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Interoceptive training to target anxiety in autistic adults (ADIE): A single-center, superiority randomized controlled trial

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ABSTRACT

Background: This trial tested if a novel therapy, Aligning Dimensions of Interoceptive Experience (ADIE), reduces anxiety in autistic adults. ADIE targets the association of anxiety with mismatch between subjective and behavioral measures of an individual's *interoceptive sensitivity* to bodily signals, including heartbeats.

Methods: In this superiority randomized controlled trial, autistic adults (18–65 years) from clinical and community settings in Southern England were randomly assigned (1:1) to receive six sessions of ADIE or an active 'exteroceptive' control therapy (emotional prosody identification). Researchers conducting outcome assessments were blind to allocation. ADIE combines two modified heartbeat detection tasks with performance feedback and physical activity manipulation that transiently increases cardiac arousal. Participants were followed-up one-week (T1) and 3-months post-intervention (T2). The primary outcome was Spielberger Trait Anxiety Score (STAI-T) at T2. Outcomes were assessed on an intention-to-treat basis using multiple imputation for dealing with missing values. This trial was registered at International Standard Randomized Controlled Trial Registry, ISRCTN14848787.

Findings: Between July 01, 2017, and December 31, 2019, 121 participants were randomly allocated to ADIE (n = 61) or prosody (n = 60) intervention groups. Data at T1 was provided by 85 (70%) participants (46 [75%] ADIE; 39 [65%] prosody). Data at T2 was provided by 61 (50%) participants (36 [59%] ADIE; 25 [42%] prosody). One adverse event (cardiac anxiety following ADIE) was recorded. A statistically significant group effect of ADIE on trait anxiety continued at T2 (estimated mean difference 3•23 [95% CI 1•13 to 5•29]; d = 0•30 [95% CI 0•09 to 0•51]; p = 0•005) with 31% of ADIE group participants meeting trial criteria for recovery (compared to 16% in the control group).

Interpretation: ADIE can reduce anxiety in autistic adults, putatively improving regulatory control over internal stimuli. With little reliance on language and emotional insight, ADIE may constitute an inclusive intervention.

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1. Introduction

Autism Spectrum Disorder (henceforth 'autism') encapsulates differences in emotional processing, sensory sensitivities, behavioral, and cognitive profiles of neurodevelopmental origin [1]. In this work, we have aligned our language with the Neurodiversity movement, which includes using Identify-first description ('autistic person' instead of 'person with autism'), and aiming to avoid using ableist language [2]. An estimated 1% of the world's population have an autism diagnosis [3], although autistic females may remain largely un-or misdiagnosed [4]. Autistic adults experience mental health problems to a much greater degree than non-autistic adults [5], with 53% of the autistic population reported to meet formal lifetime criteria for an anxiety disorder [6], compared to 10–15% of the general population [7]. Despite growing acknowledgement of mental health needs of autistic adults [8], a series of quantitative and qualitative

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Research in context

Evidence before this study

A literature search before commencement of this study was conducted on PubMed from inception of their database to Jan 31, 2017, without language restrictions, using the search terms "[*autism and therapy*]" OR "[*autism and anxiety and therapy*]" OR "[*CBT and autism*]". For autistic adults over the age of 18, we found, in line with a meta-analysis by Spain and colleagues in 2015, only one RCT focusing on anxiety symptoms. However, there are some up-to-date reviews of CBT and mindfulness-based therapies for autistic adults. One key issue is that the majority of published reports of interventions targeting anxiety in autistic adults are case studies, small case series, or RCTs with small sample size. The largest study we found included fifty participants, but no control group.

Added value of this study

To our knowledge, ADIE is the largest randomized clinical trial targeting anxiety in autistic adults (N = 121) to date. Our study compared a novel, interoception-based intervention with an exteroceptive control condition. The development of ADIE was research-driven and occurred in close collaboration with autistic adults through Public and Patient Involvement groups. Although written information was provided to participants, referring to catastrophizing thoughts around bodily sensations, and ADIE's focus on inner bodily signals has some similarity to mindfulness exercises, this novel biobehavioural therapy does not fall into either category CBT- or mindfulness-based therapies, and represents a unique, tailored, and evidence-based therapeutic approach.

Implications of all the available evidence

The research-driven development of the ADIE approach, and the significant effect of the intervention on trait anxiety indicate that there is value in targeting the mechanisms that regulate the perception of bodily signals. Given that autistic adults have specific therapeutic needs, and often do not benefit from interventions that heavily rely on language, identification of emotions, or intimate therapist-client relationships, ADIE provides a novel, brief, accessible intervention that improves some anxiety symptomatology.

studies show that many available treatments are not adequate, as they are not tailored to [9], or lack knowledge of specific autistic needs [10]. Few randomized controlled trials (RCTs) have investigated the effectiveness of interventions for anxiety in autistic adults, although some trials report reduction in anxiety after Cognitive Behavioral Therapy (CBT) and mindfulness-based therapies [11,12]. Nevertheless, there remains a need for effective, autism-friendly, non-drug approaches to anxiety for autistic individuals [13].

This trial tests a novel, research-based intervention that was developed specifically for autistic individuals with anxiety symptoms. The 'Aligning Dimensions of Interoceptive Experience' (ADIE) intervention builds on rigorous research into the role of bodily signal perception for anxiety symptomatology. The experience, expression, and regulation of emotional states, including anxiety, is intertwined with the representation and control of physiological states of bodily arousal, including stronger, faster heartbeats. Interoception refers to the sensory (neural and humoral) signalling, perceptual processing, and psychological representation of sensations from internal bodily organs [14,15]. Perceptually, interoception is usefully conceptualized within a dimensional framework [16], mapping onto measures of performance *accuracy*, subjective interoceptive *sensibility*, and *metacognitive* interoceptive awareness [16], also termed interoceptive *insight* [14]. *Accuracy* denotes performance on behavioral tasks measuring perceptual acuity to physiological events and changes within the body. Heartbeat detection tasks, such as heartbeat tracking (HBT) [17] and heartbeat discrimination (HBD) [18] tasks, seek to achieve this [17,18]. Limitations of these tasks have been well-characterized [19,20], including the acknowledgment that performance can be influenced by top-down factors, such as knowledge or expectations of one's pulse rate. Taking into account these valid criticisms, we operationalize individual results on heartbeat detection tasks as measures of *performance accuracy*, instead of purely *interoceptive accuracy*. Interoceptive *sensibility* encapsulates an individual's own subjective description of experience (of the strength and frequency) of internal sensations, recorded via self-report measures [16,21]. This likely combines aspects of both self-assessed accuracy and self-assessed attention [22], and picks up inaccuracies (or noise) in perceiving bodily signals. Self-report interoceptive measures can also index confidence in interoceptive estimations, for example via trial-by-trial measures of confidence during interoceptive task performance [16]. *Metacognitive* interoceptive awareness quantifies the degree to which an individual has insight into how accurately they can judge their own interoceptive signals, e.g., from accuracy-confidence correspondence during interoceptive task performance [16].

Individual differences in interoceptive measures are reported to correlate with emotional feeling states [24], and psychiatric disorders [14]. Such interoceptive mechanisms and their neural representation (especially within insular cortex) are central to an influential model of anxiety disorders. According to this model, individuals with high trait anxiety are particularly sensitive to interoceptive changes when aversive events are anticipated. The amplification of interoceptive signals and association with negative outcomes condition an anxious individual to focus on, and become overly sensitive to, potential changes in bodily sensations. Belief-based negative thoughts additionally modify the emotional valence of amplified bodily signals, evoking symptoms of anxiety [25]. Accurate performance on tasks that index the ability to detect internal signals was found to be lower in autistic versus non-autistic individuals [26–29]. Such imprecise sensing of interoceptive signals may cascade into dysregulation of bodily states, compromising the association of internal bodily states with emotional states, and diminishing the identification (and control) of emotions [30].

In addressing these models, we showed that autistic adults display an altered interoceptive profile when compared with non-autistics, which is linked with anxious affect [28]. In autistic adults and children [28,29], anxiety symptomatology is strongly predicted by the conjunction of low behavioral performance accuracy on heartbeat detection tasks (notably underreporting of felt heartbeats on a heartbeat tracking task) and elevated subjective interoceptive sensibility, i.e. over-reporting, on a questionnaire, the experience ('awareness') of bodily sensations [28]. The latter can be viewed as a subjective prediction (or 'belief') about interoceptive sensitivity over time, which is typically heightened in autistic individuals [29,31,32]. The mismatch between behaviorally observed deficits in interoceptive task accuracy and amplification of a subjective self-report trait measure of interoceptive expectations was termed 'interoceptive trait prediction error' (ITPE) [28]. These findings informed the design of the new therapy tested in this trial: ADIE (Aligning Dimensions of Interoceptive Experience). We hypothesized that by providing targeted performance feedback on heartbeat detection tasks, performance accuracy will increase, thereby also impacting on the subjective experience of, and ability to report, bodily sensations. By enhancing behavioral accuracy, trait anxiety will decrease via an enhanced ability to regulate interoceptive signals. Thus, the aim of this RCT was to assess the

effectiveness of ADIE in reducing trait anxiety symptoms in autistic adults, compared with an active *exteroceptive* control therapy, which was also chosen to enhance the emotional skills of autistic adults by improving recognition of emotional prosody. This training in strengthening the judgement of human prosody has face validity for autistic adults, as difficulties in perception and recognition of non-verbal prosodic cues are associated with anxiety [33,34]. Moreover, these difficulties may contribute to the degree of alexithymia, which has been identified as one fundamental driver of anxiety in autism [30,35]. The choice of an active control was preferred over treatment-as-usual by our dedicated Lived Experience Advisory Panel (LEAP). Moreover, interventions targeting anxiety in autistic adults [12] mostly consist of case studies, case series, or exploratory studies with small sample sizes and passive control conditions, making the current trial the largest to date.

2. Methods

2.1. Study design and participants

In this parallel-group, superiority, randomized controlled trial, we recruited 121 autistic adults from current and former patients of the Sussex Partnership NHS Foundation Trust Neurodevelopmental Service, and through community and third-sector organizations. Eligible participants were adults with a DSM/ADI-R or equivalent confirmed diagnosis of an Autism Spectrum Condition, aged 18–65 years, with normal or corrected-to-normal vision and hearing, and fluent understanding of English. All potential participants underwent online or phone screening, which included the Mini International Neuropsychiatric Interview (MINI, Section O: Generalized Anxiety Disorders) to assess presence of generalized anxiety independent of other explanatory factors, such as their autistic traits [36], and details of the autism diagnosis, including date and location of diagnosis, and name of the practitioner who initially diagnosed the participant. Given the high co-occurrence of autism and anxiety [6], the intervention was intended to be both inclusive and preventative. Thus, a minimum requirement for anxiety level was not specified for participation, a decision that was reached together with the Lived Experience Advisory Panel (LEAP). Initial exclusion criteria were age below 18 years, past organic brain injury, epilepsy, co-occuring diagnoses of mental health conditions other than depression and anxiety, severe cognitive impairment, heart disease, pregnancy, and specific medications that influence blood pressure/cardiovascular functioning. After initial sluggish recruitment due to the high number of co-occuring mental health diagnoses, extended trial criteria were approved on May 09, 2018, to include individuals with co-occuring conditions, only excluding those who reported transient psychotic experiences. For amendments to the Study Protocol, see Appendix pp 3-4 and 25–30. The trial was funded by *MQ:Transforming Mental Health*, and sponsored by Sussex Partnership NHS Foundation Trust. Ethical approval was obtained by the NHS Health Research Authority Blackcountry Research Ethics Committee (REF Reference 17/WM/0125). The trial was pre-registered (ISRCTN14848787). All participants provided written informed consent at baseline assessment.

2.2. Randomization and masking

Participants were randomly allocated to either the ADIE therapy or prosody control arm, using a 1:1 ratio randomization with no stratification. The randomization protocol was set up by the trial statistician (AMJ) via the web-based system *Sealed Envelope* [37] and verified by an independent statistician in the local Clinical Trials Unit. The trial manager (LQ) received randomization for each participant through the Sealed Envelope dashboard and informed participants of their allocation after the baseline assessment. Due to the nature of the interventions and associated information material, the principal and chief investigators, researchers providing treatment, and participants were aware of treatment allocation. However, participants were not informed which was the active intervention and the control intervention. Researchers collecting outcome data and the trial statistician were blind to treatment allocation.

2.3. Procedures

All procedures are explained in detail in the Appendix, pp 33–37. Autistic adults who expressed an interest in trial participation were sent study information that included the Participant Information Sheet, and either self-screened for eligibility via the online platform Qualtrics, or were screened by a research assistant by telephone or at face-to-face appointments. Eligible participants were then invited for an initial session, where a designated researcher obtained written informed consent to participate in the trial. Baseline assessments took place before blinded randomization.

A complete set of outcome measures (for references and detailed descriptions of all outcomes measures, see Appendix pp 17–18) were assessed at baseline (T0), and 1-week post therapy (T1) by a designated researcher. The primary outcome measure (Trait anxiety score on the Spielberger State and Trait Anxiety Inventory [STAI-T]), and related secondary outcome measures (State anxiety score [STAI-S], awareness section of the Porges Body Perception Questionnaire [BPQ], and Generalized Anxiety Symptoms [GAD-7]) were assessed 3-months post therapy (T2) via the online platform Qualtrics. Demographic data (age, sex assigned at birth, own identified gender, level of education, handedness, nationality, current medication, psychiatric diagnoses) were collected before randomization. Further clinical data were obtained during screening; date of diagnosis, and presence of Generalized Anxiety Disorder (MINI V.5.0.0; Section O, GAD) [36].

In the first training therapy session, participants received information leaflets and business-card-style summary cards (see Appendix pp 29–30) about the intervention they were about to receive. All participants completed a total of 6 (ADIE or control) therapy sessions, 1–3 sessions per week to allow for individual preferences and time commitments, and with the constraint that all sessions must be completed within a 2 month period. Both interventions were delivered by two trained researchers (LQ, JSM), although the control intervention was computer-based, and the researcher was only present at the beginning and end of the session.

2.3.1. Active intervention: ADIE therapy

The active ADIE therapy was designed to enhance interoceptive task performance accuracy. Here, each session entailed two blocks, between which each participant underwent a self-paced physical activity that aimed at increasing cardiovascular arousal and accompanying sensations to enhance heartbeat perception. During the pre- and post-activity training blocks, the participant completed two heartbeat detection tasks; first the heartbeat tracking (HBT) and then the heartbeat discrimination (HBD) task, signalling their confidence in their performance after each trial on a visual analogue scale, after which the participant was given veridical feedback on their performance (i.e. how many heartbeats actually occurred within the specified time-frames of the HBT task, and whether their synchronicity judgement was correct on the HBD task). In-between blocks, participants were asked to choose a light physical activity to perform for 1-2 min to the point where their heartbeats became noticeably elevated, but before discomfort occurred. Suggested methods were star jumps (jumping jacks) or jogging on the spot; to accommodate a range of physical ability across participants, other methods to elevate heart rate were accepted.

2.3.2. Control intervention: prosody training

In the active control (prosody) intervention, the participant received a computer-based training protocol, which entailed

listening to an audio clip, followed by the presentation of a choice of emotion options in the form of facial expressions, words, or faces with words. The task required the participant to decide which of the displayed emotion options best matched the emotional tone of voice in the audio clip. Individual sessions increased in difficulty. After each trial, participants received veridical, computer-generated feedback about their performance.

2.4. Outcomes

The primary outcome measure was trait anxiety (as measured at baseline by STAI-T score) at 3-months post therapy (T2). This measure was chosen for continuity between the original research leading to the development of ADIE [28], and because, in contrast to more general measures like GAD-7, it provides an index of emotional anxiety, with some physiological components. Secondary outcomes were: Functional Recovery at T1 and T2, indicated by a 6-point drop in trait anxiety and a STAI-T score below 55 (for a more detailed account of Functional Recovery in these autistic participants and related trial-specific measures, see Appendix p 39-41); symptoms of anxiety at T2, including generalized and momentary anxiety scores (STAI-S and GAD-7), trait subjective interoceptive sensibility (awareness section of the BPQ) at T2; performance accuracy on both (HDT and HBD) heartbeat detection tasks at T1; interoceptive trait prediction error (ITPE; mismatch between normalised heartbeat detection accuracy and interoceptive sensibility) [28] at T1; metacognitive interoceptive awareness (measure of performance accuracy-confidence correspondence using ROC curve analyses of heartbeat discrimination task data) [16] at T1; bodily awareness at T1 (measured using the Multidimensional Assessment of Interoceptive Awareness [MAIA]); alexithymia at T1 (measured by Toronto Alexithymia Scale [TAS-20]); states of Positive and Negative Affectivity at T1 (measured by Positive and Negative Affect Scale [PANAS]); and clinical depression score at T1 (measured by Patient Health Questionnaire [PHQ-9]). All secondary outcome measures, and calculation details of interoception scores are described in more detail in the Study Protocol (see Appendix pp 17−19).

Adverse events were recorded: Serious adverse events were defined as any event which results in death, is life-threatening, requires hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability or incapacity. Important adverse events were defined as events that are not immediately life-threatening, or do not results in death or hospitalization, but may jeopardize the participant and/or may require intervention to prevent one of the other outcomes listed as serious adverse events.

2.5. Sample size

The sample size calculation was based on the use of an independent *t*-test to detect a minimal clinically meaningful difference (MCID) in the primary outcome STAI-T of 7·65 or more at the primary time point (T2). The difference of 7·65 was based on the data we used to develop the ADIE trial (mean anxiety in autistic participants 52·65, SD = 12·03) [28]. A threshold of 5% for a two-sided test, 90% power, and a 1:1 allocation ratio were set. The results gave a sample size of 53 participants per arm (intervention and control); recruitment was increased to 120 to anticipate a 10% attrition rate. Although clustering was not considered at the design stage, a supplementary analysis allowing for post-randomization clustering to control for therapist effects was conducted.

2.6. Statistical analysis

Statistical analysis and data management followed agreed plans established by the trial statistician, and agreed by the research team, before data lock (Sections 6 and 7 of the Trial Protocol, Appendix pp 9−22). The between-group difference of the primary outcome (STAI-T) was analyzed using a maximum likelihood-based repeated measures approach. Analyses included the fixed, categorical effects of treatment (ADIE, prosody), time (T1, T2), and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline STAI-T score. An exchangeable covariance structure was used to model the random effects. Significance tests were based on two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals). Analyses were implemented using Stata™ 16 software package [38] and the analysis procedure *mixed* Stata command. The primary treatment comparison was the contrast between treatments at T2 for STAI-T. Analyses were undertaken on an intention-to-treat (ITT) basis, wherein participants were analyzed as per randomisation allocation regardless of treatment received. Given the higher-than-expected attrition rate at the primary time-point (T2) of 50%, the more robust multiple imputation by chained equations (MICE) [39] was chosen as the imputation method for missing items. Specification of the analysis and imputation model are detailed in Appendix, pp 39−40.

Standardized (Cohen's *d*) effect sizes were calculated using the unstandardized effect estimates divided by the baseline pooled standard deviations. Secondary outcomes, for which only T0 and T1 data were available, were evaluated using Analysis of Covariance (ANCOVA) at T1, with corresponding baseline scores as covariates, and treatment group (ADIE, prosody) as a fixed factor. Analyses on secondary outcomes were considered exploratory and no changes to clinical practice will be made based on these findings. Instead, they serve to aid the interpretation of any observed group differences following intervention. However, a small number of secondary outcomes were essentially measuring similar constructs, i.e., STAI-S and GAD-7 (both measuring anxiety), and BPQ and MAIA (both measuring sensibility to bodily signals), and so Bonferroni corrections for multiple comparisons were applied. Statistical significance for hypothesis tests involving these outcomes was set at $p < .025$. No other adjustments for multiple testing were recommended by the trial statistician.

Two sensitivity analyses were carried out. First, data were further re-analyzed on a complete-case basis (i.e., without imputation) to detect any substantial differences between imputed and non-imputed results, and to ensure that the high attrition rate did not alter results (Appendix, p 38, Table 1). Secondly, analyses were repeated with multiple imputation and post-randomization clustering by therapist to control for potential clustering effects (Appendix, p 39, Table 2), and the intracluster correlation coefficient (ICC) was calculated for the primary outcome for both complete case and multiple imputation data.

2.7. Data handling and monitoring

Details on all Data Management can be found in section 7 of the Trial Protocol (Appendix, pp 19−21). All data was anonymized and identifying information kept separately in password protected files on secure University servers. The research team adhered to the good practice and standards principles which were 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 27,002) for Information Security, the Data Protection Act, 1998 and the Sussex Partnership Foundation Trust Research Policy 2012.

The trial was monitored through oversight, recording and reporting lines via Sussex Partnership NHS Foundation Trust, Brighton and Sussex Medical School, the local Clinical Trials Unit, and the National Institute for Health Research (NIHR) Research and Design Service South East.

2.8. Role of the funding source

The funder of the study, the charity *MQ:Transforming Mental Health,* had no role in the study design, data collection, data analysis,

data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

Participants were recruited from July 01, 2017 to December 31, 2019. Out of the 334 individuals who were contacted to be screened for eligibility, 111 did not respond, 56 were ineligible, and 46 refused to participate (see Fig. 1). Out of the 121 remaining participants who attended baseline assessment, 60 were randomly assigned to the prosody intervention, and 61 to ADIE. Among the ADIE group, four participants did not continue to start therapy, 57 participants received treatment, out of which seven withdrew before the T1 assessment, which 46 participants attended. Seven participants did not attend the T2 (3-months post-intervention) assessment, leaving 39 participants who were assessed for this primary endpoint. In the prosody (active control) group, eight participants did not continue to the first therapy session, 52 received treatment, and a further 13 withdrew before T1 assessment, which 39 participants attended. 14 participants were not assessed at the T2 endpoint, leaving 25 participants who completed T2 assessment. Individuals who gave feedback on reasons for not starting treatment typically referred to the practicalities of time commitment for the study. Feedback from participants who were lost to follow up suggests that they viewed their participation in the study as complete, and that they would not further benefit by continuing their participation.

We used MICE to impute missing values based on the assumption that data was missing at random (MAR). Univariate logistic regression with a Compliance dummy variable indicating whether participants provided the primary outcome and the continuous primary outcome variable (STAI-T at T2) as dependent variables were used to

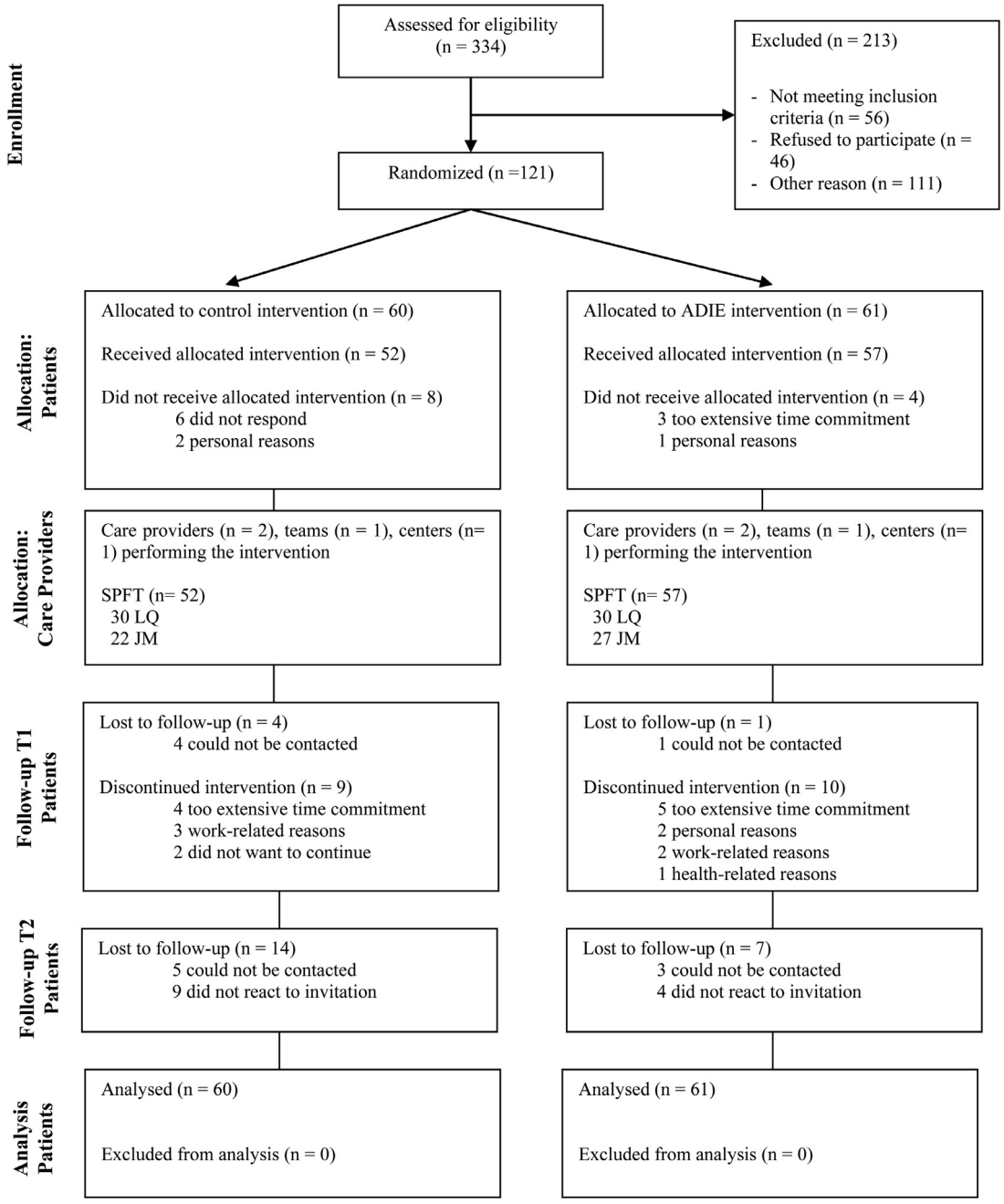

Fig. 1. Trial profile.

Table 1
Baseline demographic and clinical characteristics of the intention-to-treat population.

	ADIE (*n* = 61)	Prosody (*n* = 60)	Total (*n* = 121)
Age, Median (IQR, range), y	29 (23–43; 18–64)	31 (25–43; 19–59)	30 (24–43; 18–64)
Sex assigned at birth			
Female	29 (53%)	37 (38%)	66 (55%)
Male	32 (47%)	23 (62%)	55 (45%)
Gender Identification			
Female	26 (43%)	32 (53%)	58 (48%)
Male	33 (54%)	24 (40%)	57 (47%)
Other	2 (3%)	4 (7%)	6 (5%)
Nationality			
British	58 (95%)	57 (95%)	115 (95%)
Australian	–	1 (1.7%)	1 (0.8%)
Bulgarian	1 (1.6%)	–	1 (0.8%)
Dutch	–	1 (1.7%)	1 (0.8%)
Finnish	1 (1.6%)	–	1 (0.8%)
French	–	1 (1.7%)	1 (0.8%)
Hungarian	1 (1.6%)	–	1 (0.8%)
Education			
GCSE or similar	10 (16%)	11 (18%)	21 (17%)
A-levels or similar	14 (23%)	9 (15%)	23 (19%)
Attended college, no degree	5 (8%)	13 (22%)	18 (15%)
Undergraduate degree	15 (25%)	20 (33%)	35 (29%)
Graduate degree	17 (28%)	7 (12%)	24 (20%)
Handedness			
Handedness			
Right	55 (90%)	51 (85%)	106 (87%)
Left	1 (1.6%)	6 (10%)	7 (6%)
Ambidextrous	5 (9%)	3 (5%)	8 (7%)
Previous diagnosis of anxiety disorder (participant reported)			
	36 (59%)	37 (62%)	73 (60%)
Previous diagnosis of depression (participant reported)			
	31 (51%)	32 (53%)	63 (52%)
Other previous diagnoses (participant reported)			
ADHD	5 (8%)	2 (3%)	7 (6%)
OCD	8 (13%)	6 (10%)	14 (12%)
PTSD	–	3 (5%)	3 (2%)
C-PTSD	–	1 (2%)	1 (1%)
Dyspraxia	1 (2%)	4 (7%)	5 (4%)
Dyslexia	–	2 (3%)	2 (2%)
Eating Disorder	1 (2%)	–	1 (1%)
Currently prescribed anti-anxiolytic/anti-depressant drugs (participant reported)			
	25 (40%)	26 (43%)	51 (42%)
Meet criteria for anxiety disorder diagnosis at screening interview†			
	51 (84%)	44 (73%)	95 (79%)
Autistic Traits			
Autism Quotient			
(Mean; SD)	34·2 (7·5)	35·6 (7·3)	34·9 (7·3)
Empathy Quotient			
(Mean; SD)	23·5 (11·3)	23·3 (10·9)	23·4 (11·1)
IQ‡			
Predicted WAIS Full-Scale IQ			
Mean (SD)	113·1 (10·0)	115·6 (8·6)	114·5 (9·3)
Median (IQR, range)	115·7 (107–120, 82–124)	118·2 (110–122, 98–129)	118·2 (108–121, 82–129)
Predicted WAIS Verbal IQ			
Mean (SD)	111·3 (9·2)	113·6 (7·9)	112·6 (8·5)
Median (IQR, range)	113·7 (106–118, 82–121)	116·0 (108–119, 98–126)	116·0 (107–119, 82–126)
Predicted WAIS Performance IQ			
Mean (SD)	112·3 (8·9)	114·5 (7·7)	113·5 (8·2)
Median (IQR, range)	114·6 (107–119, 85–122)	116·8 (109–120, 99–126)	116·8 (109–120, 85–127)

Data are n (%) or n/N (%) unless otherwise specified. *Based on UK educational system. † Based on Mini-International Neuropsychiatric Interview, Section O, Generalized Anxiety Disorder; ‡Based on National Adult Reading Test (NART).

specify the imputation model. All incomplete variables were registered as imputed with Stata *mi* commands and imputed using linear regression (Stata command *regress*). Variables that predicted missingness and were associated with the dependent variable at the $\alpha < 0{\cdot}05$ level were included in the imputation model. The final imputation model included the primary outcome variable (STAI-T at T2), STAI-T at T0 and T1, STAI-S, GAD-7, PHQ-9, and MAIA Trusting score at T0 as missingness predictors, Trial arm, and the Compliance dummy variable (see Appendix, p 40, Table 3). The imputation was set at 27 iterations to account for 27% of missing data [39].

Demographic and clinical characteristics at baseline assessment (*N* = 121) are displayed in Table 1, and Table 5 in the Appendix to display baseline characteristics before and after initial attrition. Participants were 55% female and 45% male assigned at birth, with 48% identifying as *Female*, 47% identifying as *Male* and 5% identified using a different term. The majority (79%) of participants met initial diagnostic criteria for generalized anxiety (MINI Section O), but for 57%, their anxiety was better explained by or restricted to their autistic traits (for example, the reported anxiety is only provoked by changes in routine, or by circumstances engendering reported sensory

Table 2
Descriptive summaries of primary and secondary outcome measures.

	Baseline (T0)	1-week post-intervention (T1)	3-months post-intervention (T2)						
	Prosody								
(n = 60)	ADIE								
(n = 61)	Overall								
(n = 121)	Prosody								
(n = 60)	ADIE								
(n = 61)	Overall								
(n = 121)	Prosody								
(n = 60)	ADIE								
(n = 61)	Overall								
(n = 121)									
STAI Trait Anxiety*									
Patients with available data, n (%)	58 (97%)	61 (100%)	119 (98%)	39 (65%)	46 (75%)	85 (70%)	25 (42%)	36 (59%)	61 (50%)
Mean score (SD; range)	58.0 (9.9, 33–80)	58.8 (11.5, 26–79)	58.4 (10.7, 26–80)	55.7 (10.7, 35–78)	54.3 (11.3, 28–77)	55 (10.9, 28–78)	55.3 (9.8, 37–69)	54.1 (12.8, 32–80)	54.7 (11.5, 32–80)
Recovery†									
Patients with available data, n (%)	NA	NA	NA	39 (65%)	46 (75%)	85 (70%)	25 (42%)	36 (59%)	61 (50%)
Yes, n (%)	NA	NA	NA	4 (10%)	11 (24%)	15 (18%)	4 (16%)	11 (31%)	15 (25%)
Improvement‡									
Patients with available data, n (%)	NA	NA	NA	39 (65%)	46 (75%)	85 (70%)	25 (42%)	36 (59%)	61 (50%)
Yes, n (%)	NA	NA	NA	6 (15%)	9 (20%)	15 (18%)	3 (12%)	2 (6%)	5 (8%)
STAI State Anxiety*									
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	40 (67%)	46 (75%)	86 (71%)	25 (42%)	36 (59%)	61 (50%)
Mean score (SD; range)	46.4 (11.3, 20–74)	46.1 (12.8, 21–75)	46.3 (12.0, 20–75)	43.1 (11.6, 20–70)	42.5 (12.7, 23–76)	42.8 (12.1, 20–76)	49.2 (10.9, 26–66)	47.4 (11.5, 28–77)	48.1 (11.2, 26–77)
GAD-7§									
Patients with available data, n (%)	58 (97%)	61 (100%)	119 (98%)	39 (65%)	44 (72%)	83 (69%)	23 (38%)	36 (59%)	59 (49%)
Mean score (SD; range)	11.8 (5.7, 1–21)	11.6 (5.5, 0–21)	11.7 (5.6, 0–21)	10.4 (5.8, 1–21)	10.6 (6.0, 0–21)	10.5 (5.9, 0–21)	10.5 (5.2, 1–21)	10.2 (5.6, 1–21)	10.3 (5.4, 1–21)
BPQ¶									
Patients with available data, n (%)	52 (87%)	60 (98%)	112 (93%)	35 (58%)	47 (77%)	82 (68%)	25 (42%)	36 (59%)	61 (50%)
Mean score (SD; range)	125.7 (33.1, 73–215)	121.7 (33.1, 51–221)	123.5 (33.1, 51–221)	124.3 (35.6, 58–214)	116.0 (34.7, 50–221)	119.5 (35.1, 50–221)	125.6 (39.2, 61–221)	109.04 (28.4, 60–196)	116 (33.9, 60–221)
MAIA Noticing‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.7 (1.2, 0.3–5.0)	2.8 (1.1, 0.3–5.0)	2.7 (1.1, 0.3–5.0)	NA	NA	NA
MAIA Not Distracting‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.4 (1.2, 0.0–4.6)	2.2 (0.8, 0.3–4.0)	2.3 (1.0, 0.0–4.6)	NA	NA	NA
MAIA Not Worrying‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.0 (1.0, 0.0–4.0)	2.3 (1.0, 0.3–4.6)	2.2 (1.0, 0.0–4.6)	NA	NA	NA
MAIA Attention Regulation‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.0 (1.1, 0.0–4.8)	2.2 (1.0, 0.3–4.0)	2.1 (1.0, 0.0–4.8)	NA	NA	NA
MAIA Emotional Awareness‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.7 (1.3, 0.5–5.0)	2.7 (1.1, 0.6–4.2)	2.7 (1.1, 0.6–5.0)	NA	NA	NA
MAIA Self Regulation‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.1 (1.1, 0.0–4.0)	2.2 (1.0, 0.3–4.3)	2.2 (1.0, 0.0–4.3)	NA	NA	NA
MAIA Body Listening‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	1.8 (1.3, 0.0–4.3)	2.0 (1.0, 0.0–3.7)	1.9 (1.2, 0.0–4.3)	NA	NA	NA
MAIA Trusting‖									
Patients with available data, n (%)	51 (85%)	60 (98%)	111 (92%)	33 (55%)	43 (70%)	76 (63%)	NA	NA	NA
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)	2.4 (1.3, 0.0–4.2)	2.3 (1.0, 0.0–4.7)	2.4 (1.1, 0.0–4.7)	NA	NA	NA
TAS Total**									

(*continued on next page*)

Table 2 (*Continued*)

	Baseline (T0)	1-week post-intervention (T1)	3-months post-intervention (T2)						
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	40 (67%)	46 (75%)	86 (71%)	NA	NA	NA
Mean score (SD; range)	63.5 (11.1, 33–83)	62.5 (10.6, 29–81)	63.0 (10.8, 29–83)	62.0 (12.2, 32–83)	60.1 (11.2, 30–85)	61 (11.7, 30–85)	NA	NA	NA
TAS DDF††									
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	40 (67%)	46 (75%)	86 (71%)	NA	NA	NA
Mean score (SD; range)	18.2 (4.1, 7–25)	17.8 (3.9, 8–24)	18.1 (18.0, 7–25)	18.1 (4.3, 6–25)	17.3 (4.0, 8–25)	17.7 (4.1, 6–25)	NA	NA	NA
TAS DIF‡‡									
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	40 (67%)	46 (75%)	86 (71%)	NA	NA	NA
Mean score (SD; range)	25.0 (5.8, 11–35)	24.9 (5.6, 13–35)	24.9 (5.7, 11–35)	23.8 (6.1, 13–35)	23.5 (6.1, 12–35)	23.7 (6.1, 12–35)	NA	NA	NA
TAS EOT§§									
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	40 (67%)	46 (75%)	86 (71%)	NA	NA	NA
Mean score (SD; range)	20.4 (4.4, 11–34)	19.8 (4.6, 8–29)	20.0 (4.5, 8–34)	20.1 (5.3, 11–31)	19.2 (4.6, 9–29)	19.6 (4.9, 9–31)	NA	NA	NA
PANAS positive¶¶									
Patients with available data, n (%)	50 (83%)	56 (92%)	106 (88%)	34 (57%)	42 (69%)	76 (63%)	NA	NA	NA
Mean score (SD; range)	26.7 (6.9, 16–40)	25.5 (7.6, 10–42)	26.0 (7.3, 10–42)	25.7 (6.0, 15–42)	24.2 (9.4, 11–43)	24.9 (8.0,11–43)	NA	NA	NA
PANAS negative¶¶									
Patients with available data, n (%)	50 (83%)	56 (92%)	106 (88%)	34 (57%)	42 (69%)	76 (63%)	NA	NA	NA
Mean score (SD; range)	18.2 (6.3, 10–41)	17.8 (6.9, 10–35)	18.0 (6.6, 10–41)	15.0 (6.2, 10–36)	16.8 (8.6, 9–42)	16.0 (7.6, 9–42)	NA	NA	NA
PHQ9||||									
Patients with available data, n (%)	51 (85%)	56 (92%)	107 (88%)	35 (58%)	44 (72%)	79 (65%)	NA	NA	NA
Mean score (SD; range)	12.5 (6.2, 1–26)	12.9 (6.5, 0–27)	12.7 (6.3, 0–27)	11.3 (6.4, 2–27)	11.4 (6.9, 0–25)	11.4 (6.6, 0–27)	NA	NA	NA
Tracking accuracy***									
Patients with available data, n (%)	59 (98%)	61 (100%)	120 (99%)	40 (67%)	44 (72%)	84 (69%)	NA	NA	NA
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)	0.5 (0.3, −0.4–0.9)	0.8 (0.2, 0.2–1.0)	0.6 (0.3, −0.4–1.0)	NA	NA	NA
Tracking confidence†††									
Patients with available data, n (%)	58 (97%)	61 (100%)	119 (98%)	40 (67%)	44 (72%)	84 (69%)	NA	NA	NA
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)	3.9 (2.5, 0.1–8.4)	4.4 (2.4, 0.3–9.9)	4.2 (2.4, 0.1–9.9)	NA	NA	NA
Discrimination accuracy (d')‡‡‡									
Patients with available data, n (%)	55 (92%)	57 (93%)	112 (93%)	36 (60%)	41 (67%)	77 (64%)	NA	NA	NA
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)	0.2 (0.6, −1.0–1.6)	0.9 (1.1, −0.8–3.6)	0.6 (1.0, −1.0–3.6)	NA	NA	NA
Discrimination confidence†††									
Patients with available data, n (%)	58 (97%)	60 (98%)	118 (98%)	38 (63%)	44 (72%)	82 (68%)	NA	NA	NA
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)	4.8 (2.5, 0.0–9.0)	4.9 (2.5, 0.1–9.5)	4.8 (2.5, 0.0–9.5)	NA	NA	NA
Interoceptive Awareness (ROC)§§§									
Patients with available data, n (%)	59 (97%)	90 (98%)	118 (98%)	38 (63%)	42 (69%)	80 (66%)	NA	NA	NA
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)	0.5 (0.1, 0.1–0.8)	0.5 (0.2, 0.3–1.0)	0.5 (0.1, 0.1–1.0)	NA	NA	NA
ITPE Tracking									
Patients with available data, n (%)	52 (87%)	60 (98%)	112 (93%)	33 (55%)	44 (72%)	77 (64%)	NA	NA	NA
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)	0.5 (1.6, −2.3–3.7)	−0.6 (1.3, −2.8–3.1)	−0.1 (1.5, −2.8–3.7)	NA	NA	NA
ITPE Discrimination									
Patients with available data, n (%)	51 (85%)	59 (97%)	110 (91%)	32 (53%)	44 (72%)	76 (63%)	NA	NA	NA
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)	0.4 (1.3, −2.9–2.9)	−0.5 (1.5, −3.2–3.5)	−0.1 (1.5, −3.2–3.5)	NA	NA	NA

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 orientated Thinking; PANAS=Positive and Negative Affect Scale; PHQ-9 = Patient Health Questionnaire nine-item; ROC = Receiver Operating Curve; ITPE = Interoceptive Trait Prediction Error; *Possible range 20–80; †Indicated by a 6-point drop and overall ≤ 55 STAI Trait anxiety score; ‡Indicated by a 6-point drop regardless of overall STAI Trait anxiety score; §Possible range 0–21; ¶Possible range 45–225; ||Possible range 0–5; **Possible range 20–100; ††Possible range 5–25; ‡‡Possible range 7–35; §§Possible range 8–40; ¶¶Possible range 10–50; ||||Possible range 0–27; ***Possible range −1·0–1·0; †††Possible range 0–10; ‡‡‡Possible range 0–6.93; §§§Possible range 0–1.

Table 3
Comparison of outcome measures between ADIE and Prosody control intervention at 3-months post-intervention (T2)/1-week post-intervention (T1) derived by multiple imputation.

	B (SE; 95% CI)	*d* (95% CI)	*p* value
Primary Outcome			
STAI trait anxiety T2	3·225 (1·14; 1·13, 5·29)	0·30 (0·09, 0·51)	0·005*
Secondary Outcomes			
STAI_S at T2	1·780 (1·96; −2·08, 5·64)	0·14 (−0·17, 0·47)	0·365
GAD7 at T2	0·508 (0·82; −1·11, 2·12)	0·09 (−0·20, 0·38)	0·536
BPQ at T2	13·300 (4·12; 5·19, 21·41)	0·40 (0·16, 0·65)	0·001*
Tracking accuracy at T1	0·220 (0·05; 0·12, 0·32)	0·50 (0·26, 0·71)	> 0·001*
Discrimination Accuracy (d') at T1	0·746 (0·21; 0·33, 1·16)	1·10 (0·47, 1·66)	0·001*
ROC at T1	0·029 (0·03; −0·04, 0·10)	0·26 (−0·33, 0·84)	0·383
ITPE Tracking at T1	−1·124 (0·30; −1·74, −0·51)	−0·73 (−1·13, −0·33)	0·001*
ITPE Discrimination at T1	−1·006 (0·30; −1·60, −0·41)	−0·78 (−1·23, −0·32)	0·001*
MAIA Noticing at T1	0·345 (0·23; −0·11, 0·80)	0·35 (−0·11, 0·80)	0·133
MAIA Not Distracting at T1	−0·266 (0·19; −0·64, 0·11)	−0·25 (−0·60, 0·10)	0·163
MAIA Not Worrying at T1	0·312 (0·21; −0·12, 0·74)	0·25 (−0·09, 0·60)	0·150
MAIA Attention Regulation at T1	0·315 (0·19; −0·06, 0·69)	0·33 (−0·06, 0·71)	0·095
MAIA Emotional Awareness at T1	0·151 (0·20; −0·25, 0·55)	0·11 (−0·19, 0·41)	0·448
MAIA Self Regulation at T1	0·136 (0·17; −0·21, 0·48)	0·13 (−0·20, 0·46)	0·435
MAIA Body Listening at T1	0·287 (0·19; −0·10, 0·68)	0·25 (−0·09, 0·59)	0·146
MAIA Trusting at T1	−0·106 (−0·19; −0·48, 0·27)	−0·08 (−0·36, 0·20)	0·573
TAS Total at T1	−0·843 (1·81; −4·46, 2·78)	−0·08 (−0·40, 0·25)	0·643
TAS DDF at T1	−0·347 (0·76; −1·86, 1·17)	−0·08 (−0·45, 0·28)	0·649
TAS DIF at T1	0·030 (0·83; −1·63, 1·69)	0·01 (−0·29, 0·30)	0·971
TAS EOT at T1	−0·487 (0·80; −2·09; 1·12)	−0·11 (−0·46, 0·24)	0·545
PHQ9 at T1	−0·559 (1·05; −2·66, 1·54)	−0·09 (−0·43, 0·25)	0·595
PANAS positive at T1	−0·118 (1·54; −3·19, 2·95)	−0·02 (−0·41, 0·38)	0·939
PANAS negative at T1	2·749 (1·36; 0·17, 5·48)	0·40 (0·02, 0·80)	0·039*

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 orientated Thinking; PHQ = Patient Health Questionnaire; PANAS = Positive and Negative Affect Scale.

overload). Therefore, 22% of participants met full criteria for generalized anxiety disorder, where symptoms could not be explained by core characteristics of their autism alone.

All outcome measures at all time points are summarized in Table 2 (also see Appendix Fig. 6–29) and effect sizes for each outcome are displayed in Table 3 and Fig. 2. For the primary outcome (STAI-T) at T2, there was a small-moderate, statistically significant between-group effect in favour of the ADIE (vs control) intervention (estimated mean difference 3·23 [95% CI 1·13 to 5·29]; d = 0·30 [95% CI 0·09 to 0·51]; p = 0·005; Table 3, Fig. 3). This represented an overall greater reduction in trait anxiety in ADIE compared to the prosody therapy group. Although the confidence interval did not reach our target 'clinically-meaningful' drop in trait anxiety of 6 points (nor did the 95% CI include the MCID of 7·65 used for sample size calculation), Functional Recovery at T2 was reached by 31% of ADIE and 16% of control participants (Appendix, p 41, Table 4, Fig. 4 and 5). However, this group difference remained subthreshold ($\chi^2(1, N = 61)=1·68$, p = 0·194; not shown).

No statistically significant group differences were detected for state anxiety (STAI-S) at T2, nor generalized anxiety (GAD-7) at T2. A small-moderate between-group effect on BPQ scores was detected at T2, where BPQ scores decreased in the ADIE but not control group (Appendix, Fig. 9), indicating a change in subjective interoceptive sensibility, operationalised as reduced reporting of the 'awareness' of bodily sensations. There were moderate to large between-group effects for heartbeat detection on both tasks, indicating that the ADIE, but not control, group increased in performance accuracy. On the HBT task, ADIE participants increased their accuracy from an average of 0·48 [95% CI 0·45 to 0·51] to 0·76 [95% CI 0·74 to 0·78] (Appendix, Fig. 10), while average d' as an index of accuracy on the HBD increased from 0·30 [95% CI 0·25 to 0·35] to 1·03 [95% CI 0·96 to 1·09] (Appendix, Fig. 11). Moderate-large between-group effects were detected for changes (reduction) in interoceptive trait prediction error, ITPE, for both HBT and HBD. There was a small-moderate between-group effect for Negative Affectivity, indicating a decrease in negative affect in the control, and no change in the ADIE group (Table 3). No other effects reached criteria for statistical significance (Table 3).

Complete case analysis for primary and secondary outcomes (other than measures of Functional Recovery, which were already made on a complete case basis), are listed in the Appendix (p 38, Table 1). As the findings are similar, adjustment for missing data via multiple imputation did not alter interpretation of these results. Similarly, results for post-randomization cluster analysis allowing for therapist effects are consistent with original results (Appendix, p 39, Table 2). This is in line with the small ICCs found for both complete case data (ICC = 0·02; not shown) and multiple imputed data (ICC = 0·01; not shown), which indicate little dependence of the primary outcome on cluster effects. However, given the small number of therapist-clusters (k = 2), these results should be read with caution. A larger study with a variety of therapists would be needed to estimate the therapist ICC more robustly.

One adverse outcome was identified and managed accordingly: A participant from the ADIE group with a family history of cardiac disease developed cardiac anxiety subjectively related to enhanced heartbeat awareness.

4. Discussion

To our knowledge, this is the largest clinical trial of an intervention for anxiety in autistic adults to date [12]. The novel intervention, ADIE, departs from standard CBT approaches in the focus on interoceptive differences relating to anxiety in autistic adults. Our trial data showed a positive effect of the ADIE therapy on reducing trait anxiety

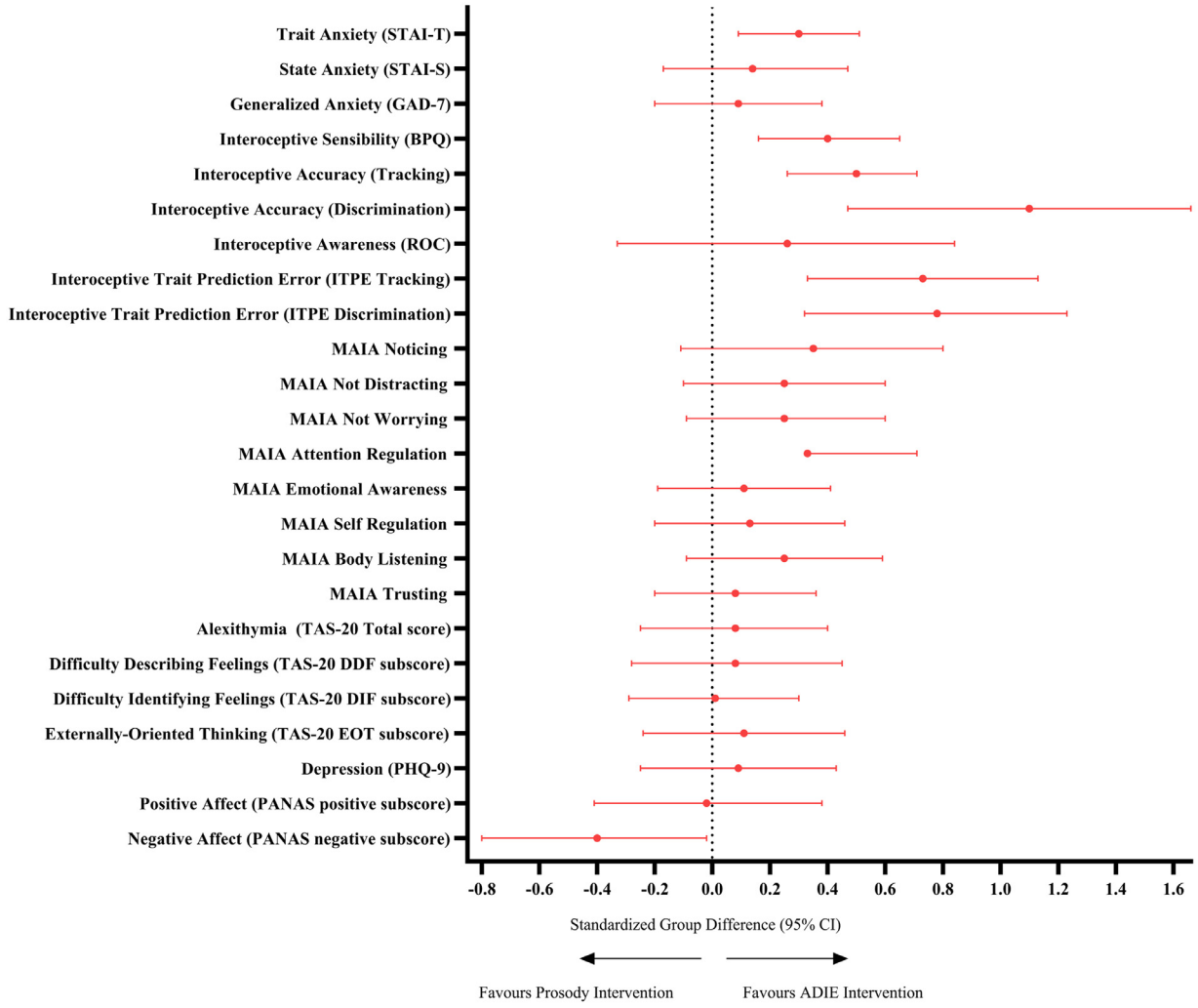

Fig. 2. Forest plot of standardized group differences between ADIE and prosody intervention for all outcome measures. Outcomes interpreted as being in favour of the ADIE group whose standardized group difference was below zero were multiplied by −1 for this figure, such that all outcomes higher than zero could be interpreted in favour of the intervention. Error bars are 95% CIs. 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 orientated Thinking; PANAS=Positive and Negative Affect Scale; PHQ-9 = Patient Health Questionnaire nine-item; ROC = Receiver Operating Curve; ITPE = Interoceptive Trait Prediction Error.

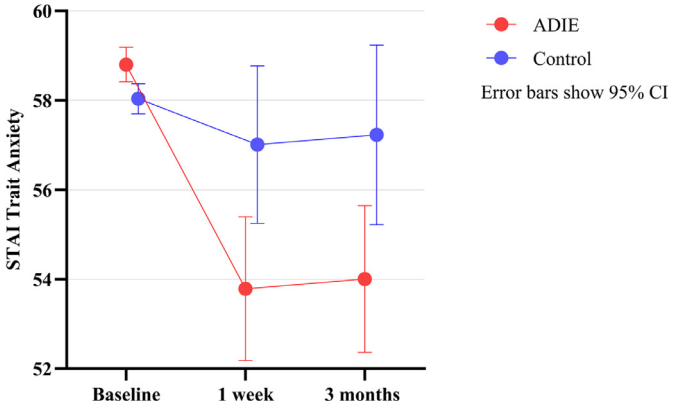

Fig. 3. Primary outcome (STAI trait anxiety) over time and per trial arm. Data plot of STAI trait anxiety over time and per trial arm (red = ADIE, blue = control). Baseline scores are mean estimates of Baseline Covariate from the predictive model, 1 week and 3 months scores are predictive margins from the mode. ADIE = Aligning Dimensions of Interoceptive Experience; STAI=Spielberger State Trait Anxiety Index. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

3-months post-intervention (the primary outcome) compared to an active control therapy. However, across the whole group, this reduction fell short of our predefined criteria of a minimal clinically meaningful difference (6-point change exceeding the confidence interval). Our stringent use of an active control condition rather than a passive 'no intervention' or 'treatment as usual' control group, along with attrition of the sample size by 3-months post-intervention, may have attenuated the group effect size, although it must also be taken into account that active control conditions are routinely used to prevent overinflating effect size. Nevertheless, 31% of participants in the ADIE group reached agreed levels for Functional Recovery status at 3-months post-intervention, compared to only 16% in the control group. ADIE also elicited differences from the control therapy in interoceptive sensitivity, accuracy, and interoceptive trait prediction error (ITPE). Moreover, treatment compliance with the ADIE intervention group was high (79%), although it needs to be acknowledged that attrition at follow-up was much higher than expected (Fig. 1). Overall, we show that our targeted interoceptive training can decrease trait anxiety, and modify interoceptive abilities in autistic adults, when compared to an exteroceptive control intervention.

The empirical findings that led to the development of ADIE drove our hypothesis that decreasing mismatch between performance

accuracy and subjective sensibility in interoceptive sensing will lead to decreased trait anxiety [16]. In this trial, ADIE increased performance accuracy on both heartbeat tracking and heartbeat discrimination tasks and attenuated subjective interoceptive sensibility (i.e. reducing the over-reporting of subjective experiences of bodily sensations). Interestingly, changes in moment-to-moment interoceptive awareness (metacognitive insight, as measured by ROC) [16] did not reach statistical significance following the ADIE intervention. Thus, while participants may not alter their confidence-accuracy correspondence, the marked drop in interoceptive sensibility score suggests they perceive such sensations as less intense and intrusive. Mechanistically, interoceptive training with ADIE might improve an individual's ability both to predict and regulate internal states [25]. Increased accuracy in the perception of interoceptive changes may minimize the amplification of poorly attributed interoceptive representations that otherwise fuel anxious affect, thereby reducing trait anxiety. In addition, more precise access to interoceptive sensations may also aid early regulation, before anxiety states become overwhelming, although these explanations remain speculative.

In comparison to other recent clinical trials, even of autistic adults, baseline trait anxiety was notably more elevated in our participants: Baseline STAI-T score was mean 58·4 (SD 10·7), compared, for example, to a mean score of 50·3 (SD 13·7) in the group studied by Gaigg and colleagues [41]. This is relevant to our secondary outcome of Functional Recovery. Moreover, for 57% participants, the autism diagnosis was deemed to provide a sufficient explanatory account for anxiety symptoms, suggesting a distinction between 'intrinsic' and 'co-occuring' anxiety in autistic adults. Intolerance of uncertainty and alexithymia are established drivers for anxiety in autism, which can present differently from non-autistic patients [30]. It is noteworthy that the Spielberger State and Trait Anxiety Inventory (STAI) and related measures were developed for non-autistic individuals. Thus this outcome score may not fully capture idiosyncrasies in the expression of anxiety by our autistic participants [9]. This might also mean that our definition of a clinically significant change (a drop of 6 points or more in STAI-T) was not entirely appropriate for our trial population. However, our trial represents an important step; there are few, typically small, RCTs of anxiety treatments in autistic adults [41–43]. The current recommended treatment approach for anxiety in autism is, alongside pharmacological intervention, CBT [44]. A recent meta-analysis found that standard CBT-based therapy in autistic adults displays a small, statistically non-significant effect size (g = 0·24) when anxiety is assessed by self-report measures, as in this trial [13]. ADIE led to a comparable, slightly larger, and statistically significant (d = 0·30) effect on self-reported anxiety. Although the confidence interval of our observed effect on anxiety did not meet the 'neurotypical' clinically significant change score, ADIE, in contrast to the active control, performed at least equally to CBT.

ADIE provides a brief, accessible intervention that is not heavily dependent on language or the ability to identify different emotions, unlike many emotion-focussed therapies [12,40]. Nevertheless, the heterogeneous nature of anxiety across autistic adults can lead to differing therapeutic outcomes. Our study also has specific limitations: First, for stringency and based on preference by our LEAP, we used an active control therapy, but no additional treatment-as-usual or waiting list control group. This limits our ability to judge the potential impact of ADIE on anxiety, or whether the decrease in trait anxiety was the natural progression of these symptoms in our sample. Also, since the study involved travel for most participants, our study sample favoured the self-selection of autistic adults who were able, or had support, to travel independently, and communicate with the researchers beforehand. Most participants were verbal, and all had the English language skills required to read and understand study information and answer questionnaires. Our study therefore accessed a sub-set of the autistic population. Masking of subjective, self-report outcome measures is notoriously difficult in RCTs. The outcome assessments were therefore conducted by a researcher blind to the participant's treatment allocation. The active control condition sought to improve communication, a reported source of anxiety for many autistic individuals [33,34], by improving emotional prosody recognition skills. This likely elicited comparable expectations of decreased anxiety as the interoceptive intervention. Although our computer-driven interventions depended little on provider-participant interaction, neither the researcher-therapists, nor participants were blind to treatment allocation. This may have introduced bias. However, the relatively large sample size, pragmatic design, active control therapy, overall good compliance and blinding of outcome assessments represent strengths of the study. We recorded only one adverse event in the ADIE and none in the control group.

There is discussion regarding nomenclature and approaches to measure interoceptive perceptual sensitivity [19,45,46], within a general resurgence of interest in how performance accuracy on perceptual tasks relates to veridical sensitivity to sensory events. Fresh data have reinforced a long-acknowledged need to temper interpretation of performance accuracy on the heartbeat tracking (HBT) task, since performance is unsurprisingly influenced by (trainable) top-down factors including response bias, estimations and expectations, that add to the simple detection of heartbeat sensations [19,45]. In this trial, the convergent use of HBT and HBD (analyzed using signal detection theory) and trial-by-trial measures of confidence [16,28] provide some mitigation of concerns regarding cross-individual biases and estimation. Novel candidate interoception tasks have emerged since the start of this trial, which would have to be considered for practicality and feasibility in a clinical setting for the target population. If the therapeutic mechanism driving the observed anxiety reduction engendered by ADIE is indeed the modulation of higher-order interoceptive representations, however, these issues would be largely tangential.

We observed a statistically significant, small-moderate between-group effect of ADIE on trait anxiety in autistic adults. This accessible, empirically-motivated interoceptive therapy was developed in close collaboration with Public and Patient Involvement (Lived Experience) groups to be adapted for autistic individuals. ADIE can be delivered after minimal training, and can therefore be implemented as a treatment option by Assistant Psychologists, a low-cost and accessible work force in the NHS. A current clinical trial that adapted ADIE for individuals with co-morbid connective tissue and anxiety disorders [47] has delivered the intervention remotely during COVID-19 lockdown restrictions. Funding for this trial included the development of the dedicated app 'HeartRater', which implements all procedures and enables remote delivery, therefore making it widely accessible. ADIE may also be tailored to help other clinical groups that share similar interoceptive profiles to autistic adults, including patients with functional somatic and neurological disorders, and sub-populations of people with psychosis [23].

Declaration of Competing Interest

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Data Sharing

De-identified individual participant data and a data dictionary defining each field in the set will be made available to others, along with the study protocol and statistical analysis plan to be made available with the publication on a University of Sussex repository: https://doi.org/10.25377/sussex.13522259. No specific access criteria are needed other than institutional user logon and statement of purpose for use.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101042.

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