Information leaflets (Fig. 1) about the intervention were designed together with the ADIE Lived Experience Advisory Panel and included basic CBT-based information about anxiety, the intervention, and additional resources. They were handed out by the researcher before the first session began, and participants were given time to read through the leaflet and ask any questions they may have.
After this, each training session entailed two blocks, between which participants underwent a self-paced, light physical activity that aimed to enhance heartbeat perception.

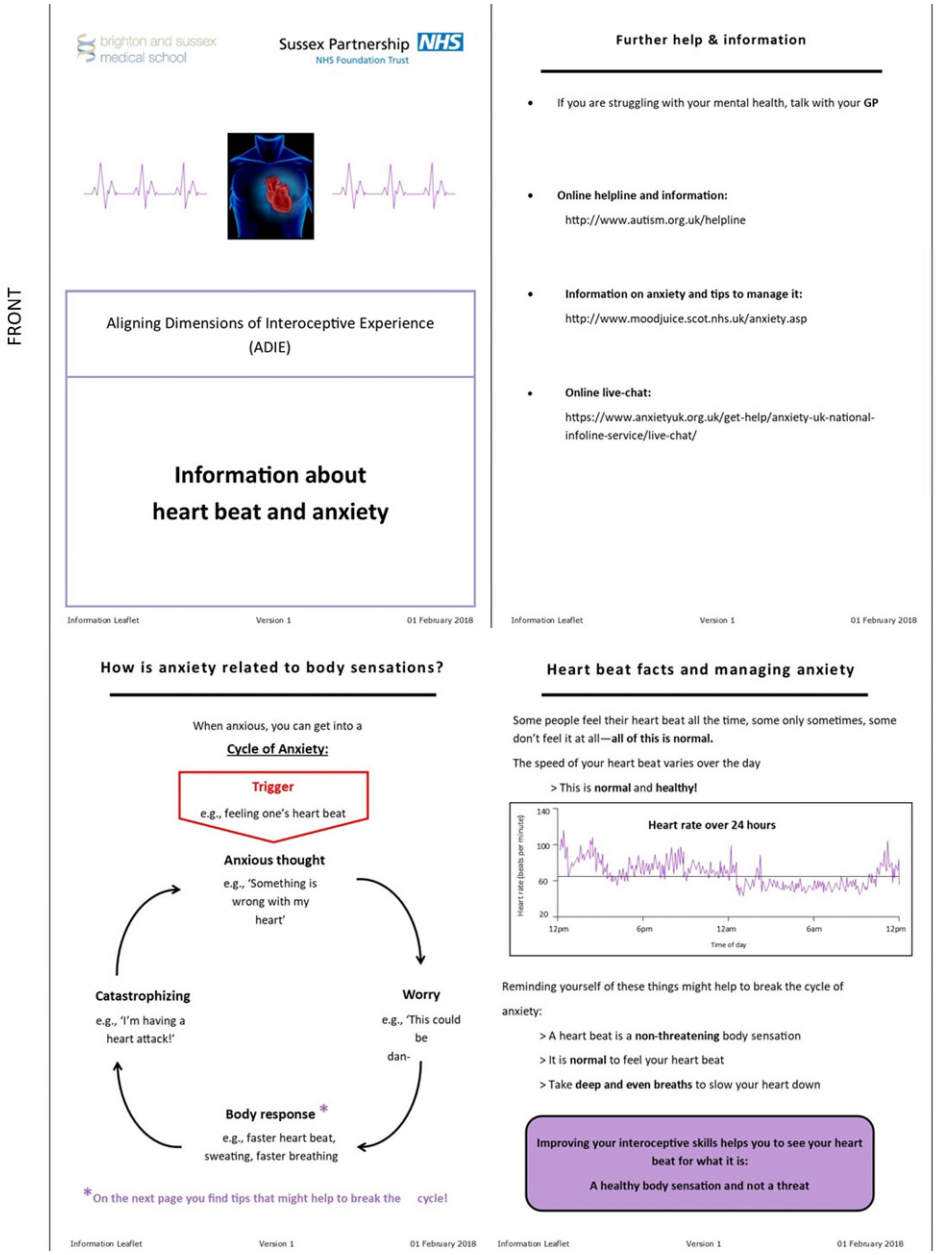


Figure 1: Information Leaflet for ADIE intervention

During the pre- and post-exercise block, each participant first completed the heartbeat tracking task (counting heartbeats in a specified time-frame [10, 15, 20, 25, 30, 35, 40, 45, 50 seconds], to determine the ratio of reported to actual heartbeats as a measure of performance accuracy) and, for each trial, noted their confidence in their answer on a VAS scale and was 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 with a short trial duration (10-20 seconds), which is increased in the next trial if the participant accurately names the number of heartbeats, decreased if the participant does not accurately report the number of heartbeats, or may be repeated if performance is on threshold of accuracy. Participants may be presented with "mixed" intervals, i.e., "jumping" between trial durations, if their performance is stably accurate.

Twenty trials of the heartbeat discrimination task then follow (where tones are played in sync our out of sync with the participants' heart beats. Participants report synchronicity judgements, and correct judgements serve as a measure of performance 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 synch").

Activity manipulation (Fig. 2): In between these task blocks, each participant is required to engage in a physical activity 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.

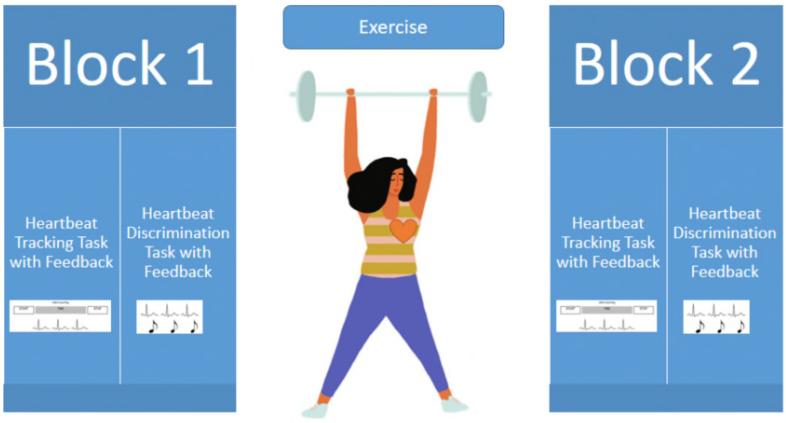


Figure 2: Schematic depiction of an active intervention session

1.2.2 Control / comparison procedure

Information leaflets (Fig. 3) about the intervention were designed together with the ADIE Lived Experience Advisory Panel and included basic information about prosodic emotion understanding, the intervention, and additional resources. They were handed out by the researcher before the first session began, and participants were given time to read through the leaflet and ask any questions they may have. In the active control prosody training therapy, participants received a computer-based training protocol to enhance prosodic emotion recognition. The individual sessions increased in difficulty as outlined below. After each individual trial, participants received computer generated feedback about whether they were right or wrong.

Session one. The initial session was comprised of four randomized training blocks totalling 100 trials. The first two blocks used only the six basic emotions whereas the second two blocks used only complex emotions. A two-choice training paradigm was employed. As with baseline, participants were presented with a series of audios alongside two visual emotion choices. Each block ended 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 utilised a two-choice training approach, this time combining basic and complex emotions into the same trials. Two blocks of 38 trials were employed. The first block consisted of opposing valence presentations, whereas the second block utilised same valence presentations.

Session three. Session three introduced *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 integrated these with the complex emotions. Once again a two-choice training procedure was employed.

Session four. The fourth session incorporated 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 consisted of two blocks of 50 trials and utilised four-choice training. Block one utilised only adult voices and block two utilised only children's voices. The four-choice formula in training sessions once again utilised 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 replicated session five, however, this time, presentations of children and adults were mixed within the same blocks and different stimuli are used. This session essentially integrated all learning from the previous five sessions.

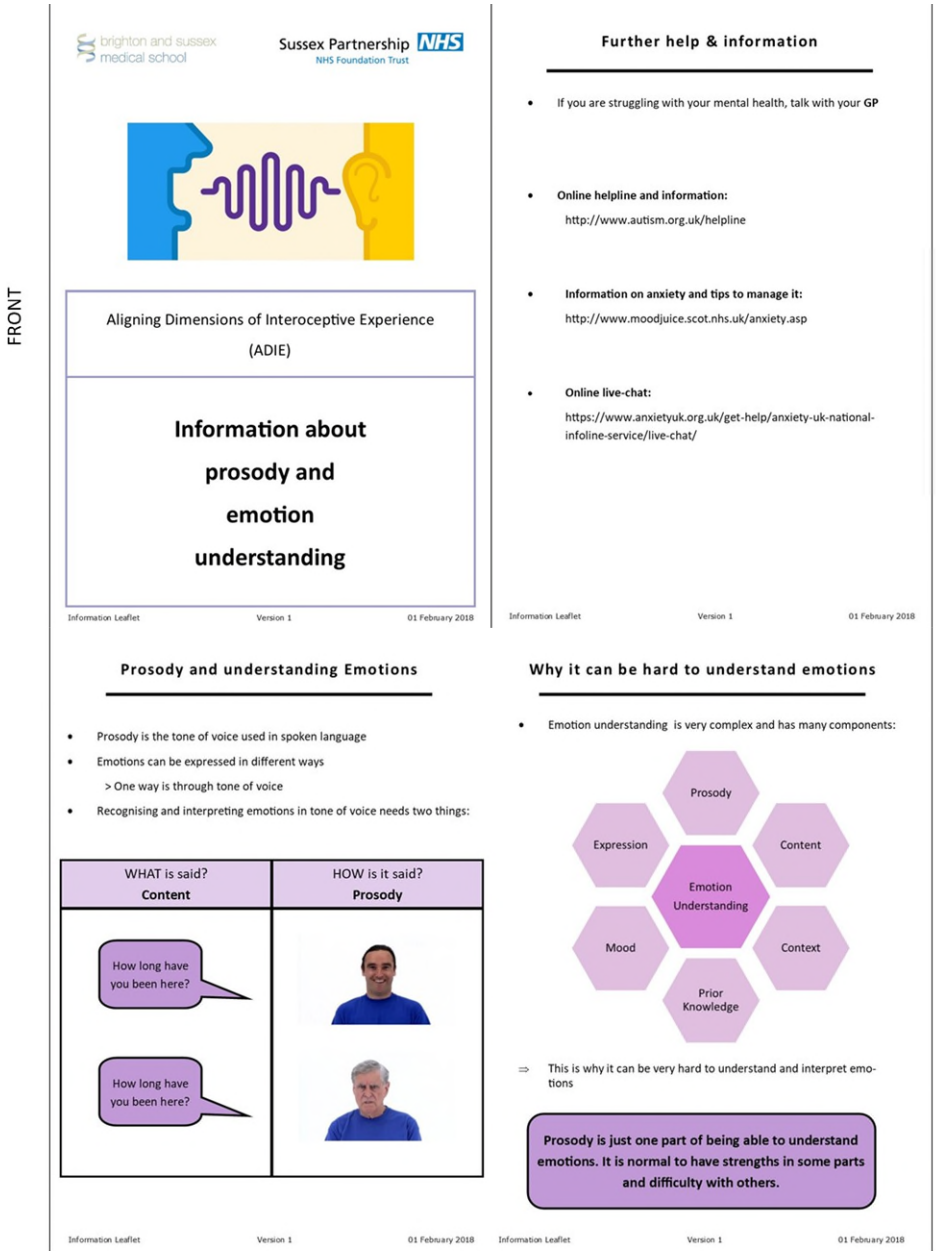


Figure 3 Information Leaflet for the Prosody control group

1.3 1-week post-intervention assessment (T1)

One week after the last intervention session, participants were invited to a follow-up assessment which was conducted by a researcher blind to their allocation. Participants were instructed not to disclose their allocation to the researcher. All measures taken at Baseline Assessment were repeated as outlines in section 1.1.

1.4 3-months post-intervention assessment (T2)

Participants were, if possible, contacted by a researcher via phone or email and asked to complete an Online Survey via the platform Qualtrics. This included the primary outcome measure and formed the primary time point for intervention assessment (STAI-T at T2), STAI-S, BPQ, and GAD.

2 Complete Case Analysis

Table 1: Comparison of outcome measures between ADIE and Prosody control intervention at 3-months post-intervention (T2)/1-week post-intervention (T1) derived from Complete Case Analysis without multiple imputation

	B **(SE; 95% CI)**	***d*** **(95% CI)**	**p value**
Primary Outcome			
STAI trait anxiety T2	3·261 (1·12; 1·06, 5·46)	0·30 (0·10, 0·51)	·004*
Secondary Outcomes			
STAI state anxiety T2	1·719 (1·99; -2·17, 5·61)	0·14 (-0·18, 0·47)	0·387
GAD7 T2	0·309 (0·88; -1·41, 2·03)	0·05 (-0·25, 0·37)	0·724
BPQ 3 T2	9·742 (4·768; 0·40, 19·09)	0·29 (0·01, 0·58)	0·041*
Tracking accuracy T2	0·215 (0·05; 0·12, 0·31)	0·51 (0·29, 0·73)	<0·001*
Discrimination accuracy T1	0·720 (0·21; 0·29, 1·147)	1·00 (0·41, 1·59)	0·001*
ROC T1	0·028 (0·03; -0·02, 0·09)	0·25 (-0·33, 0·82)	0·393
ITPE Tracking T1	-0·992 (0·28; -1·55, -0·44)	-0·67 (-1·04, -0·29)	0·001*
ITPE Discrimination T1	-0·952 (0·29; -1·52, -0·38)	-0·73 (-1·16, -0·29)	0·001*
MAIA Noticing T1	0·349 (0·22; -0·08, 0·78)	0·36 (-0·08, 0·80)	0·111
MAIA Not Distracting T1	-0·280 (0·18; -0·64, 0·08)	-0·27 (-0·62, 0·08)	0·125
MAIA Not Worrying T1	0·224 (0·21; -0·19, 0·63)	0·19 (-0·16, 0·53)	0·279
MAIA Attention Regulation T1	0·300 (0·18; -0·06, 0·66)	0·31 (-0·06, 0·68)	0·100
MAIA Emotional Awareness T1	0·199 (0·19; -0·18, 0·57)	0·16 (-0·15, 0·47)	0·295
MAIA Self-Regulation T1	0·143 (0·18; -0·22, 0·51)	0·14 (-0·21, 0·49)	0·434
MAIA Body Listening T1	0·335 (0·20; -0·06, 0·73)	0·28 (-0·05, 0·61)	0·092
MAIA Trusting T1	-0·154 (0·19; -0·52, 0·22)	-0·12 (-0·41, 0·17)	0·409
TAS Total T1	-1·034 (1·77; -4·55, 2·48)	-0·10 (-0·42, 0·23)	0·560
TAS DDF T1	-0·554 (0·74; -20·4, 0·93)	-0·14 (-0·52, 0·24)	0·495
TAS DIF T1	-0·035 (0·81; -1·65, 1·58)	-0·01 (-0·29, 0·28)	0·966
TAS EOT T1	-0·539 (0·76; -2·06, 0·98)	-0·12 (-0·46, 0·22)	0·482
PHQ9 T1	-0·045 (0·99; -2·01, 1·92)	-0·01 (-0·32, 0·30)	0·964
PANAS positive T1	-0·428 (1·66; -3·75, 2·89)	-0·06 (-0·52, 0·40)	0·798
PANAS negative T1	3·093 (1·39; 0·32, 5·87)	0·47 (0·05, 0·89)	0·030*

p values are not adjusted for multiple testing. *B* = unstandardized effect; *d*=standardized effect; 95% CI for *d* calculated using the pooled baseline standard deviation for Cohen's *d*; STAI=Spielberger Trait-State Anxiety Inventory; GAD-7=Generalized Anxiety Disorder Questionnaire; BPQ=Body Perception Questionnaire Awareness Section; ROC=Receiver Operating Curve; ITPE=Interoceptive Trait Prediction Error; MAIA=Multidimensional Assessment of Interoceptive Awareness; TAS=Toronto Alexithymia Scale; DDF=Difficulty Describing Feelings; DIF=Difficulty Identifying Feelings; EOT=Externally Oriented Thinking; PHQ=Patient Health Questionnaire; PANAS=Positive and Negative Affect Scale

3 Analysis with post-randomization clustering by therapist

Table 2: Comparison of outcome measures between ADIE and Prosody control intervention at 3-months post-intervention (T2)/1-week post-intervention (T1) derived from Complete Case Analysis derived by multiple imputation with post-randomization clustering by therapist

	B **(SE; 95% CI)**	***d*** **(95% CI)**	**p value**
Primary Outcome			
STAI trait anxiety T2	3·178 (1·15; 0·91, 5·44)	0·30 (0·09, 0·51)	0·006*
Secondary Outcomes			
STAI state anxiety T2	2·075 (1·93; -1·73, 5·88)	0·17 (-0·14, 0·49)	0·284
GAD7 T2	0·389 (0·83; -1·24, 2·02)	0·07 (-0·22, 0·36)	0·638
BPQ 3 T2	13·275 (5·93; 1·59, 24·96)	0·40 (0·05, 0·76)	0·026
Tracking accuracy T2	0·219 (0·05; 0·12, 0·31)	0·49 (0·28, 0·7)	<0·001*
Discrimination accuracy T1	0·756 (0·22; 0·32, 1·19)	1·14 (0·49, 1·79)	0·001*
ROC T1	0·029 (0·04; -0·04, 0·1)	0·25 (-0·37, 0·87)	0·418
ITPE Tracking T1	-1·078 (0·27; -1·61, -0·54)	-0·71 (-1·06, -0·36)	<0·001*
ITPE Discrimination T1	-1·012 (0·3; -1·61, -0·41)	-0·78 (-1·25, -0·32)	0·001*
MAIA Noticing T1	0·331 (0·21; -0·09, 0·75)	0·34 (-0·09, 0·77)	0·120
MAIA Not Distracting T1	-0·240 (0·18; -0·6, 0·12)	-0·22 (-0·55, 0·11)	0·191
MAIA Not Worrying T1	0·289 (0·21; -0·12, 0·7)	0·23 (-0·1, 0·56)	0·165
MAIA Attention Regulation T1	0·310 (0·17; -0·04, 0·66)	0·33 (-0·04, 0·71)	0·081
MAIA Emotional Awareness T1	0·163 (0·19; -0·21, 0·54)	0·13 (-0·17, 0·42)	0·391
MAIA Self-Regulation T1	0·137 (0·17; -0·21, 0·48)	0·13 (-0·2, 0·46)	0·436
MAIA Body Listening T1	0·286 (0·2; -0·12, 0·69)	0·25 (-0·11, 0·6)	0·165
MAIA Trusting T1	-0·093 (0·19; -0·47, 0·28)	-0·07 (-0·35, 0·21)	0·619
TAS Total T1	-0·961 (1·84; -4·64, 2·72)	-0·09 (-0·42, 0·24)	0·603
TAS DDF T1	-0·345 (0·77; -1·89, 1·2)	-0·08 (-0·46, 0·29)	0·657
TAS DIF T1	-0·035 (0·85; -1·73, 1·66)	-0·01 (-0·31, 0·29)	0·967
TAS EOT T1	-0·548 (0·81; -2·17, 1·07)	-0·12 (-0·47, 0·23)	0·500
PHQ9 T1	-0·400 (1·07; -2·54, 1·74)	-0·07 (-0·43, 0·29)	0·709
PANAS positive T1	-0·131 (1·52; -3·17, 2·91)	-0·02 (-0·41, 0·38)	0·932
PANAS negative T1	2·792 (1·36; 0·06, 5·52)	0·41 (0·01, 0·81)	0·045*

B = unstandardized effect; *d*=standardized effect; 95% CI for *d* calculated using the pooled baseline standard deviation for Cohen's *d*; STAI=Spielberger Trait-State Anxiety Inventory; GAD-7=Generalized Anxiety Disorder Questionnaire; BPQ=Body Perception Questionnaire Awareness Section; ROC=Receiver Operating Curve; ITPE=Interoceptive Trait Prediction Error; MAIA=Multidimensional Assessment of Interoceptive Awareness; TAS=Toronto Alexithymia Scale; DDF=Difficulty Describing Feelings; DIF=Difficulty Identifying Feelings; EOT=Externally Oriented Thinking; PHQ=Patient Health Questionnaire; PANAS=Positive and Negative Affect Scale

4 Details of multiple imputation approach used for analysis of primary and secondary outcome measures

The standard intention-to-treat principle requires that all participants who were randomized in a clinical trial are included in the analysis.[8] Multiple imputation (MI) is an approach commonly used in longitudinal studies and trials to deal with missing data due to loss to follow-up.[9] MI creates a specified number of complete data sets, each of which is then analysed, pooling the results using "Rubin's rules" [10]. MI requires several steps. First, it needs to be ascertained whether data is missing completely at random (MCAR) or at random (MAR). If the MCAR/MAR assumption is not met, MI might not be appropriate.[11] Secondly, patterns of missing data and predictor variables are established to build a stable imputation model. All variables that are used in the analysis model need to be included in the imputation model. Auxiliary variables, i.e., variables that are not included in the analysis, but are highly correlated with the outcome variables, can be included in the imputation model to increase its efficiency.[12]

We used Little's χ^2 test[13] to establish whether data was MCAR, which was confirmed by a non-significant result (p=0·834). We therefore used Multiple Imputation by Chained Equations (MICE)[14] to

derive between-group differences for primary and secondary outcomes. After detecting that 27% of data was missing, we set the imputation to 27 iterations.

To inform which variables to choose for the MI model, we computed a binary dummy variable of whether participants provided the primary outcome or not (0=no, 1=yes). This binary variable and the continuous primary outcome variable (STAI trait anxiety at 3-months post-intervention) were used as dependent variables. Using univariate logistic regression methods, we established which Baseline variables predicted loss to follow-up and primary outcome scores. All baseline variables (see Table X and X in the main paper) were included in this process, with the exception of continuous measures that had both a total and sub-scores. In these cases, only the total score was included. To further specify the imputation model, only those variables which were univariately associated with the dependent variable at the $\alpha<0{\cdot}05$ level were considered, and only those with the lowest p-value were chosen to be included in the model (Table 2).

MI includes an imputation and an analysis step. As specified in the data analysis plan in the Study Protocol, we used linear mixed regression models for primary and secondary outcomes with the MI procedure outlines above.

Table 3 shows all variables included in the imputation step. All incomplete variables were registered as imputed with Stata mi commands and imputed using linear regression (Stata command regress).

Table 3: Variables included in the multiple imputation model for primary and secondary outcomes

	Type of measure	**Reason**	**Imputation method used in chained equations model**
STAI Trait anxiety score at 3-months post-intervention	Continuous	Dependent variable of analysis model	Linear regression model
STAI Trait anxiety score at 1-week post-intervention	Continuous	Previous measure to contribute to prediction/explanatory variable of analysis model	Linear regression model
STAI Trait anxiety score at baseline			Linear regression model
Trial arm (Intervention)	Binary dummy variable: 0 = Prosody arm 1 = Interoception arm	Explanatory variable of interest from analysis model	NA (complete)
Compliance	Binary dummy variable: 0 = ≤4 therapy sessions 1 = ≥4 therapy sessions	Post-randomisation predictor of missingness	NA (complete)
STAI State anxiety score at baseline	Continuous	Post-randomisation predictor of missingness p<.001 correlation with continuous outcome	Linear regression model
GAD7 score at baseline			Linear regression model
PHQ9 score at baseline			Linear regression model
MAIA Trusting score at baseline			Linear regression model

5 Details of secondary outcome 'Recovery'

We followed Fisher & Durham's[15] approach of clinical significance for STAI trait anxiety score changes in determining which criteria must be met for study participants to reach Recovery. This approach is based on Jacobson's[16] methodology for defining clinically significant change through a cut-off point and criterion c, indicating a reliable change index (RCI). Fisher and Durham compared STAI-T scores of GAD (Generalized Anxiety Disorder) and non-GAD patients to determine these values for the STAI-T. In doing so, they calculated criteria for four exclusive treatment outcome categories indicating Recovery, Improvement, No Change, or Deterioration. For patients to reach Recovery, two conditions must be met by post-treatment scores and change scores. First, the cut-off point for the post-treatment score, for the

STAI-T calculated to be ≤45, indicated that an individual is more likely to be drawn from a non-GAD than a GAD-sample. This is the first requirement for clinical significance. Secondly, the RCI, that is, the difference between post- and pre-treatment score, determines whether the amplitude of change on the STAI-T reliably indicates clinically meaningful change. The RCI, in their sample, was calculated to be 8.

Following this approach of meeting the two pre-specified criteria of RCI and cut-off point, we calculated these values based on the data we used to develop the ADIE trial[17]. In calculating the MCID, we used a common approach for calculating the minimal clinically important differences (MCID) in pre- and post-treatment scores, and divided the Standard Deviation of the autistic sample in our data by two, resulting in an RCI of 6. Given the generally higher STAI-T baseline scores in autistic populations, and based on our data, we set the cut-off point at 55.

This resulted in the following four exclusive treatment outcomes:

1. Recovery, indicated by a 6-point drop and a score of ≤55 on STAI-T
2. Improvement, indicated by a 6-point drop and a score of >55 on STAI-T
3. No Change, indicated by a drop or increase of less than 6 points (>-6 or <6)
4. Deterioration, indicated by an increase of more than 6 points

Table 4: Treatment outcomes in the ADIE and Prosody control group at T1 and T2

		T1					T2			
	N	**Recovery**	**Improvement**	**No Change**	**Deterioration**	**N**	**Recovery**	**Improvement**	**No Change**	**Deterioration**
ADIE	46	11 (24%)	11 (20%)	26 (56%)	0 (0%)	36	11 (31%)	2 (6%)	22 (61%)	1 (3%)
Prosody	39	4 (10%)	6 (15%)	29 (75%)	0 (0%)	25	4 (16%)	3 (12%)	14 (56%)	4 (16%)
Total	85	15 (18%)	15 (18%)	55 (64%)	0 (0%)	61	15 (25%)	5 (8%)	36 (59%)	5 (8%)

All data are n/N (%)

Figure 4: Treatment Outcomes at T1 (1-week post-intervention) in %

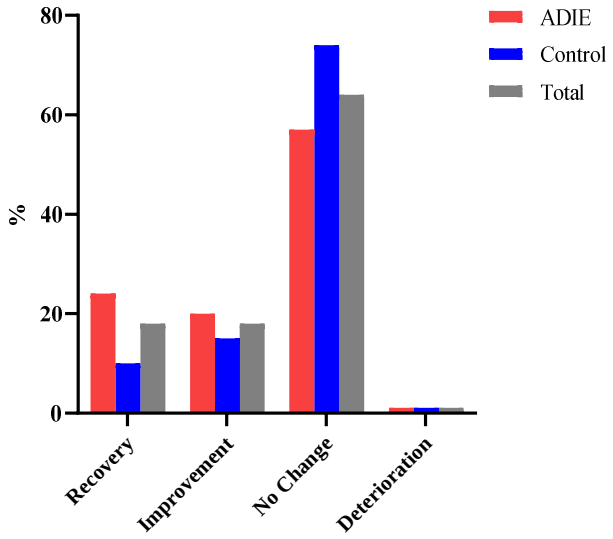
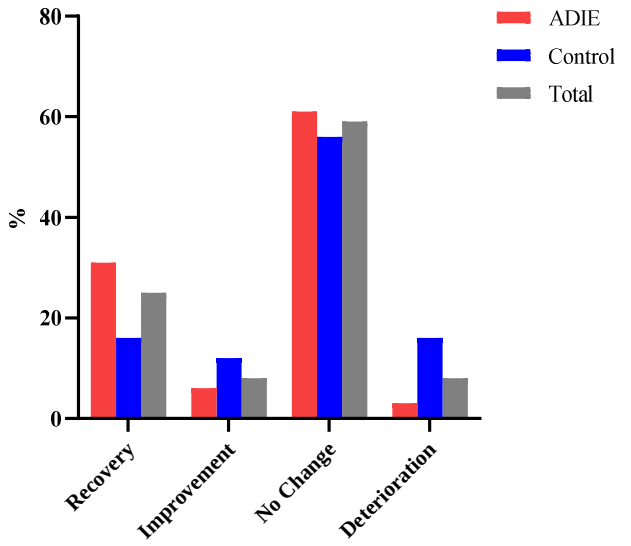


Figure 5: Treatment Outcomes at T2 (3-months post-intervention) in %



6 Data plots for primary and secondary outcome measures

Data plots show predictive margins from mixed effect models after multiple imputation over time and per trial arm. Means from Baseline Covariates are included to illustrate effects over time. For raw data means at all time points, see main manuscript, Table 2.

Figure 6: Primary Outcome STAI Trait Anxiety

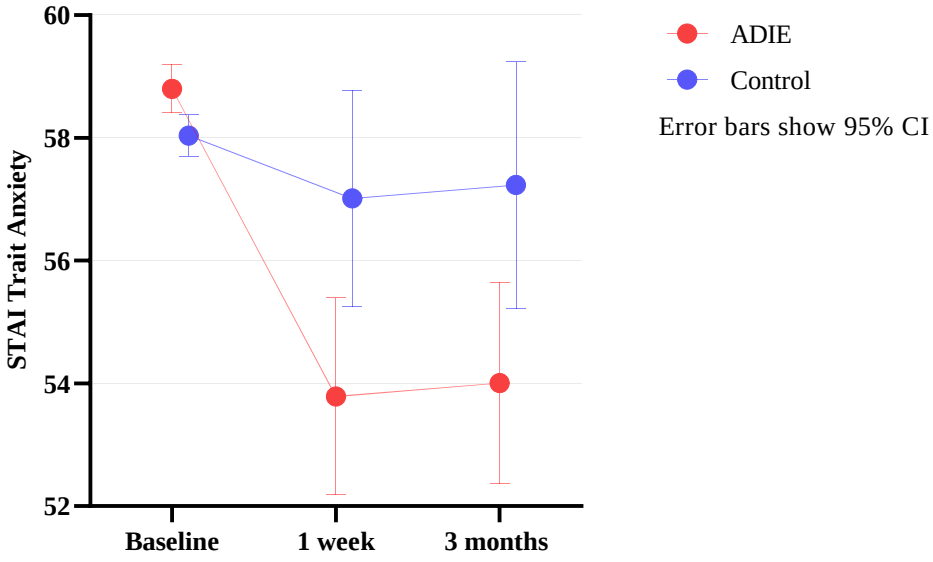


Figure 7: STAI State Anxiety

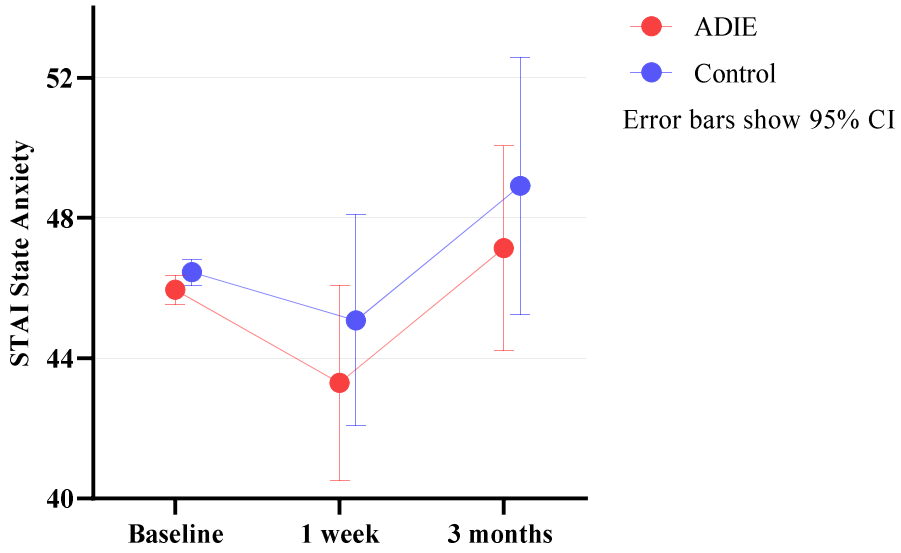


Figure 8: Generalized Anxiety Disorder (GAD-7)

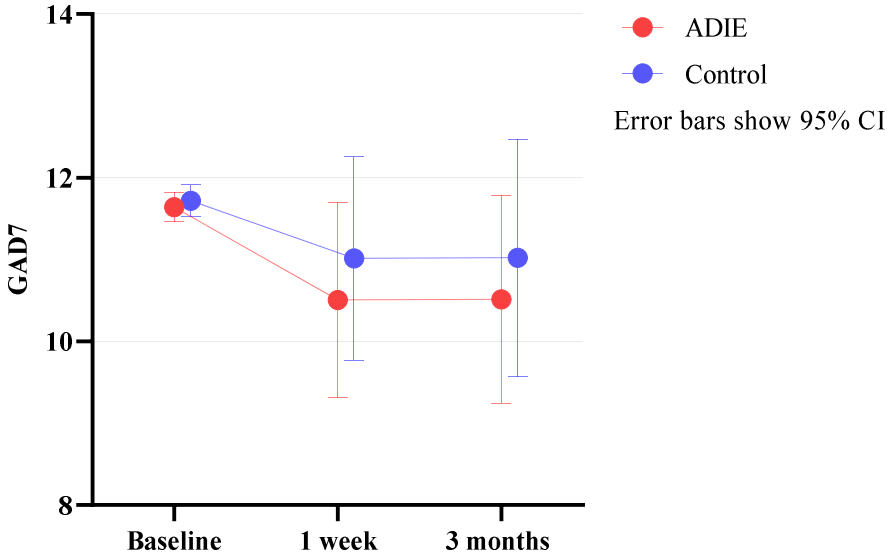


Figure 9: Interoceptive Sensibility (BPQ)

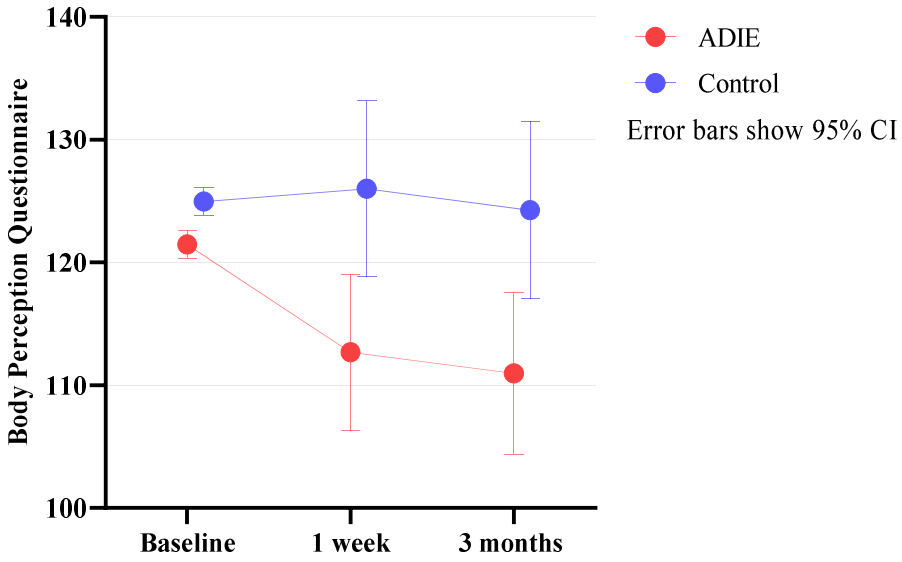


Figure 10: Performance Accuracy (Tracking Task)

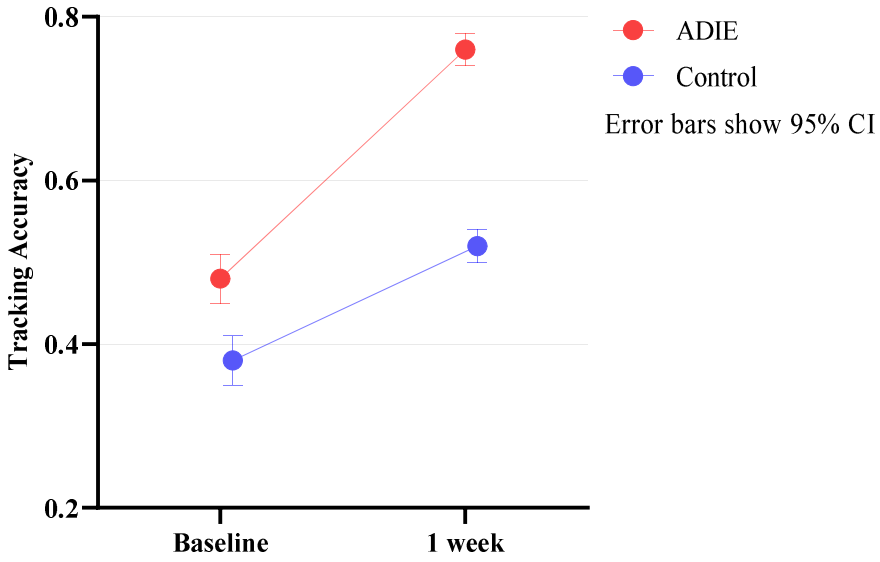


Figure 11: Performance Accuracy (Discrimination Task)

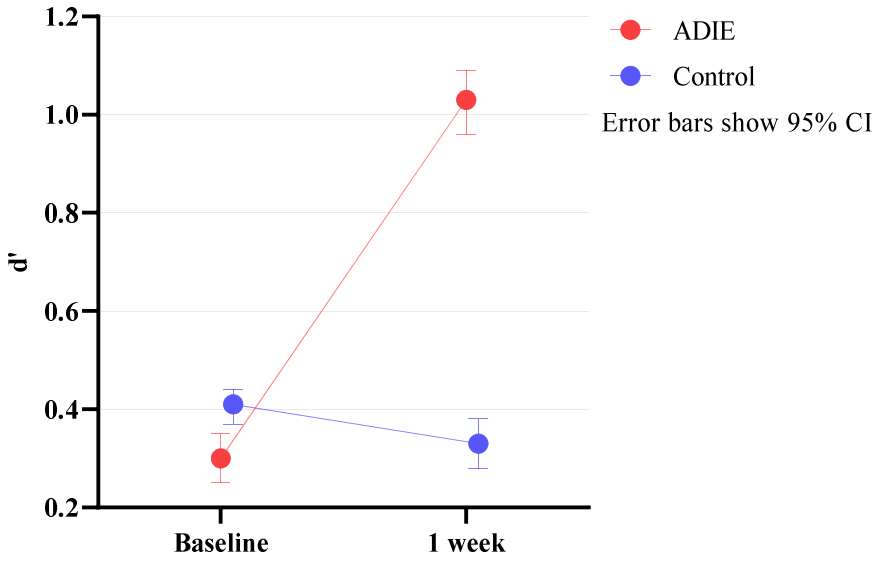


Figure 12: Interoceptive Awareness (ROC)

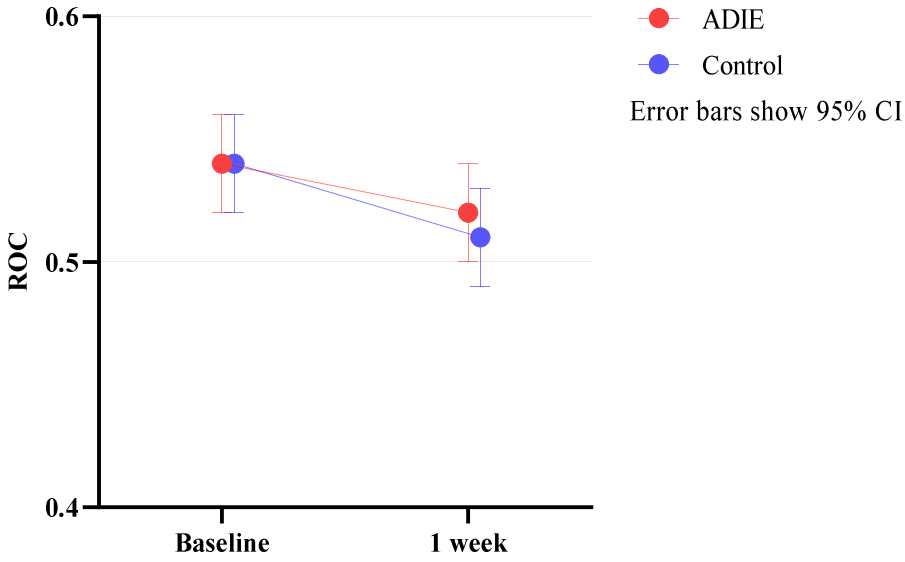


Figure 13: Interoceptive Trait Prediction Error (Tracking Task)

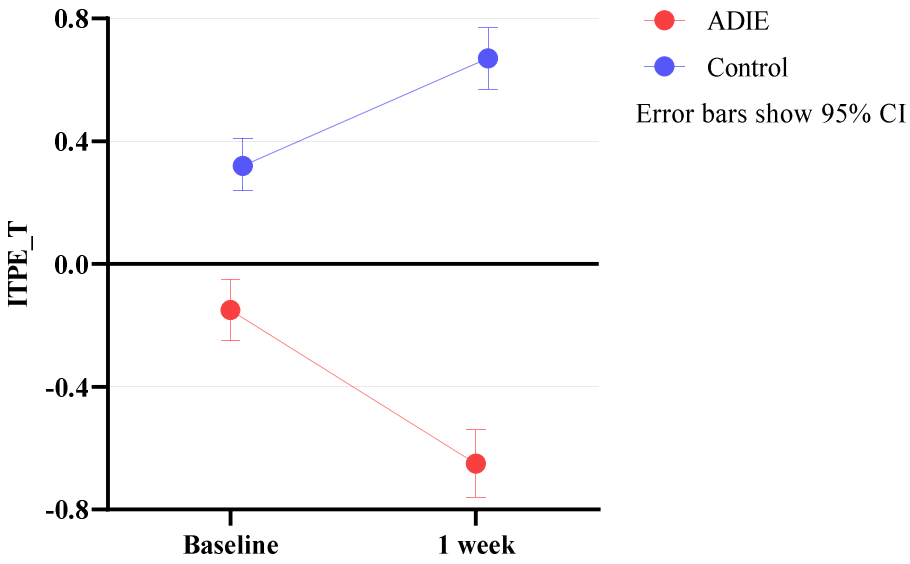


Figure 14: Interoceptive Trait Prediction Error (Discrimination Task)

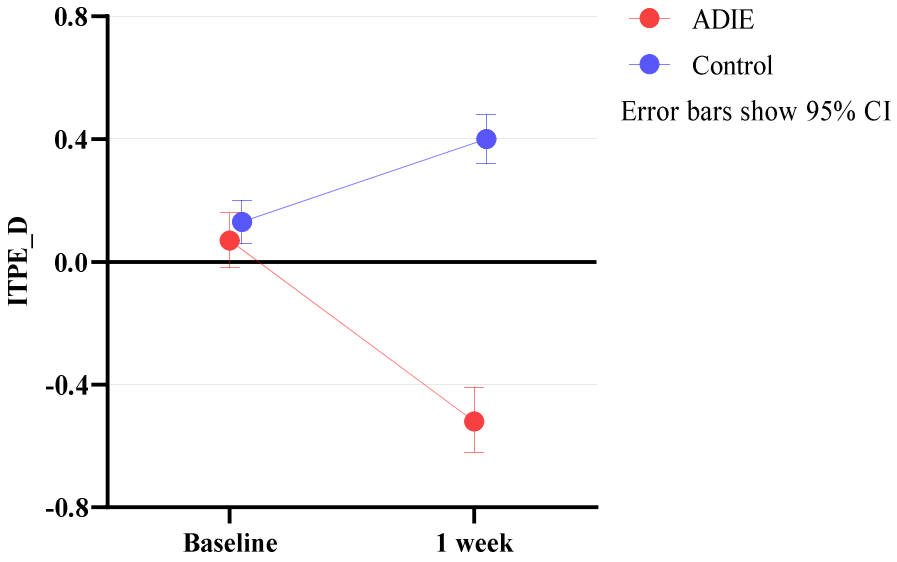


Figure 15: Depression (PHQ-9)

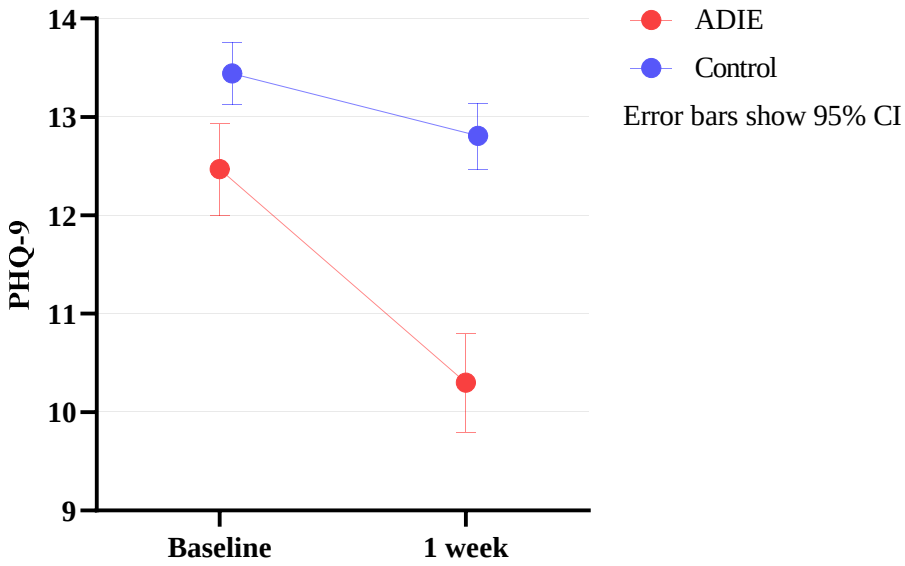


Figure 16: Positive Affect (PANAS positive)

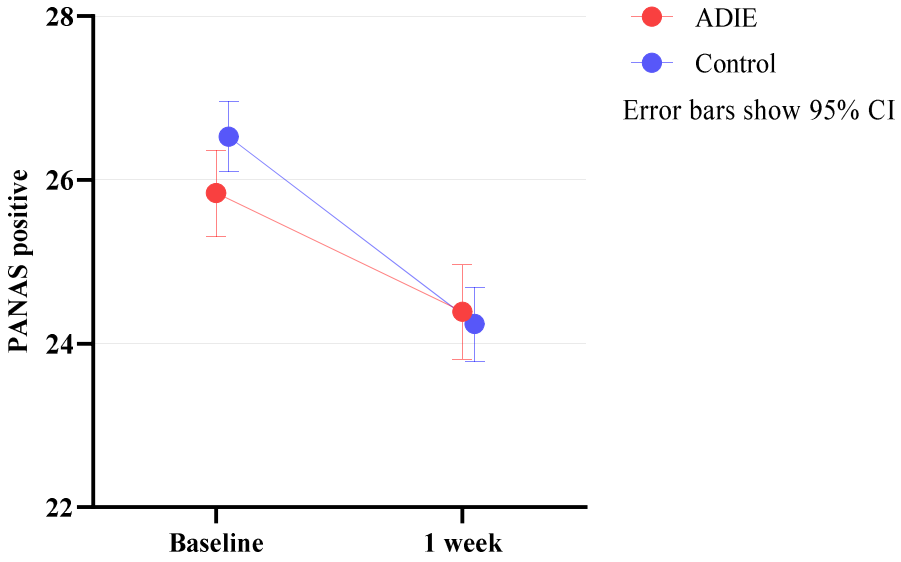


Figure 17: Negative Affect (PANAS negative)

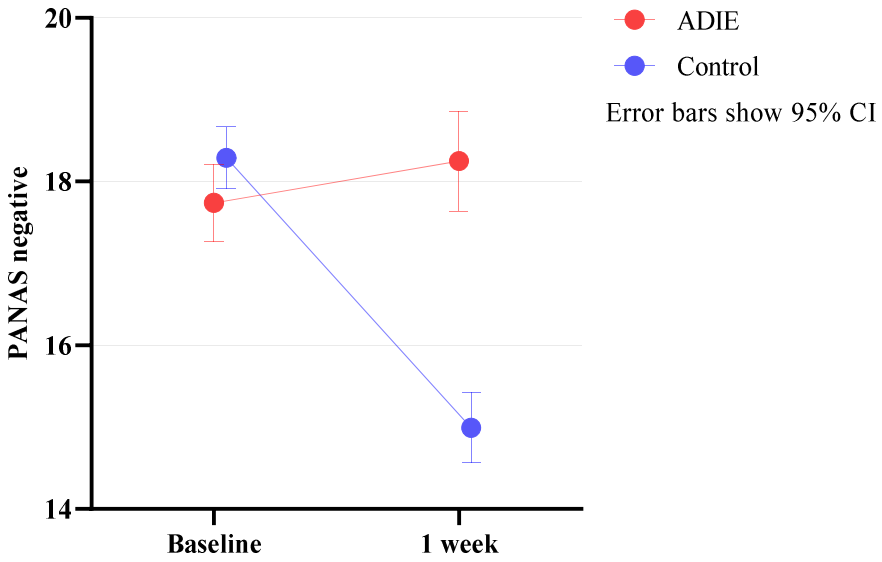


Figure 18: MAIA Noticing

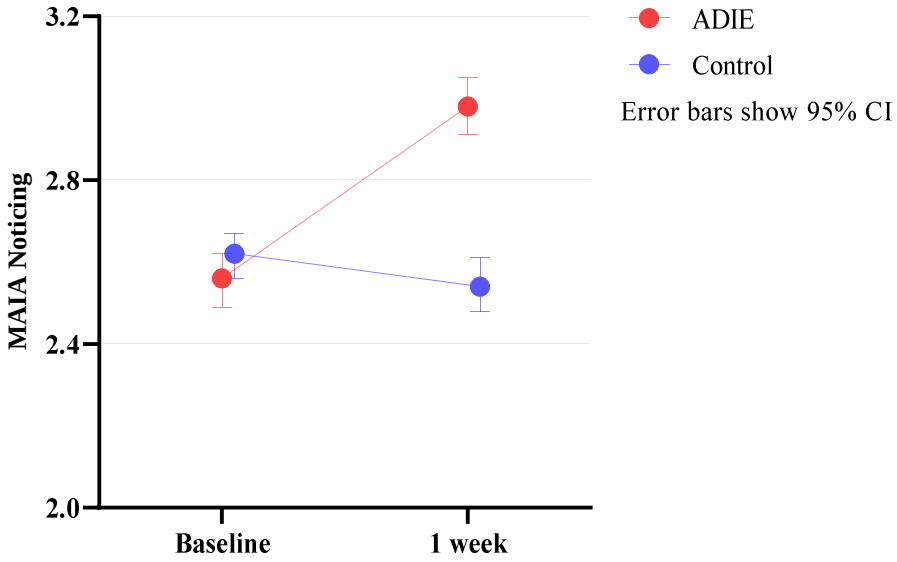


Figure 19: MAIA Not Distracting

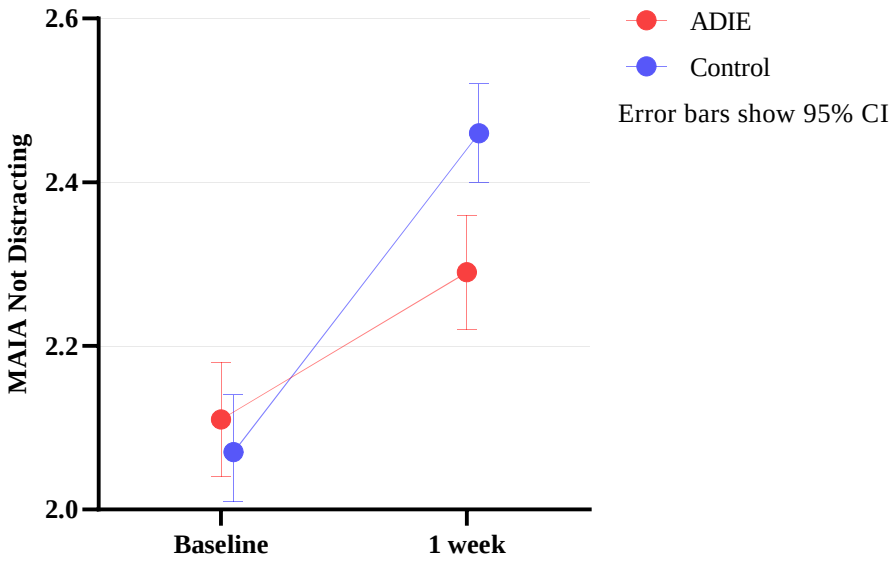


Figure 20: MAIA Not Worrying

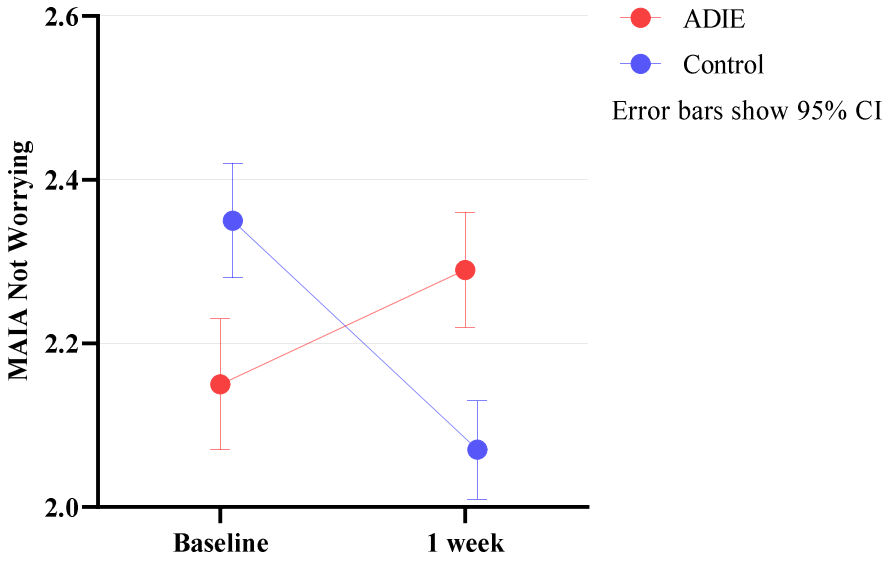


Figure 21: MAIA Attention Regulation

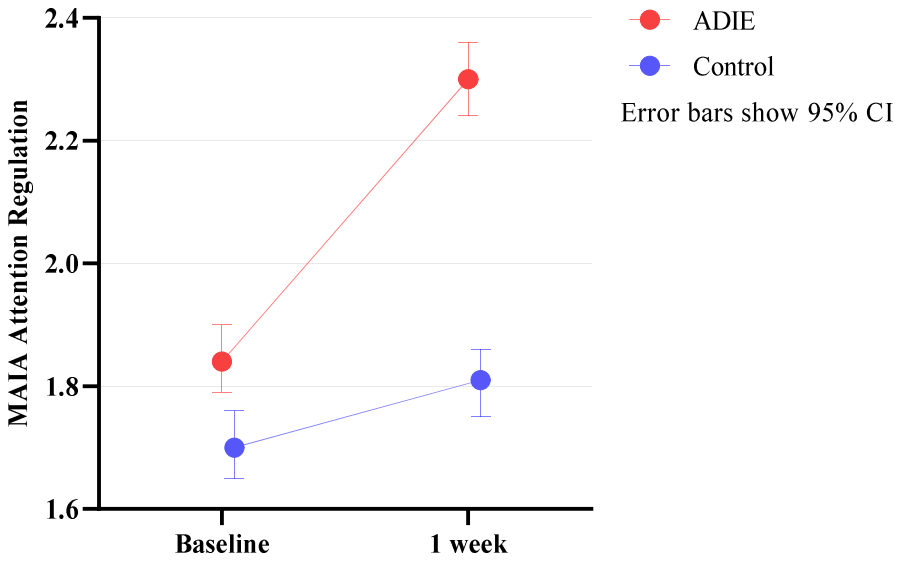


Figure 22: MAIA Emotional Awareness

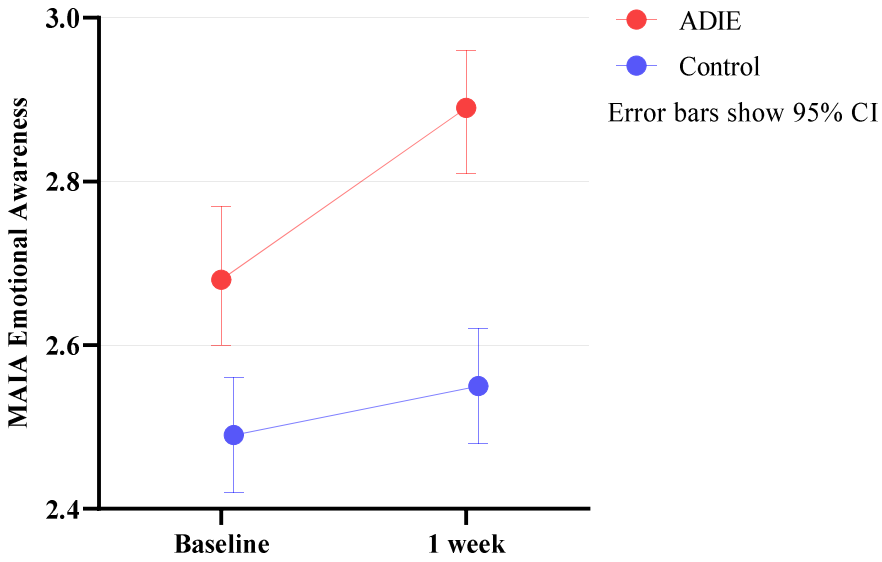


Figure 23: MAIA Self Regulation

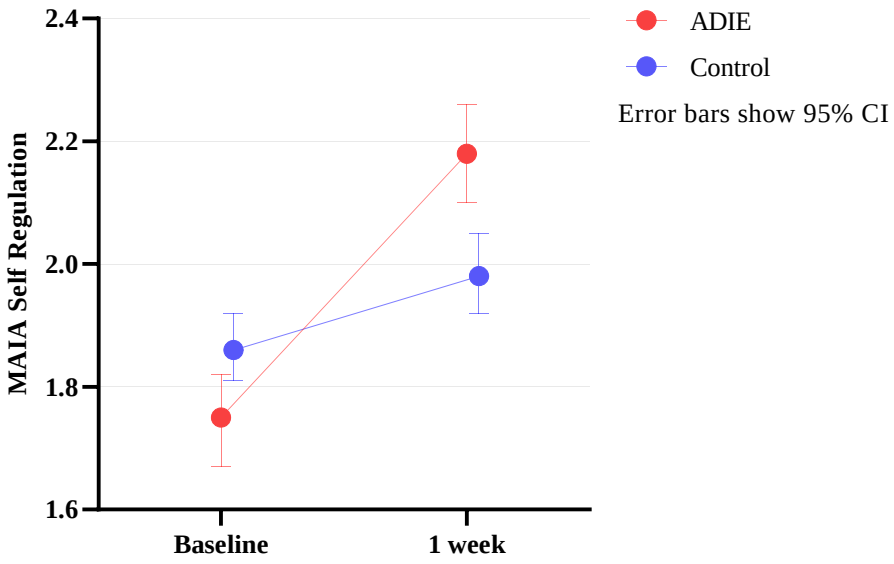


Figure 24: MAIA Body Listening

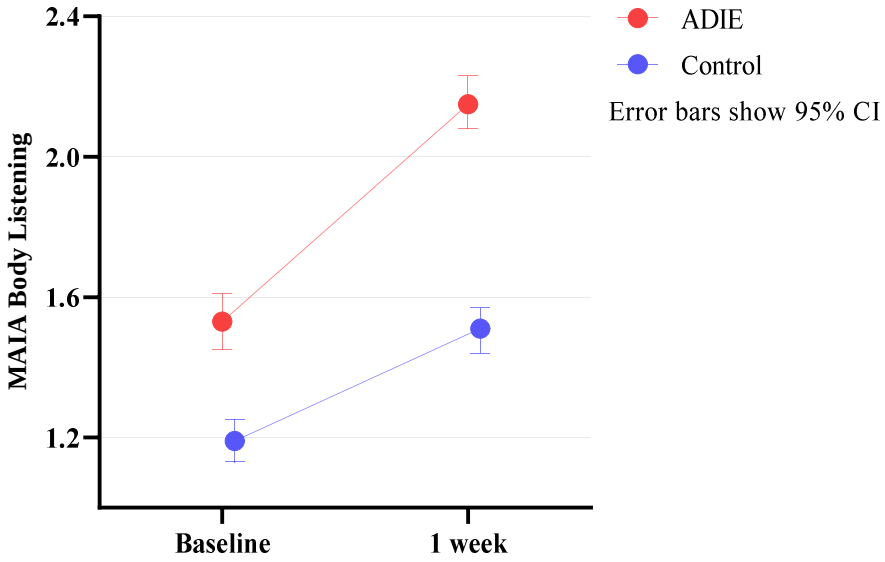


Figure 25: MAIA Trusting

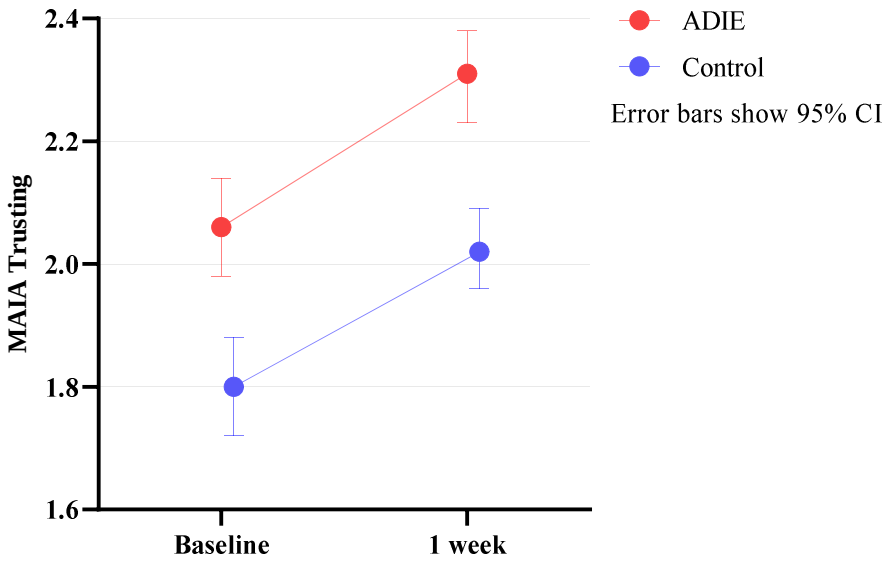


Figure 26: Alexithymia (TAS-20 Total Score)

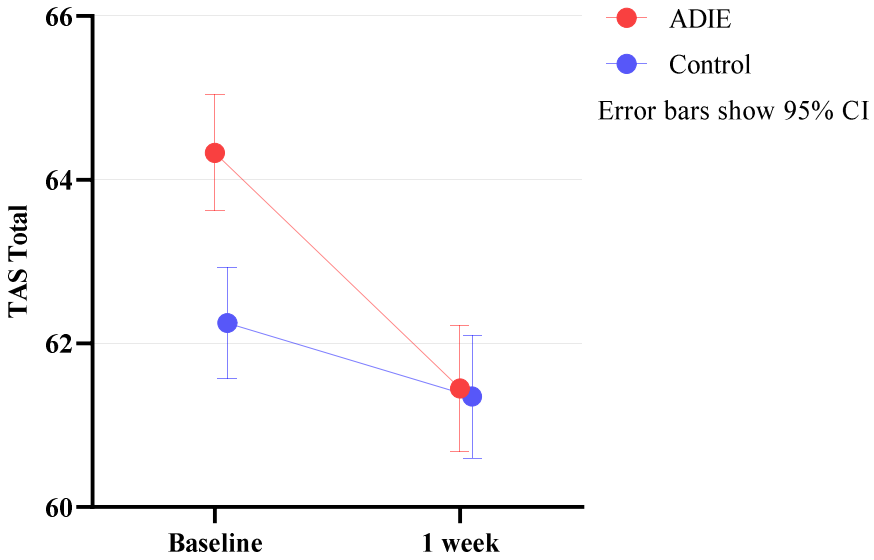


Figure 27: Difficulty Describing Feelings (TAS-20 DDF Sub score)

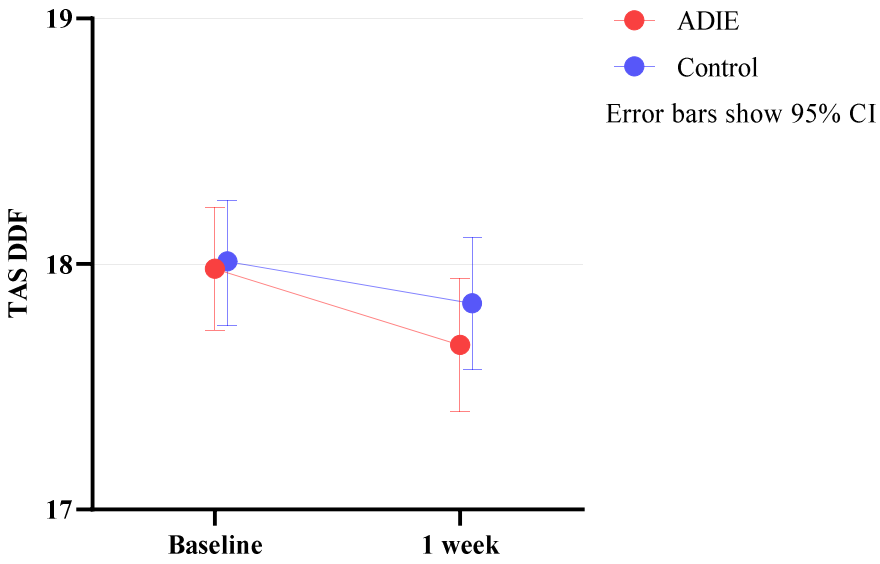


Figure 28: Difficulty Identifying Feelings (TAS-20 DIF Sub score)

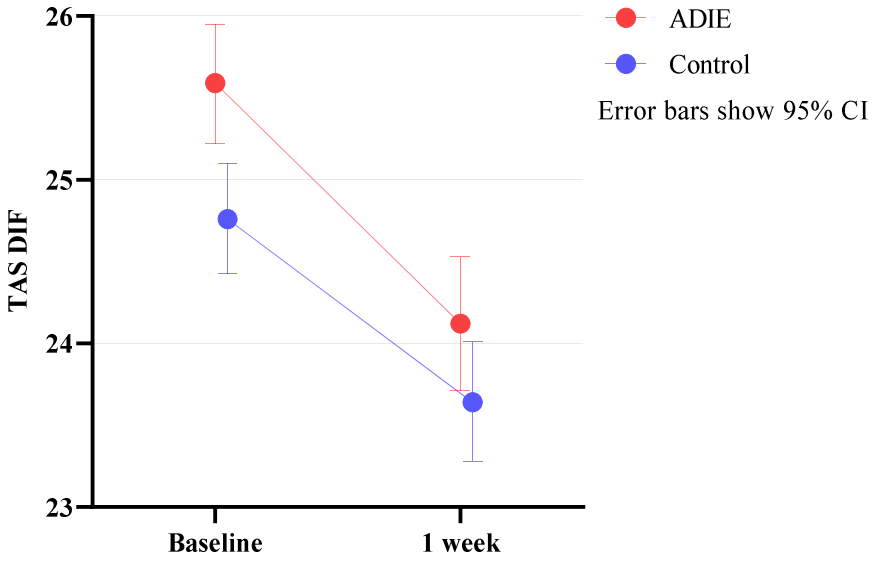
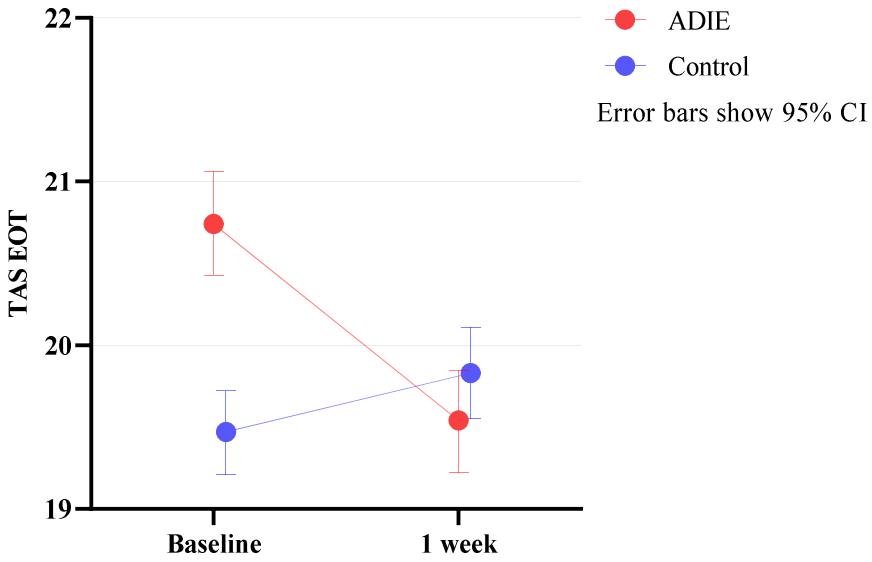


Figure 29: Externally-Oriented Thinking (TAS-20 EOT Sub score)



7 Baseline Characteristics

Table 5: Baseline Characteristics before and after initial attrition

	Prosody (n=60)	**ADIE (n=61)**	**Overall (n=121)**	**Prosody (n=48)**	**ADIE (n=57)**	**Overall (n=105)**
Age, Median (IQR, range), y	29 (23-43; 18-64)	31 (25-43; 19-59)	30 (24-43; 18-64)	34 (26-45; 19-59)	30 (23-43; 18-64)	31 (25-43; 18-64)
Sex assigned at birth						
Female	32 (62%)	29 (48%)	66 (55%)	30 (62·5%)	27 (47·4%)	57 (54·3%)
Male	23 (38%)	32 (52%)	55 (45%)	18 (37·5)	30 (52·6%)	48 (45·7%)
Gender Identification						
Female	32 (53%)	33 (54%)	58 (48%)	25 (52·1%)	24 (42·1%)	49 (46·7%)
Male	24 (40%)	26 (43%)	57 (47%)	19 (39·6%)	31 (54·4%)	50 (47·6%)
Other	4 (7%)	2 (3%)	6 (5%)	4 (8·3%)	2 (3·5%)	6 (5·7%)
Nationality						
British	58 (95%)	57 (95%)	115 (95%)	45 (93·8%)	54 (94·7%)	99 (95%)
Australian	-	1 (1·7%)	1 (0·8%)	1 (2·1%)	-	1 (1%)
Bulgarian	1 (1·6%)	-	1 (0·8%)	-	1 (1·8%)	1 (1%)
Dutch	-	1 (1·7%)	1 (0·8%)	1 (2·1%)	-	1 (1%)
Finnish	1 (1·6%)	-	1 (0·8%)	-	1 (1·8%)	1 (1%)
French	-	1 (1·7%)	1 (0·8%)	1 (2·1%)	-	1 (1%)
Hungarian	1 (1·6%)	-	1 (0·8%)	-	1 (1·8%)	1 (1%)
Education						
GCSE or similar	10 (16%)	11 (18%)	21 (17%)	10 (20·8%)	10 (17·5%)	20 (19%)
A-levels or similar	14 (23%)	9 (15%)	23 (19%)	4 (8·3%)	12 (21·1%)	16 (15·2%)
Attended college, no degree	5 (8%)	13 (22%)	18 (15%)	9 (18·8%)	4 (7%)	13 (12·4%)
Undergraduate degree	15 (25%)	20 (33%)	35 (29%)	18 (37·5%)	14 (24·6%)	32 (30·5%)
Graduate degree	17 (28%)	7 (12%)	24 (20%)	7 (14·6%)	17 (29·8%)	24 (22·9%)
Handedness						
Right	55 (90%)	51 (85%)	106 (87%)	41 (85·4%)	51 (91·2%)	93 (88·6%)
Left	1 (1·6%)	6 (10%)	7 (6%)	5 (10·4%)	2 (1·8%)	6 (5·7%)
Ambidextrous	5 (9%)	3 (5 %)	8 (7%)	2 (4·2%)	4 (7%)	6 (5·7%)
Previous diagnosis of anxiety disorder (participant reported)	36 (59%)	37 (62%)	73 (60%)	29 (60·4%)	34 (59·6%)	63 (60%)
Previous diagnosis of depression (participant reported)	31 (51%)	32 (53%)	63 (52%)	26 (54·2%)	28 (49·1%)	54 (51·4%)
Other previous diagnoses (participant reported)						
ADHD	5 (8%)	2 (3%)	7 (6%)	1 (2·1%)	5 (8·8%)	6 (5·7%)
OCD	8 (13%)	6 (10%)	14 (12%)	5 (10·4%)	7 (12·3%)	12 (11·4%)
PTSD	-	3 (5%)	3 (2%)	2 (4·2%)	1 (2·1%)	2 (1·9%)
C-PTSD	-	1 (2%)	1 (1%)	1 (2·1%)	-	1 (1%)
Dyspraxia	1 (2%)	4 (7%)	5 (4%)	3 (6·3%)	1 (1·8%)	4 (3·8%)
Dyslexia	-	2 (3%)	2 (2%)	2 (4·2%)	1 (1·8%)	2 (1·9%)
Eating Disorder	1 (2%)	-	1 (1%)	-	-	1 (1%)
Currently prescribed anti-anxiolytic/anti-depressant drugs (participant reported)	25 (40%)	26 (43%)	51 (42%)	20 (41·7%)	22 (38·6%)	42 (40%)
Meet criteria for anxiety disorder diagnosis at screening interview†	44 (73%)	51 (84%)	95 (79%)	32 (66·7%)	47 (82·5%)	79 (75%)

Autistic Traits						
Autism Quotient						
Mean score (SD, range)	34·2 (7·5, 17-49)	35·6 (7·3, 14-47)	34·9 (7·3, 14-49)	34·43 (8·1, 17-49)	35·39 (7·36, 14-47)	34·95 (7·69, 14-49)
Empathy Quotient						
Mean score (SD, range)	23·5 (11·3, 6-61)	23·3 (10·9, 4-50)	23·4 (11·1, 4-61)	23·85 (11·64, 6-61)	23·82 (10·9, 4-50)	23·84 (11·19, 4-61)
IQ‡						
Predicted WAIS Full-Scale IQ						
Mean (SD)	113·1 (10·0)	115·6 (8·6)	114·5 (9·3)	112·58 (10·34)	116·27 (8·36)	114·71 (9·36)
Median (IQR, range)	115·7 (107-120, 82-124)	118·2 (110-122, 98-129)	118·2 (108-121, 82-129)	115·7 (106-121, 82-123)	119·4 (110-122, 98-129)	118·2 (110-122, 82-129)
Predicted WAIS Verbal IQ						
Mean (SD)	111·3 (9·2)	113·6 (7·9)	112·6 (8·5)	110·83 (9·51)	114·23 (7·68)	112·79 (8·61)
Median (IQR, range)	113·7 (106-118, 82-121)	116·0 (108-119, 98-126)	116·0 (107-119, 82-126)	113·7 (105-118, 98-129)	117·1 (109-120, 82-123)	116·0 (108-119, 83-126)
Predicted WAIS Performance IQ						
Mean (SD)	112·3 (8·9)	114·5 (7·7)	113·5 (8·2)	111·81 (9·18)	115·09 (7·42)	113·7 (8·3)
Median (IQR, range)	114·6 (107-119, 85-122)	116·8 (109-120, 99-126)	116·8 (109-120, 85-127)	114·6 (107-119, 85-121)	117·9 (110-120, 99-127)	116·8 (109-120, 85-127)
STAI Trait Anxiety						
Mean score (SD, range)	58·0 (9·9, 33-80)	58·8 (11·5, 26-79)	58·4 (10·7, 26-80)	57·23 (10·32, 33-80)	58·54 (11·53, 26-79)	57·94 (10·96, 26-80)
STAI State Anxiety						
Mean score (SD, range)	46·4 (11·3, 20-74)	46·1 (12·8, 21-75)	46·3 (12·0, 20-75)	46·23 (11·33, 20-68)	46·13 (13·14, 21-75)	46·17 (12·28, 20-75)
GAD-7						
Mean score (SD, range)	11·8 (5·7, 1-21)	11·6 (5·5, 0-21)	11·7 (5·6, 0-21)	11·31 (5·49, 1-20)	11·51 (5·62, 0-21)	11·42 (5·54, 0-21)
BPQ						
Mean score (SD, range)	125·7 (33·1, 73-215)	121·7 (33·1, 51-221)	123·5 (33·1, 51-221)	123·35 (34·37, 73-215)	122·41 (33·55, 51-221)	122·82 (33·74, 51-221)
MAIA Noticing						
Mean score (SD, range)	2·7 (1·0, 0-4·7)	2·5 (1·0, 0·6-4·4)	2·6 (1·0, 0-4·7)	2·74 (0·99, 0-4·69)	2·58 (0·95, 0·75-4·38)	2·65 (0·97, 0-4·69)
MAIA Not Distracting						
Mean score (SD, range)	2·0 (1·1, 0-4·3)	2·1 (1·0, 0·0-5·0)	2·1 (1·0, 0·0-5·0)	2·06 (1·14, 0-4·33)	2·16 (1·01, 0-5)	2·12 (1·06, 0-5)
MAIA Not Worrying						
Mean score (SD, range)	2·3 (1·2, 0·3-4·7)	2·2 (1·2, 0·0-4·7)	2·2 (1·2, 0·0-4·7)	2·31 (1·24, 0·33-4·67)	2·15 (1·15, 0-4·67)	2·22 (1·19, 0-4·67)
MAIA Attention Regulation						
Mean score (SD, range)	1·8 (1·0, 0·0-4·7)	1·8 (0·9, 0·1-3·9)	1·8 (1·0, 0·0-4·7)	1·79 (1·07, 0·18-4·71)	1·85 (0·94, 0·14-3·86)	1·83 (1, 0·14-4·71)
MAIA Emotional Awareness						
Mean score (SD, range)	2·6 (1·3, 0·0-5·0)	2·5 (1·2, 0·0-4·8)	2·5 (1·2, 0·0-5·0)	2·55 (1·23, 0-5)	2·56 (1·17, 0·2-4·8)	2·56 (1·19, 0-5)
MAIA Self Regulation						
Mean score (SD, range)	1·8 (1·0, 0·0-4·0)	1·8 (1·1, 0·0-4·3)	1·8 (1·0, 0·0-4·3)	1·84 (0·99, 0-4)	1·84 (1·09, 0-4·25)	1·84 (1·04, 0-4·25)
MAIA Body Listening						

Mean score (SD, range)	1·4 (1·3, 0·0-4·6)	1·5 (1·1, 0·0-4·2)	1·5 (1·2, 0·0-4·6)	1·42 (1·32, 0-4·58)	1·53 (1·14, 0-4·17)	1·49 (1·21, 0-4·58)
MAIA Trusting						
Mean score (SD, range)	2·0 (1·4, 0·0-5·0)	2·2 (1·2, 0·0-4·3)	2·1 (1·3, 0·0-5·0)	1·98 (1·46, 0-5)	2·18 (1·18, 0-4·33)	2·1 (1·3, 0-5)
TAS Total						
Mean score (SD, range)	63·5 (11·1, 33-83)	62·5 (10·6, 29-81)	63·0 (10·8, 29-83)	63·17 (10·71, 33-83)	62·18 (10·68, 29-81)	62·63 (10·65, 29-83)
TAS DDF						
Mean score (SD, range)	18·2 (4·1, 7-25)	17·8 (3·9, 8-24)	18·1 (18·0, 7-25)	17·96 (3·99, 7-25)	17·89 (3·81, 8-24)	17·92 (3·88, 7-25)
TAS DIF						
Mean score (SD, range)	25·0 (5·8, 11-35)	24·9 (5·6, 13-35)	24·9 (5·7, 11-35)	24·92 (5·77, 11-35)	24·66 (5·61, 13-35)	24·78 (5·66, 11-35)
TAS EOT						
Mean score (SD, range)	20·4 (4·4, 11-34)	19·8 (4·6, 8-29)	20·0 (4·5, 8-34)	20·29 (4·69, 11-34)	19·63 (4·63, 8-29)	19·93 (4·65, 8-34)
PANAS positive						
Mean score (SD, range)	26·7 (6·9, 16-40)	25·5 (7·6, 10-42)	26·0 (7·3, 10-42)	26·76 (6·83, 16-40)	25·58 (7·88, 10-42)	26·1 (7·42, 10-42)
PANAS negative						
Mean score (SD, range)	18·2 (6·3, 10-41)	17·8 (6·9, 10-35)	18·0 (6·6, 10-41)	18·22 (6·74, 10-41)	17·9 (6·91, 10-35)	18·04 (6·8, 10-41)
PHQ9						
Mean score (SD, range)	12·5 (6·2, 1-26)	12·9 (6·5, 0-27)	12·7 (6·3, 0-27)	11·9 (6·32, 1-26)	12·69 (6·25, 0-27)	12·34 (6·26, 0-27)
Tracking accuracy						
Mean score (SD, range)	0·4 (0·4, -1·0-0·95)	0·5 (0·4, -1·0-0·95)	0·4 (0·4, -1·0-0·95)	0·37 (0·44, -1-0·95)	0·48 (0·42, -1-0·95)	0·43 (0·43, -1-0·95)
Tracking confidence						
Mean score (SD, range)	3·7 (2·2, 0·2-8·5)	3·7 (2·3, 0·0-8·7)	3·7 (2·3, 0·0-8·7)	3·47 (2·26, 0·17-8·48)	3·79 (2·36, 0-8·7)	3·64 (2·31, 0-8·7)
Discrimination accuracy (d')						
Mean score (SD, range)	0·4 (0·7, -1·0-2·1)	0·1 (0·7, -1·5-1·9)	0·2 (0·7, -1·5-2·1)	0·33 (0·67, -0·98-1·92)	0·09 (0·75, -1·5-1·92)	0·2 (0·72, -1·5-1·92)
Discrimination confidence						
Mean score (SD, range)	4·9 (2·3, 0·1-8·7)	4·3 (2·6, 0·0-8·6)	4·6 (2·5, 0·0-8·7)	4·81 (2·27, 0·12-8·52)	4·46 (2·63, 0-8·63)	4·62 (2·47, 0-8·63)
Interoceptive Awareness (ROC)						
Mean score (SD, range)	0·5 (0·1, 0·3-0·8)	0·6 (0·1, 0·3-0·8)	0·5 (0·1, 0·3-0·8)	0·54 (0·12, 0·29-0·81)	0·55 (0·11, 0·32-0·84)	0·55 (0·12, 0·29-0·84)
ITPE Tracking						
Mean score (SD, range)	0·2 (1·5, -2·4-5·7)	-0·1 (1·5, -3·1-3·8)	0·0 (1·5, -3·1-5·7)	0·24 (1·59, -2·35-5·69)	-0·11 (1·52, -3·09-3·81)	0·04 (1·55, -3·09-5·69)
ITPE Discrimination						
Mean score (SD, range)	0·0 (1·2, -1·8-2·8)	0·0 (1·4, -4·0-3·1)	0·0 (1·3, -4·0-3·1)	0 (1·25, -1·81-2·77)	0·1 (1·39, -4·01-3·06)	0·06 (1·33, -4·01-3·06)

ADIE=Aligning Dimensions of Interoceptive Experience; STAI=Spielberger Trait-State Anxiety Inventory; GAD-7=Generalized Anxiety Disorder seven-item; BPQ=Body Perception Questionnaire Awareness Section; MAIA=Multidimensional Assessment of Interoceptive Awareness; TAS=Toronto Alexithymia Scale; DDF=Difficulty Describing Feelings; DIF=Difficulty Identifying Feelings; EOT=Externally Oriented Thinking; PANAS=Positive and Negative Affect Scale; PHQ-9=Patient Health Questionnaire nine-item; ROC=Receiver Operating Curve; ITPE=Interoceptive Trait Prediction Error; *Based on UK educational system· † Based on Mini-International Neuropsychiatric Interview, Section O, Generalized Anxiety Disorder; ‡Based on National Adult Reading Test (NART); §t-statistic; ¶χ^2; ‖Welch's t-statistic

IV. References in Appendix (excluding Trial Protocol References)

1. Porges S. Body perception questionnaire. Laboratory of Developmental Assessment, University of Maryland 1993.
2. Bagby RM, Parker JD, Taylor GJ. The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure. *J Psychosom Res* 1994; 38(1): 23-32.
3. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. *J Autism Dev Disord* 2001; 31(1): 5-17.
4. Spielberger CD. State-Trait anxiety inventory. *The Corsini encyclopedia of psychology* 2010.
5. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS One* 2012; 7(11): e48230.
6. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988; 54(6): 1063-70.
7. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16(9): 606-13.
8. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012; 10(1): 28-55.
9. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011; 342: d40.
10. Rubin BM, Katkin ES, Weiss BW, Efran JS. Factor analysis of a fear survey schedule. *Behav Res Ther* 1968; 6(1): 65-75.
11. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393.
12. Lee KJ, Roberts G, Doyle LW, Anderson PJ, Carlin JB. Multiple imputation for missing data in a longitudinal cohort study: a tutorial based on a detailed case study involving imputation of missing outcome data. *Int J Soc Res Methodol* 2016; 19(5): 575-91.
13. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. *J Am Stat Assoc* 1988; 83(404): 1198-202.
14. Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007; 16(3): 219-42.
15. Fisher PL, Durham RC. Recovery rates in generalized anxiety disorder following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990. *Psychol Med* 1999; 29(6): 1425-34.
16. Jacobson NS, Truax P. Clinical significance : A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1992; 59(1): 12-9.
17. Garfinkel SN, Tiley C, O'Keeffe S, Harrison NA, Seth AK, Critchley HD. Discrepancies between dimensions of interoception in autism: Implications for emotion and anxiety. *Biol Psychol* 2016; 114: 117-26.