

Testing the feasibility of neurofeedback interventions in mental, behavioural and neurodevelopmental disorders

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Abstract

Background

Neurofeedback techniques utilise measured brain activity to help individuals self-regulate activation of specific brain regions in real time. This paper explores the feasibility of neurofeedback interventions in seven individual clinical studies conducted across several mental, behavioural and neurodevelopmental disorders: alcohol dependence; post-traumatic stress disorder; autism; increased body weight and adolescent anxiety.

Methods

An overarching conceptual and design framework was utilised, which included a standardised protocol template, common trans-diagnostic outcome measures, a single clinical database and a joint Trials Steering Committee. Individual study teams selected and implemented the most appropriate design based on several key features including proof of concept versus feasibility, required sample size, and for randomised studies: allocation concealment, two versus 3-arm design and choice of comparator. Standard statistical summary measures were used to construct CONSORT flowcharts and tabulate feasibility objectives for each study. For all studies the primary end point was defined as end of intervention. Success criteria for progression to definitive trials were assessed.

Results

All studies met pre-defined success criteria for recruitment, retention and intervention uptake, although some variability was evident. No pre-defined criteria were set for adherence, intervention delivery, acceptability or contamination, although no issues relating to these criteria were identified.

Conclusions

Neurofeedback interventions in mental, behavioural and neurodevelopmental disorders are feasible to deliver despite variability in individual study designs, populations and clinical indications. Progression criteria were broadly met with some variability which may be attributable to differences in study populations.

Trial registrations:

All included studies were registered on ClinicalTrials.gov. NCT02486900 (01/07/2015), NCT02544971 (09/09/2015), NCT02477722 (23/06/2105), NCT02148770 (28/05/2014), NCT02440451 (12/05/2015), NCT02445625 (15/05/20215), NCT02463136 (04/06/2015)

Background

Neurofeedback describes a set of techniques, including electroencephalography (EEG) and functional magnetic resonance imaging (fMRI)[1] in which measured brain activity is used to help individuals self-regulate activation of a given brain region or signal in real time. fMRI, although higher cost and potentially less accessible than EEG methods, offers greater sensitivity than other approaches and may therefore be more effective in clinical populations. Interest in this approach has increased steadily since the early 2000s when real-time fMRI methods were first reported[2,3] and early phase studies have been conducted in various populations including participants with depression, anxiety, post-traumatic stress disorder (PTSD), attention-deficit hyperactivity disorder (ADHD), autism, obesity, chronic pain and neurogenerative disorders[3]. There is significant heterogeneity in experimental designs, however. Studies have tended to employ small sample sizes, leading to underpowered analyses. Moreover, published accounts of early phase intervention studies often lack sufficient detail relating to feasibility outcomes including recruitment, retention, reach (i.e., the degree to which recruited participants are representative of the target population) and acceptability, and are not reported according to CONSORT pilot and feasibility guidelines[4].

There is a need therefore to test the feasibility and acceptability of neurofeedback interventions for clinical applications, in addition to establishing efficacy for specific conditions. A standardised approach to experimental design, intervention description, implementation and evaluation across conditions adds to the evidence base and facilitates meta-analyses of clinical efficacy across different conditions[5] with similar targets for intervention i.e., behavioural regulation.

The aim of this paper is to report feasibility findings from the seven clinical studies conducted as part of the BRAINTRAIN Consortium, comprising 13 partners across the European Union and associated countries of the 7th Framework Programme. Current practices in neurofeedback interventions[5] and efficacy outcomes are described elsewhere (separately for single-centre studies[6–13] and in an Individual Patient Data (IPD) meta-analysis in a companion paper(ref)). Although the clinical studies of BRAINTRAIN were conducted as single-centre early phase trials, they adhered to an overarching conceptual and design framework characterised by:

1. A common rationale: evaluating feasibility and efficacy of neurofeedback protocols based on pathophysiological models of mental, behavioural and neurodevelopmental disorders with limited treatment options
2. A common mechanism for support in clinical trials methodology (provided by the Centre for Trials Research at Cardiff University) and trials oversight (joint Trials Steering Committee)

3. A joint database for clinical and psychometric data
4. Common measures to assess outcomes in a trans-diagnostic framework (for example, measures of depression and anxiety) and common psychometric measures to predict neurofeedback success, allowing for meta-analysis across trials

Methods

Presented here are the overarching features that were discussed, selected and implemented when the design of each feasibility study was considered with each individual team.

Proof of concept versus feasibility trial. For early phase research, a proof-of-concept study allows the demonstration in principle that recruitment and intervention methods and processes are viable in the target group of participants. Often following on from a proof-of-concept study, a feasibility trial allows the additional demonstration that randomisation is also feasible and is a step closer towards an efficacy trial.

Randomised versus single arm feasibility. Four studies implemented an individually randomised design, and three studies implemented a single arm before / after design. Randomisation allowed for additional feasibility objectives which determined the acceptability and feasibility of randomising participants to treatment and control conditions. Participants were randomised in a 1:1 ratio using minimisation to balance for selected factors.

Allocation concealment. For all randomised studies, allocation concealment was achieved via the implementation of a web-based randomisation algorithm built into the central database hosted by the Centre for Trials Research (CTR), Cardiff University.

Two arm vs 3 arm randomisation. One study (the treatment of PTSD) utilised a 3-arm randomisation (allocation ratio 1:1:1) and the remaining randomised studies used a 2-arm design. For the 3-arm study, the two groups of primary interest for comparison were pre-selected, for the meta-analysis the two active treatment arms were combined and compared to the control arm (*see accompanying IPD meta-analysis paper*).

Choice of control. The choice of control (sham treatment or no treatment) was discussed with each team. There are no defined standards for the design of control conditions in neurofeedback (NF) trials, and the most appropriate choice is likely to depend on the context (i.e., the research question or stage of evaluation)[14]. Options include treatment as usual (TAU) and sham neurofeedback. The comparison between NF + TAU and TAU controls for generic effects of improvement over time and non-specific trial effects. The comparison between real and sham NF additionally controls for the effects of effort and experience of a high-technology environment. The BRAINTRAIN studies used both options (see Table 1).

Table 1
Key design characteristics of BRAINTRAIN studies

Clinical indication	Design	Participant population	N	Intervention	Comparator	Follow-up duration
Alcohol dependence (Cardiff, UK)[6–8] NCT02486900	2-arm randomised trial	Alcohol-dependent outpatients (18 + years) who had completed inpatient detoxification 1–6 months prior to participation	52 (25 intervention; 27 control)	6 sessions of NF-guided self-regulation over 4 months + TAU	TAU	4, 8 and 12 months
PTSD treatment (Tel Aviv, Israel) [11] NCT02544971	3-arm randomised trial	Adults 18–65 years; 14 + months since diagnosis of chronic PTSD	59 (20 per intervention arm; 19 controls)	15 amygdala-targeted electrical fingerprint (EFP)-NF over 13 weeks in either a neutral context (NF-N) or a trauma-related context (NF-T)	TAU	15 weeks and 6 months
PTSD prevention (Tel Aviv, Israel) [Unpublished] NCT02477722	2-arm randomised trial	Adults 18–65 years with exposure to a traumatic event in past 14 days and symptoms of acute stress	36 (17 intervention; 19 controls)	6 sessions of amygdala targeted electrical fingerprint (EFP)-NF over 4 weeks	TAU	6 weeks and 6 months
Increased body weight (Tübingen, Germany)[13] NCT02148770	2-arm randomised trial	Overweight and obese adults (18–65 years, BMI 25 to 40 kg/m ²)	50 (25 per arm)	Single session left dorsolateral prefrontal cortex (dlPFC) targeted fMRI NF	Sham NF	4 weeks
Autism ^a (Coimbra, Portugal)[10] NCT02440451	Single arm within-group design	Young people 16 + years with a diagnosis of autism (DSM-5 criteria)	15 (N.B., recruited sample males only)	5 sessions social brain targeted real time fMRI-NF over 2 months	n/a	6 months post-intervention
Autism ^b (Coimbra, Portugal)[9] NCT02445625	Single arm within-group design	Young people 16 + years with a diagnosis of autism (DSM-5 criteria)	15 (N.B., recruited sample males only)	7 EEG brain computer interface (BCI) sessions over 4 months	n/a	6 months post-intervention
Adolescent anxiety (Oxford, UK)[12] NCT02463136	Single arm within-group design	Females 14–17 years; trait-anxiety score 20–60	50	Single-session emotion regulation circuit targeted fMRI NF	n/a	Post-intervention

****Insert Table 1 here****

Sample size. The sample sizes for each study were determined primarily on the basis of feasibility. However, study teams also estimated sample sizes for early phase efficacy effects and 95% confidence intervals.

Analysis. Standard statistical summary measures were used to construct CONSORT flowcharts and tabulate feasibility objectives for each study. Although not presented here, all comparisons of efficacy measures were presented as differences between arms and accompanying 95% confidence intervals. The direction and magnitude of the differences in outcome measures were assessed. For all studies the primary end point was defined as the time point at the end of the intervention, any second longer term follow-up time points were secondary for feasibility. Key study characteristics are presented in Table 1.

Research governance. Training was provided to all study teams by Centre for Trials Research (CTR) staff, covering research governance and Good Clinical Practice (GCP) for clinical trials. A single protocol template was developed for BRAINTRAIN studies, and standardised processes for assessing and reporting adverse events, incidental findings and participant withdrawal were developed. Individual study teams were responsible for gaining ethical and research governance approvals locally as required, and a central record of these documents was kept by CTR.

Incidental findings. At the time of consent, participants were advised that MRI scans would be performed using a research protocol as opposed to diagnostic MRI, and as such do not replace usual medical care. Given that scans may however reveal a suspected abnormality, patient information sheets and consent forms explained the possibility of incidental findings, and the procedure to be followed should this occur. Participants were required to explicitly consent to secondary review of their scans by a neurologist/radiologist should this be indicated, and to the research team contacting their doctor to advise further follow-up if necessary (or to direct referral for follow-up, depending on local procedures).

The following procedure was developed in the event of incidental findings on MRI:

1. To avoid distress to participants arising from false alarms, staff would not disclose their concerns to the participant
2. The authorised person would report their concerns to a neurologist/radiologist, supplying a digital copy of the image and a description of the cause for concern
3. The neurologist/radiologist would review the scan and associated report and decide whether further follow-up is necessary
4. In the event further follow-up was required, the Lead Researcher would be responsible for ensuring the participant's named doctor was contacted to arrange further follow-up.

No incidental findings were reported across BRAINTRAIN studies, however.

MRI contraindications. Participants in all MRI studies were ineligible if any of the following criteria were applicable: claustrophobia, pregnancy, active medical implants, passive implants deemed unsuitable for MRI, metallic dust in the eyes, certain types of metal prostheses and surgical clips, previous experience with metalworking without eye protection.

Adverse events. Study teams were advised to assess and report Serious Adverse Events (SAEs) according to the definitions below, and to local procedures. A central log of SAEs was maintained by CTR. Across all studies, a single event was reported and subsequently assessed as unrelated to the neurofeedback intervention.

Definitions

Serious Adverse Event (SAE)

Any adverse event that

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is another medically important condition ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures does not constitute an adverse event.

*** Note: Other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Causality. Assignment of causality was made by the Investigator responsible for the care of the participant (Table 2).

Table 2
Assessment of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial/study or intervention
Unlikely	There is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after intervention) with the study/trial or intervention. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other treatment).
Possible	There is some evidence to suggest a causal relationship with the trial/study or intervention (e.g. because the event occurs within a reasonable time after intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a judgement of the causal relationship.

Expectedness. The assessment of whether or not an SAE was an expected consequence of receiving the intervention was provided by the Lead Researcher. Reporting procedures outlined in the study protocol were followed.

Reporting procedures. An SAE form should be completed for all SAEs within 24 hours. Additional information should be sent within 5 days if the event has not resolved at the time of reporting. All events should be followed up through to resolution.

Urgent Safety Measures (USMs). An urgent safety measure is an immediate change in a trial procedure or temporary halt to a trial procedure, put in place prior to approval in order to protect participants from any immediate hazard to health and safety following new safety information (SAE or other information received from an external source). The Lead Researcher may carry out USMs to protect participants from immediate harm.

Informed consent

and withdrawal. All study participants provided written informed consent according to GCP, based on the content of study-specific information sheets and discussion with a researcher. The following procedure and classification of withdrawal was used across all BRAINTRAIN studies. Participants were informed that they had the right to withdraw consent for participation in any aspect of the study at any time, and that their medical care would not be affected by declining to participate or withdrawing from a study. Should a participant initially consent but subsequently withdraw from a study, distinction would be made as to which aspect of the study they are withdrawing from i.e. (1) withdrawal from intervention; (2) withdrawal from follow-up; (3) withdrawal from entire study and participant does not want data to be used. A participant could withdraw or be withdrawn from an intervention for the following reasons (1) withdrawal of consent for intervention by the participant; (2) any alteration in the participant's condition or circumstances which justified the discontinuation of the intervention in the Investigators' opinion.

Outcomes. All clinical studies within BRAINTRAIN were focused on the assessment of feasibility, according to the criteria detailed in Table 3. The studies also provided initial estimates of efficacy; a number of core outcome measures have been included in all studies to allow comparison across clinical conditions, as detailed in Table 4.

Table 3
Primary feasibility outcomes and progression criteria

Eligibility	Definition	Success criteria for progression	
		% of screened participants eligible for the study	
		> 50%	Go (green)
		30–50%	Mitigating strategies (amber)
		< 30%	STOP (red)
Recruitment/Consent	% of eligible participants consented into the study	> 80%	Go (green)
		50–80%	Mitigating strategies (amber)
		< 50%	STOP (red)
Retention (primary end point)	% of consented participants with outcome data the primary endpoint	> 80%	Go (green)
		50–80%	Mitigating strategies (amber)
		< 50%	STOP (red)
Retention (secondary end point)	% of consented participants with outcome data the secondary endpoint	Not defined	
Intervention uptake	% of consented participants commencing the intervention (at least one intervention session completed)	> 90%	Go (green)
		60–90%	Mitigating strategies (amber)
		< 90%	STOP (red)
Adherence/ Completion	% of consented participants completing all intervention sessions	> 80%	Go (green)
		50–80%	Mitigating strategies (amber)
		< 50%	STOP (red)
Compliance	Number of sessions performed/number of planned sessions x 100% for those consented	Not defined	
Intervention delivery	Fidelity of delivery of intervention according to protocol	Not defined	
Acceptability	Qualitative reports	Majority of reports positive;	Go (green)
		Minor issues identified that can potentially be resolved;	Mitigating strategies (amber)
		Major problems with acceptability reported.	STOP (red)
Contamination	Effects of other interventions targeting similar clinical outcomes that are additional to usual care (e.g. specific psychotherapeutic programmes)	This was minimised by placing the interventions at a point in the care pathway at which clinical treatment plans had already been agreed	

Table 4
BRAINTRAIN core outcome measures

Measure	Outcome(s)	Description	Population	Timepoint
Demographic questionnaire	Age, gender, education, SES		All	Baseline
Thought control questionnaire (TCQ) [16]	Thought control (distraction, punishment, worry; re-appraisal; social control)	30-item measure to assess the effectiveness of strategies used for the control of unpleasant and unwanted thoughts	All except PTSD and PTSD prevention	Baseline (baseline and post-intervention for adolescent anxiety)
Thought control ability questionnaire (TCAQ) [17]	Thought control	25-item measure of individual differences in perceived ability to control unwanted and intrusive thoughts	All except PTSD and PTSD prevention	Baseline (baseline and post-intervention for adolescent anxiety)
Wechsler Abbreviated Intelligence Scale (WASI-II)[18]	IQ	Global intelligence/IQ measure	All except PTSD and PTSD prevention	Baseline
Profile of Mood States (POMS)[19]	Anger; confusion; depression; fatigue; tension and vigour	65 self-report questions	All except PTSD; PTSD prevention and adolescent anxiety	Baseline-post intervention (each session)
Hospital Anxiety and Depression Scale (HADS)[20]	Anxiety; depression	14-item scale (7 depression and 7 anxiety items)	All except PTSD; PTSD prevention and adolescent anxiety	Baseline and post-intervention
Beck Depression Inventory (BDI)[21]	Depression	21-item measure of clinical depression	All except adolescent anxiety	Baseline and post-intervention
Debriefing interview questionnaire		Covers: strategies; general experience of the process; adverse effects; awareness of group allocation	All	Post-intervention
NEO Five Factor Inventory (NEO-FFI) [22]	Neuroticism, Extraversion, Openness to Experience, Agreeableness, Conscientiousness	60-item 5-factor personality questionnaire	PTSD, PTSD prevention and binge eating/obesity only	Baseline and post-intervention (baseline only for binge eating/obesity)
Cognitive Emotion Regulation Questionnaire (CERQ) [23]	Emotional regulation/cognitive coping	36-item measure of cognitive coping strategies	PTSD, PTSD prevention and binge eating/obesity only	Baseline and post-intervention
State/Trait Anxiety Inventory (STAI)[24]	State/trait anxiety	20-item measure of state and trait anxiety	PTSD, PTSD prevention and adolescent anxiety only	Baseline and post-intervention

Feasibility outcomes. Key feasibility criteria are listed in Table 3. Also included in Table 3 are success criteria for progression to definitive trials according to a ‘traffic light’ system[15]. Ranges indicate where progression to a definitive study is: (1) indicated without modification (green); (2) indicated with some modification to specific criteria (amber e.g. recruitment methods, to be detailed by each study if applicable) or (3) not recommended given major concerns regarding feasibility (red).

****Insert Table 3 here****

Core efficacy outcomes. Measures listed in Table 4 were included across BRAINTRAIN studies to allow comparison across clinical conditions. Detail relating to condition-specific measures are provided elsewhere[6–13].

****Insert Table 4 here****

Ethical considerations, data ownership and confidentiality. Participants in individual studies consented to use of their data for relevant research purposes. Each study team submitted the main finding as part of the BRAINTRAIN consortium final report and as published papers.

Results

The overall feasibility of delivering neurofeedback interventions in mental, behavioural and neurodevelopmental disorder is summarised in Table 5. All studies met the majority of pre-defined success criteria for recruitment, retention and intervention uptake (> 50% approached eligible; 50–80% of those eligible recruited; 50–80% retention at the primary endpoint; 60–90% uptake), although some variability was evident.

Table 5
Overall feasibility of neurofeedback interventions

Feasibility criteria	Eligibility	Recruitment/consent	Retention (primary end point)	Intervention uptake	Adherence	Intervention delivery	Acceptability	Contamination	Mitigating strategies
Threshold	> 50% (G) 30–50% (A) < 30% (R)	> 80% (G) 50–80% (A) < 50% (R)	> 80% (G) 50–80% (A) < 50% (R)	> 90% (G) 60–90% (A) < 90% (R)	> 80% (G) 50–80% (A) < 50% (R)				
Alcohol dependence (Cardiff, UK) [6–8] NCT02486900	53.6 (52/97)	100 (52/52)	69.2 (36/52)	80 (20/25)	Not reported	Not reported	Not reported	Not reported	Level of retention intervention uptake related to vulnerability of population. Increased consent (appointment by text/phone) increase rates definitive trial.
PTSD treatment (Tel Aviv, Israel) [11] NCT02544971	68.7 (57/83)	100 (57/57)	66.7 (38/57) 73.7 neutral NF (14/19); trauma NF 61.1 (11/18)	81.1 (30/37) 89.5 neutral NF (17/19); 72.2 trauma NF (13/18)	64.9 (24/37) 68.4 neutral NF (13/19); 61.1 trauma NF (11/18)	Not reported	Not reported	Not reported	Level of retention intervention uptake related to vulnerability of population. Increased consent (appointment by text/phone) increase rates definitive trial. Lower uptake as opposed to sham. Additional questionnaire work may point to mitigating strategies.
PTSD prevention (Tel Aviv, Israel) [Unpublished] NCT02477722	45.6 (36/79)	100 (36/36)	91.7 (33/36) 88.2 EEG (15/17); 94.7 fMRI (18/19)	94.4 (34/36) 94.1 EEG (16/17); 94.7 fMRI (18/19)	94.4 (34/36) 94.1 EEG (16/17); 94.7 fMRI (18/19)	Not reported	Not reported	Not reported	Eligibility rates 50% of those approached. A piloting of ideas approaches may increase eligibility approached in definitive trial.
Increased body weight (Tübingen, Germany)[13] NCT02148770	68.4 (50/73)	80.8 (40/50)	100 (40/40) 94.7 fMRI (18/19); 100 sham NF (21/21)	97.5 (39/40) 84.2 fMRI (16/19); 100 sham NF (21/21)	92.5 (37/40)	Not reported	Not reported	Not reported	Slightly lower fMRI as opposed to sham NF. Questionnaire work to identify for discontinuation intervention at point to mitigate strategies.
Autism ^a (Coimbra, Portugal)[10] NCT02440451	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	0 (0/15)	n/a
Autism ^b (Coimbra, Portugal)[9] NCT02445625	88.2 (15/17)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	100 (15/15)	0 (0/15)	n/a
Adolescent anxiety (Oxford, UK) [12] NCT02463136	74.2 (89/120)	56.2 (50/89)	82 (41/50)	82 (41/50)	82 (41/50)	Not reported	Not reported	Not reported	Drop out between screening and recruitment (n discontinued intervention (r indicate issue acceptability. work to identify for declining/disc may point to mitigating strategies.
G = green; A = amber; R = red									

No pre-defined criteria were set for adherence, intervention delivery, acceptability or contamination, and were not specifically reported in some studies. However, no issues relating to these criteria were identified in any study: contamination is likely to have been very minimal and good acceptability can be inferred from generally high retention rates.

****Insert Table 5 here****

Discussion

The seven studies conducted as part of the BRAINTRAIN consortium utilised a common overarching methodology, including a protocol template, clinical database, safety reporting procedures, common feasibility outcomes, a sub-set of core clinical outcome measures and a single independent oversight committee. This approach was found to be feasible, despite variability in individual study designs, populations and clinical indications.

As is evident from Table 5, feasibility criteria were broadly met across indications, with some variability. For recruitment, retention and intervention uptake, this variability is most likely attributable to the vulnerable nature of some study populations (particularly alcohol dependence and those with symptoms and/or a diagnosis of PTSD).

However, further exploration of reasons for decline/drop-out may point to specific issues that future definitive studies could address. For instance, in the anxiety in adolescents study the high dropout rate was a result of initial interest from parents/carers which did not translate into scheduling appointments due to conflicting family commitments. This rate, in a healthy cohort with subclinical symptoms, may not reflect the potential willingness to participate in a future clinical sample where both participants and parents are more committed. Additional contacts with participants between visits may also improve retention and uptake in future trials. Eligibility of the population approached was lower than anticipated for the PTSD prevention study: this relates in part to difficulty in identifying relevant populations prior to diagnosis. However, further piloting of identification approaches in a future definitive trial may be worth exploring.

No pre-defined criteria were set for adherence, although high levels of intervention uptake (starting intervention and/or completion at least one session) and overall high retention are indicative of acceptable adherence and acceptability. It was the experience of the investigators, confirmed by other work, for example in Parkinson’s disease[25], that the potential discomfort of the scanning session does not play a major role in determining retention. Once the MRI procedure has been explained properly and participants have become accustomed to the scanner environment, they are generally rather willing to attend repeated sessions if this is required by the study protocol. Future trials however could make use of additional mitigating strategies to increase likelihood of retention and intervention uptake/adherence, including appointment reminders (e.g., via text) and incentives[26]. Given the intensive and highly specialised nature of study interventions, contamination was likely to have been low and no issues were reported.

Conclusions

In summary, fMRI interventions are feasible across a broad range of mental, behavioural and neurodevelopmental disorders, from adolescence to adulthood. Various strategies are suggested to maximise recruitment, reach and retention in future randomised studies. Qualitative exploration of factors influencing participation in fMRI trials would be of benefit, particularly to further explore facilitators/barriers, the influence of context and factors likely to affect implementation[27]. No specific criteria were set in the BRAINTRAIN studies for adherence, intervention delivery (fidelity) or contamination: future neurofeedback trials should aim to explicitly address these issues, shedding further light on feasibility of this patient-centred approach.

Abbreviations

- ADHD**
Attention Deficit Hyperactivity Disorder
- BDI**
Beck Depression Inventory
- CERQ**
Cognitive Emotion Regulation Questionnaire
- CTR**
Centre for Trials Research
- DIPFC**
Single session left dorsolateral prefrontal cortex
- DSM**
Diagnostic and Statistical Manual of Mental Disorders
- EEG**
electroencephalography
- EFP**
electrical fingerprint
- fMRI**
functional magnetic resonance imaging
- GCP**
Good Clinical Practice

HADS

Hospital Anxiety and Depression Scale

IQ

Intelligence Quotient

MRI

Magnetic Resonance Imaging

NF

Neurofeedback

POMS

Profile of Mood States

PTSD

Post Traumatic Stress Disorder

STAI

State/Trait Anxiety Inventory

TAU

Treatment As Usual

TCQ

Thought control questionnaire

TCAQ

Thought control ability questionnaire

USM

Urgent Safety Measure

WASI

Wechsler Abbreviated Intelligence Scale

Declarations

Ethics approval and consent to participate:

This research was conducted in accordance with the declaration of Helsinki. Each individual study sought ethics approval from their own institutional ethics committees including the following:

Consent for publication:

All participants provide their consent for participation in each individual study

Competing interests:

The authors declare that they have no competing interests

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Author Contribution

RM drafted the manuscript; KH, RP, ER and RM provided study design and management for the original studies; SM, MC-B, MH, HP, TF, KC-K, TH carried out the original studies and provided input to the draft manuscript, DEJL conceived the original BRAINTRAIN consortium and provided clinical insight and context. All authors read and approved the final manuscript.

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Availability of data and materials:

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