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A double-blind, randomised, sham-controlled trial testing the efficacy of fMRI neurofeedback on clinical and cognitive measures in children with ADHD.

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ABSTRACT

Objective. Functional MRI neurofeedback (fMRI-NF) could potentially be a novel, safe non-pharmacological treatment for ADHD. A proof-of-concept randomised controlled trial (RCT) of fMRI-NF of right inferior frontal cortex (rIFC), compared to an active control condition, showed promising improvement of ADHD symptoms (albeit in both groups) and in brain function. However, comparison versus a placebo condition in a larger trial is required to test efficacy.

Methods. This pre-registered (ISRCTN14491589), Medical Research Council UK funded (MR/P012647/1) double-blind, sham-controlled largest RCT so far tested the effectiveness and efficacy of fMRI-NF of rIFC on symptoms and executive functions in 88 boys with ADHD (44 active; 44 sham arm). To investigate treatment-related changes, groups were compared at post-treatment and at 6-month follow-up, controlling for baseline scores, age, and medication status. Primary outcome were post-treatment scores on the ADHD-Rating Scale (ADHD-RS).

Results. No significant group differences were found on the ADHD-RS. Both groups showed similar decreases in other clinical and cognitive measures, except for a significantly greater decrease in irritability and improvement in motor inhibition in the sham relative to the active fMRI-NF at post-treatment covarying for baseline. There were no significant side effects or adverse events. The active relative to the sham group showed enhanced activation in rIFC and other frontal and temporo-occipito-cerebellar self-regulation areas. However, there was no progressive rIFC upregulation, correlation with ADHD-RS scores, or transfer of learning.

Conclusions. Contrary to hypothesis, our findings do not suggest that fMRI-NF of rIFC is effective in improving clinical symptoms or cognition in boys with ADHD.

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1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is defined as persistent, age-inappropriate and impairing symptoms of inattention and/or hyperactivity/impulsiveness(1) with high prevalence (5-7%)(2). Meta-analytic evidence shows underactivation in fronto-striato-thalamic and fronto-parieto-cerebellar networks(3-5), particularly in right inferior frontal cortex (rIFC), which mediates cognitive control and attention functions(4-6). Psychostimulant medication, the first-line treatment for ADHD(7, 8), most consistently increases/normalises IFC activation(9), but is not indicated for all, has side effects(10) and poor adherence in adolescents(8, 11). Furthermore, evidence for long-term efficacy is limited(12), possibly due to brain adaptation(13).

FMRI-neurofeedback (fMRI-NF) which enables self-regulation of brain activation in specific regions/networks by providing feedback of brain activity in real-time(14, 15), could be a novel alternative to pharmacological treatment. FMRI-NF can target areas associated with ADHD, e.g., the opercular rIFC or basal ganglia, that are not accessible with electroencephalography (EEG)-NF. Moreover, EEG-NF has shown small effect sizes of improving ADHD in latest meta-analyses, and self-regulation learning is faster with fMRI-NF(6, 16).

In the first proof-of-concept single-blind randomised controlled trial (RCT) of fMRI-NF in ADHD(17), ADHD boys successfully learned progressive increase of activation in rIFC (active group; N=18) or left parahippocampal gyrus (lPHG; active control; N=13) after 11 runs in four 1-hour fMRI-NF sessions, which was associated with improved ADHD symptoms in both groups relative to baseline, with no side effects. At follow-up, improvement was more pronounced in rIFC group (Cohen's *d*~1) but no longer significant in lPHG group, suggesting potential delayed consolidation or plasticity effects. Cognitively, only the rIFC group showed trend-level improved sustained attention (Cohen's *d=2)* and successfully upregulated rIFC during a 'transfer' run (regulation without feedback(14)), which correlated with reduced

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ADHD symptoms(17). In an fMRI stop-signal task, the rIFC compared to lPHG group showed significantly increased fronto-striatal activation during inhibition and error monitoring after compared to before treatment(17, 18); and functional connectivity increases in lFC-cingulo-striatal networks, but decreases between rIFC with default-mode network areas(19). However, these promising findings were limited by small sample sizes, single-blind design, and no placebo (sham) control condition.

To address these limitations, this largest-to-date, double-blind, sham-controlled RCT in ADHD boys tested the effectiveness and efficacy of 15 runs of active versus sham rIFC fMRI-NF over four 1-hour sessions using a range of clinical, cognitive and fMRI measures. Based on our previous findings, we hypothesised (a) that the active compared to the sham group would show significant improvements in ADHD symptoms at post-treatment covarying baseline; (b) improvements at post-treatment in clinical and cognitive measures and sustained clinical and/or cognitive improvements at 6-months follow-up, with no side or adverse effects; and (c) progressively increased rIFC activation across sessions/runs and a transfer effect, in correlation with reduced ADHD symptoms.

2. METHODS

2.1. Trial design

In this pre-registered (ISRCTN14491589) double-blind, sham-controlled, parallel RCT, participants were block-randomised into an active or sham group with a 1:1 ratio and varying block sizes, stratified by medication status (non-medicated/stable ADHD medication) and by age group (under/over 14y6m). Randomisation was conducted independently by the King's Clinical Trial Unit.

Families and researchers involved in data collection were blind to group allocations. Once a participant was allocated into a treatment arm, one researcher was unblinded to administer the treatment to participants via a shielded computer terminal. This unblinded

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researcher had no direct interaction with the participants/families and was prohibited from sharing the information to other team members. Blinding integrity was examined from the blind participants', caregivers', and researchers' guesses of group allocation at post-treatment.

This trial was approved by the UK National Health Service Health Research Authority, London Bromley Research Ethics Committee (Ref. No. 17/LO/1368), was in accordance with the Declaration of Helsinki 1975 and is reported following the CONSORT guidelines.

2.2. Participants

Eighty-eight boys (10-18-years) participated, meeting the DSM-5 diagnostic ADHD criteria confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia interviews (KSADS;(20)), and with a *t*-score≥60 in the Conners 3P(21) DSM-5 inattention and/or hyperactivity-impulsivity domains. Participants were medication-naïve or on stable ADHD medication at least 2 weeks before baseline until post-treatment assessment. Stimulant users were requested to abstain from taking medication 24 hours before each assessment but could remain on medication throughout the study if preferred. Exclusion criteria were IQ<80(22); co-occurring psychiatric disorders, except oppositional defiant and conduct disorder; neurological conditions, or contraindication to MRI. Parents/participants gave informed consents/assents and received £180 plus travel cost reimbursement.

2.3. Sample size calculation/power analysis

A *priori* power analysis assuming Cohen's *d*=.60 based on the change of ADHD-RS scores from baseline to post-assessment during rIFC fMRI-NF in our proof-of-concept

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study(17) suggested N=45 per group. Five participants were added per group to allow for 10% attrition (17, 24, 25, Supplementary Methods).

2.4. Procedure

Participants were invited for seven visits(Fig 1), including eligibility screening and baseline assessment (visit 1), fMRI-NF interventions (visits 2-5), and post-treatment and 6-month follow-up assessments (visits 6 and 7).

2.5. fMRI-NF

2.5.1. Intervention

Treatment comprised fifteen active or sham fMRI-NF runs over four 1-hour scan sessions, to replicate the successful proof-of-concept study design and maximise run numbers across 4-hour MRI scans. Each run had seven 30-second "Rest" and six 40-second "Self-regulation" blocks. During the Self-regulation blocks, NF was given to participants *via* a video of a rocketeer flying up from ground-level into space (https://osf.io/fz2y7/), projected on a screen. The speed of the rocketeer was determined by the participant's brain activity. Increased/decreased rlFC activation led to upward/downward movement of the rocketeer. Performance scores were based on the percentage of the maximum video length displayed (i.e., 0-10 points for 0-100%)(Fig 1), and were shown at the end of each run. No specific instructions were given, but participants were told that concentrating might help to self-upregulate brain activation. After the last fMRI-NF run of the last session, a transfer run was completed which was identical to the previous runs except without feedback (Supplementary Methods). Participants also completed a fMRI stop-signal task before and after NF training which will be presented elsewhere.

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2.5.2. Sham condition

The sham group underwent identical procedures but received sham NF, i.e., the rocketeer video was simulated using data from the last active participant completing a minimum of 8 fMRI-NF runs (Supplementary Methods).

2.5.3. Acquisition and real-time processing of fMRI-NF data

Imaging data were acquired at the Centre for Neuroimaging Sciences, King's College London, on a GE Discovery MR750 3T scanner (GE Medical Systems, Chicago, USA) with a 12-channel head coil receiver. FMRI-NF scans were T2*-weighted Echo Planar Imaging sequence, interleaved from top to bottom (Supplementary Methods).

Game control was enabled by real-time transfer and analyses of fMRI data, facilitated by a custom fMRI interface and the AFNI software(26) that pre-processed and corrected head motion in real-time. Data were acquired from a region of interest (ROI) in rIFC opercular and triangular parts, co-registered to a structural localiser, the AFNI CA_N27_ML/TT_N template (14,138 voxels in the Talairach space). The fMRI-NF signal was the mean signal of the ROI. Detailed description of the fMRI-NF signal and its formula is presented in the Supplementary Methods.

2.6. Outcomes

Fig 1 shows the study outcome measures and visits. The primary outcome was parent-rated ADHD-rating scale (ADHD-RS)(27) at post-treatment. Secondary outcomes included ADHD-RS at 6-month follow-up, and parent- or participant-rated clinical outcomes, i.e., Conners 3-Parents ADHD-index(21), parent- and participant-rated Affective Reactivity Index (ARI)(28), and participant-rated Mind Excessively Wandering Scale (MEWS)(29) at baseline, post-treatment and follow-up, and parent-rated Weekly Rating of Evening and Morning Behavior-Revised (WREMB-R)(30) and Columbia Impairment Scale (CIS)(31), at baseline and post-treatment. Secondary cognitive outcomes at all three assessments, included

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measures from the adult Maudsley Attention and Response Suppression (MARS(32)) task battery; i.e., motor inhibition, (go/no-go task; probability of inhibition), interference inhibition (Simon task; Simon reaction time (RT) effect), and sustained attention (Continuous Performance Task (CPT); omission and commission errors). Also included were measures of vigilance (Mackworth Clock Vigilance task(33); omission and commission errors); cognitive flexibility (computerised Wisconsin Card Sorting Task; perseverative and non-perseverative errors)(34); working memory (list-sorting task of the NIH Toolbox(35); total score); and composite response prematurity, processing speed and intrasubject response variability from the MARS go/no-go, Simon, and CPT tasks combined (Supplementary Methods). Mood questionnaires(36) assessing the participants' mood before and during MRI scans, motivational state, performance and liking of scans were taken after each scan. Feedback from participants and parents about their experience and effectiveness of fMRI-NF(17), respectively, were taken at post-treatment (Supplementary Methods). Parent-rated safety measures included side-effects questionnaire at baseline and post-treatment(37) and adverse-events questionnaire (adapted from 38) at post-treatment (Supplementary Methods).

2.7. Statistical methods

As pre-specified(39), primary analyses of treatment effectiveness were conducted with intention-to-treat (ITT) involving randomised participants who undertook fMRI scanning. We conducted a series of 2×2 repeated-measures analyses of covariance (rANCOVAs) with outcomes as dependent variables, covarying for their values at baseline, age, and medication status, with Group (active/sham), Time (post-treatment/follow-up), and Group×Time as fixed effects. Equivalent univariate ANCOVAs were used for outcomes measured at baseline and post-treatment (i.e., WREMB-R, CIS, side effects), or at post-treatment only (i.e., adverse effects). Significant Group×Time interactions were explored using simple-effect analyses. The two-tailed rANCOVAs were run using the *Mixed* command

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with restricted maximum likelihood estimator and exchangeable covariance structure using IBM SPSS software 26(Armonk, NY). Data were assumed missing at random. False discovery rate (FDR) multiple comparison corrections were applied per fixed effect for secondary clinical and cognitive domains separately; simple-effect analyses were uncorrected for multiple testing. Secondary ANOVAs assessed changes of scores within groups across timepoints, uncorrected for multiple testing. Treatment efficacy, estimated using complier average causal effect (CACE)(40), and sensitivity analyses exploring impacts of medication changes and of nationally implemented COVID-19 lockdown on follow-up findings were conducted in STATA16 (College Station, TX)(Supplementary Methods). Fisher's exact test (FET) tested the association between treatment group allocation and guesses by researchers, participants and their parents to test blinding effectiveness.

2.7.1. FMRI analyses

Structural MRI images were re-oriented and skull-stripped. All functional images were head-motion corrected and were co-registered to the structural image and a standard template. Data were high-pass filtered (100s) and smoothed with a Gaussian kernel of 5mm full-width-at-half-maximum.

Individual BOLD activations representing the Rest and Self-regulation blocks were contrasted and the resulting images were entered into group analyses (Supplementary Methods).

Group×Session ANCOVAs covaried for age, medication status, and movement. Analyses were at a whole-brain level and with small volume correction region of interest (ROI, with pre-threshold masking), within the same regions used for NF, i.e.,opercular and triangular rIFC, exploring group differences in final *versus* baseline run activation, in linear regression across all runs, and in transfer activation.

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All fMRI analyses used a cluster threshold of $\alpha<0.05$, and a family-wise error-rate correction.

Associations between brain activation and clinical symptoms were analysed within the active fMRI-NF group. For each participant, the average BOLD activation extracted from the significant group difference cluster (i.e., rIFC) was averaged across the last two runs and compared with the baseline to compute an fMRI-NF learning score(15, 41). Pearson's correlations tested for associations between fMRI-NF learning scores and ADHD-RS total score changes from baseline to post-treatment. Similar exploratory correlations were run for secondary measures (ARI, go/no-go inhibition) within the sham group (Supplementary Results).

3. RESULTS

Between January 2, 2018 and March 11, 2020, 122 families completed baseline assessments and 94 (77.0%) were randomised into active or sham groups. Six participants (6.4%) refused scanning and dropped out, leaving 44 participants per group(Fig S1). The trial was discontinued prematurely due to the COVID-19 lockdown. Groups did not significantly differ at baseline(Table S1), except the active versus sham group had more ADHD-combined presentations (X^2[1,N=88])=6.47; p=.011).

3.1. Clinical and cognitive outcomes

Primary outcome. The rANCOVAs showed no significant Group×Time interaction, nor Group effect on ADHD-RS total scores, as primary post-treatment or secondary 6-month follow-up outcomes. Time effect showed significantly increasing ADHD-RS scores from post-treatment to follow-up (F[1,82.7]=8.44; p=.005)(Table 1, Fig 2). Within-group ANOVAs showed significantly reduced scores for both groups, relative to baseline, at post-treatment (ps<.001) and follow-up (ps<.009)(Table S2).

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Secondary outcomes. There were no significant effects on any clinical measures but a significant Group×Time interaction in parent-rated ARI (F[1,83.1]=7.73; p=.028), explained by simple-effects of lower ARI in sham than active fMRI-NF at post-treatment (F[1,136.5]=4.04; p=.046) but not follow-up. Cognitively, there were no significant effects but a Group×Time interaction in go/no-go probability of inhibition (F[1,75.8]=8.78; p=.048); simple-effect analyses indicated lower go/no-go probability of inhibition in the active relative to sham at post-treatment (F[1,142.7]=4.45; p=.037), but not follow-up.

Within-group ANOVAs showed reduction in Conners 3-P ADHD index from baseline to post-treatment and to follow-up for both groups (ps<.033) and in ARI at post-treatment relative to baseline in sham only (p=.018). Reduction of go/no-go inhibition was found from baseline to post-treatment in the sham group only, and from baseline to follow-up in the active group only (ps<.01); and for both groups from baseline to post-treatment *and* to follow-up in CPT omission/commission errors, MCT omission errors and WCST perseverative errors (ps=.001-.027)(Table S2).

Secondary CACE analyses showed similar findings for ADHD-RS and go/no-go probability of inhibition (Table S3); sensitivity analyses revealed no significant effects of changing medication from post-treatment to follow-up or of COVID-19 lockdown (Supplementary Results).

3.2. Neuroimaging outcomes

All 88 participants were included in the final fMRI analyses, but 17% of runs in each group were excluded due to excessive head motion (relative mean displacement>0.9mm(42)). The first fMRI-NF run for each participant was excluded, a common practice since it is often used for familiarising participants with NF training(43), and since there were unusually high wide-spread brain activation patterns in this run (Supplementary Methods).

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3.2.1. Group×Session ANCOVA

fMRI-NF sessions. Whole-brain, but not ROI, analyses, showed significant Group×Session interaction. The sham relative to active group showed higher BOLD activation in Session 3 relative to Session 4 in left thalamus (p=.009, Montreal Neurological Institute [MNI] peak coordinates: [x=-20, y=-26, z=6], cluster size [k]=317 voxels)(Fig 3).

Group effect was significant across sessions. The active relative to sham group had greater whole-brain activation in rIFC, right dorsomedial and left middle frontal gyri, right middle and superior temporal gyri, bilateral middle occipital gyrus, cerebellum and occipital lobes (Table 2, Fig 3), and higher ROI activation in two rIFC clusters (cluster#1: p<.001, [56, 40, 14], k=337, Brodmann area (BA) 45; cluster#2: p=.032, [42, 10, 36], k=29, BA44). Conversely, sham relative to active showed higher whole-brain activation in right middle/posterior cingulate/precuneus (Table 2, Fig 3), and higher ROI activation in ventral rIFC (p=.040; [40, 28, 4]; k=22, BA47). See within session group differences in Supplementary Results.

Baseline and final fMRI-NF run. Between-group differences were non-significant for the final *versus* baseline run contrast, or *vice versa*, at whole-brain or at ROI level.

The active group had increased activation in the final run relative to baseline in precuneus (Table 2, Fig 3), and decreased whole-brain activation in right thalamus/putamen, premotor cortex, bilateral insula, and in the rIFC ROI (Table 2, Fig 3). The sham group had significantly reduced activation in rIFC in the final run relative to baseline at both whole-brain and ROI levels(Table 2, Fig 3). The reverse contrast revealed no significant findings.

Transfer run. Twenty-nine participants (n_{ACTIVE}=10; n_{SHAM}=19) were excluded from analysis because of motion. Only the sham group showed significant activation increase in left supramarginal gyrus (p=.046, [-58, -26, 24], k=227). Neither between- nor within-group differences were significant at ROI level.

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Linear regression. No significant between- or within-group effects were found in linear increase of activation across the 15 runs at whole-brain or ROI levels.

3.2.2. Correlation between outcomes and rIFC activation

No significant correlation was found between rIFC activation changes (final *vs*. baseline run) and changes (post-treatment *vs.* baseline) of ADHD-RS total score (Pearson's r=.001, p=.99; two-tailed, n=41(see supplement for other correlations).

3.2.3. Influences of covariates

Among the covariates (i.e., medication, age, and relative mean displacement of head motion), motion was most strongly correlated with whole-brain activation, and relative mean displacement with rIFC ROI activation that differed between groups (r=.59, p<.0001; triangular part: r=.61, p<.0001; opercular part: r=.64, p<.0001).

3.3. Side effects and adverse effects

Side effects did not differ between groups at post-treatment (F[1,81]=.22; p=.64). Adverse events i.e., anxiety/worry (14%), and distractibility (20.9%), were higher, but not significantly, in sham than active (2.3% and 4.7%, respectively; F[1,82]=3.75; p=.06). RIFC activation neither correlated with anxiety/worry (Spearman's ρ=-1.7, p=.28, two-tailed) nor distractibility(ρ=-1.4, p=.40, two-tailed) in the sham group exploratory analyses.

3.4. Blinding integrity

Actual group allocation corresponded with the researchers' (p=.018, FET; two-tailed), but not with the participants'(p=.55) or parent's guesses (p=.51, FET; two-tailed).

4. Discussion

In the largest double-blind sham-controlled RCT of fMRI-NF of rIFC versus sham in children with ADHD to date, we found, contrary to the hypothesis, no improvement in ADHD-

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RS total scores or other clinical and cognitive measures. Instead, relative to active, the sham group showed reduced irritable mood and improved motor inhibition at post-treatment only, the latter of which could be a training effect that was unobserved in the active group. No significant side or adverse effects were found. At the fMRI level, the active relative to sham group, showed overall increased activation in rIFC (alongside other dorsomedial frontal and temporo-occipito-cerebellar self-regulation regions) across all sessions. However, there was neither *progressively increasing* upregulation across sessions/runs, nor correlations between changes in rIFC activation and ADHD-RS, nor transfer of learning, indicating no progressive training effects. The findings do not suggest fMRI-NF of rIFC as an effective treatment for ADHD.

The absence of clinical or cognitive effects of active versus sham fMRI-NF of rIFC extends findings of our proof-of-concept trial of no superior clinical or cognitive effects of rIFC fMRI-NF compared to an active (i.e., parahippocampal) fMRI-NF control condition(19). Like in the previous trial, both groups improved in clinical and most cognitive measures. In the previous trial, such improvements could be attributed to region-nonspecific brain self-regulation effects in both groups. Such self-regulation was not expected for sham treatment but recent evidence suggests that attempts to self-regulate and concentrate on stimuli during sham NF could lead to activation in self-control regions(44). In our study, such focus and self-regulation attempts likely explain the overall increased activation in the sham group in rIFC self-control and in posterior parietal visual spatial attention areas, which might have exerted unintended clinical/cognitive effects and diminished group differences. Further, the parahippocampal control condition in the previous study(17) may have been a greater contrast, leading to more positive findings. Thus, our findings contribute to the ongoing debate of whether sham fMRI-NF is the most appropriate control for NF studies (as opposed to alternative region, mental rehearsal, or bidirectional NF controls)(15, 45, 46). They also raise the question whether regions *not* involved in self-control and feedback monitoring might be better targets for sham-controlled fMRI-NF.

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Also unlike the previous trial(17), there was neither *progressive* linear upregulation of rIFC activation across runs/sessions nor correlation between rIFC activation changes with ADHD symptom improvements, despite overall increase of rIFC activation across session in active versus sham. Therefore, the differential rIFC engagement between groups alone might have been insufficient, in the absence of progressive training effects, to produce clinical or cognitive benefits. While such findings are not encouraging, several factors could have mitigated effects. Most participants (~65%) were medicated, which could mask potential NF clinical or cognitive effects, or limit potential rIFC upregulation effects, given that stimulants already increase activation in this region(4, 5, 7). Replication in a medication-naïve cohort would clarify this. Further, our cohort was relatively younger than in the proof-of-concept study, and the more severe ADHD symptoms typical of younger subjects could hamper NF learning(47).

The parallel improvement of ADHD symptoms and other clinical/cognitive measures in both groups echoes similar observations from other neurotherapies (e.g., EEG-NF, brain stimulation)(16), and could reflect non-specific psychosocial or placebo effects of neurotechnology-based intervention(48).

Motion had a significant effect on NF-related brain activation, raising queries on suitability of NF for patient groups with high motion artefacts such as ADHD.

The use of a rigorous double-blind sham-control RCT design with a prespecified analysis plan(39) constitutes a substantial methodological advance on previous fMRI-NF ADHD trials(17, 49). However, there were limitations. The inclusion of boys and parent-reports only, limits finding generalisability for other population and contexts. The inclusion of mostly medicated participants could have masked fMRI-NF effects. The study could have been underpowered for detecting smaller effect sizes. Despite randomisation, there were significant differences in ADHD presentation between sham and active groups, albeit on interview assessments only and not on other clinical ADHD measures (i.e., ADHD-RS and

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Conners 3-P). Finally, the significant convergence between treatment condition and guesses from researchers might indicate compromised blinding but this is unlikely to have influenced outcomes given maintained blinding integrity in participants and parents.

In conclusion, this largest double-blind sham-controlled RCT of fMRI-NF in ADHD failed to provide evidence that rIFC fMRI-NF is more effective than sham in improving clinical symptoms or cognition in ADHD boys. Future studies should investigate whether fMRI-NF of alternative ROIs/networks implicated in ADHD may be more effective in improving clinical and cognitive problems. Optimal protocols for fMRI-NF in ADHD including choice of target region, number of runs/sessions, neurofeedback stimuli and appropriate control conditions, medication or potential brain saturation effects should be systematically tested, perhaps with the use of neuroadaptive Bayesian optimisation methods(50). In addition, identification of ADHD subgroups/individuals through normative modelling of multivariate brain activation or functional connectivity patterns(51) could potentially provide better NF targets(52,53).

5. Previous presentation

The findings of this trial have not been presented elsewhere.

6. Disclosures

Katya Rubia has received a grant from Takeda pharmaceuticals for another project and speaker's bureau from Lundbeck and Supernus which were paid to KCL and used for research. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Fig 1. Schematic representation of the RCT

Abbreviations. K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; SCQ = Social Communication Questionnaire; WASI-II = Wechsler Abbreviated Scale of Intelligence 2nd Ed.; Conners 3-P = Conners 3rd Edition - Parent; ADHD-RS = Attention Deficit Hyperactivity Disorder-Rating Scale; WREMB-R = Weekly Rating of Evening and Morning Behavior-Revised; CIS = Columbia Impairment Scale; ARI = Affective Reactivity Index; MEWS = Mind Excessively Wandering Scale; MARS = Maudsley Attention and Response Suppression task battery; CPT = continuous performance task; WCST = Wisconsin card sorting task; WM = working memory. Each fMRI-NF run contains seven Rest (R, 30 seconds) blocks presented alternatingly with six Self-regulation (S, 40 seconds) blocks. *ADHD-RS total score, measured at baseline and post-treatment assessments, is the primary outcome for the study.

Fig 2. Primary outcomes and outcomes with significant effects of group at post-treatment

Panels A-C(i) show post-treatment and follow-up data for (A) ADHD-RS, (B) affective reactivity index, and (C) go/no-go probability of inhibition, covarying for their baseline values, medication status, and age; while panels A-C(ii) show the unadjusted mean values of these outcome measures at baseline, post-treatment and the 6-month follow-up. Error bars indicate 95% confidence intervals. Indicated on the panels are the significant effects of [a] Time, the simple effects of [b] Group at post-treatment, the effects of Time between [c] baseline and post-treatment and between [d] baseline and the follow-up within each treatment group, the simple effect of [e] Time between baseline and post-treatment within the sham group, and the simple effect of [f] Time between baseline and the follow-up within the active group. *p<.05, **p<.01, ***p<.001.

Fig 3. Brain activation findings.

Axial slices showing brain activation at false positive error-corrected cluster-level of $p < 0.05$. (A) Group×Session interaction effect, (B) Main effect of Group, at the whole-brain and ROI level; from the ANOVA analyses of Group×Session and Group effects. Clusters in red correspond to Active versus Sham contrasts, and clusters in blue correspond to Sham versus Active. (C) Axial slices showing brain activation from the Baseline and Final fMRI-NF Runs within-group analyses: within the Active group (left) and within the Sham group (right). Clusters in red correspond to Baseline run (i.e., Run 2) versus Final run (i.e., run 11) contrasts, and clusters in blue correspond to Final versus Baseline run. The right side of the image corresponds to the right side of the brain. MNI z-coordinates are shown with z-statistic images overlaid.

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Table 1. Clinical and neurocognitive outcome estimated marginal means at post-treatment and follow-up, fixed-effect, and simple-effect statistics

Measures	EMM Post-treatment				EMM Follow-up				Fixed effects						Simple effects			
	Sham		Active		Sham		Active		Group		Time		Group × Time		Post-treatment		Follow-up	
	M	*(SE)*	*M*	*(SE)*	*M*	*(SE)*	*M*	*(SE)*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
A. Primary clinical outcome																		
ADHD RS Total (P)	28.7	1.48	30.6	1.48	32.7	1.53	33.2	1.48	0.48	.49	8.44	**.005***	0.37	.55	0.84	.36	0.06	.80
B. Secondary clinical outcomes																		
Conners 3P ADHD Index (P)	11.7	0.76	11.8	0.76	12.0	0.78	12.1	0.77	0.01	.93	0.20	.66	0.001	.98	0.004	.95	0.008	.93
ARI (P)	0.63	0.07	0.83	0.07	0.91	0.07	0.81	0.07	0.34	.56	6.50	.013	7.73	**.007**[a]*	4.04	**.046***	1.03	.31
ARI (C)	0.63	0.06	0.63	0.06	0.63	0.06	0.63	0.06	0.03	.86	0.28	.60	0.031	.86	0.063	.80	<.001	.99
MEWS (C)	16.4	1.01	15.2	1.04	15.2	1.04	13.5	1.02	1.78	.19	2.32	.13	0.06	.82	0.75	.39	1.32	.25
CIS (P)	18.4	1.19	21.0	1.19	--	--	--	--	2.42	.12	--	--	--	--	--	--	--	--
WREMB-R (P)	17.2	0.95	19.8	0.95	--	--	--	--	3.66	.06	--	--	--	--	--	--	--	--
Side effects (P)	12.5	1.08	12.5	1.08	--	--	--	--	0.22	.64	--	--	--	--	--	--	--	--
Adverse effects (P)	16.7	0.56	15.2	0.56	--	--	--	--	3.75	.06	--	--	--	--	--	--	--	--
C. Secondary cognitive outcomes																		
Go/no-go probability of inhibition	55.0	2.15	48.5	2.01	50.6	2.1	54.5	2.03	0.12	.73	0.58	.45	8.78	**.004**[b]*	4.45	**.037***	2.12	.15
Simon incompatibility RT effect	61.1	3.91	62.1	3.66	52.0	3.82	59.6	3.7	1.79	.19	1.89	.17	1.12	.29	0.24	.63	2.76	.10
CPT omission errors	9.46	1.24	10.6	1.16	10.6	1.16	12.1	1.17	0.95	.33	1.76	.19	0.03	.87	0.82	.37	0.43	.51
CPT commission errors	1.37	0.30	1.53	0.28	1.42	0.29	1.76	0.28	0.09	.76	1.96	.17	0.67	.42	0.03	.86	0.46	.50
MCT omission errors	29.5	2.19	32.1	2.07	32.1	2.15	31.2	2.09	0.11	.74	0.28	.60	1.29	.26	0.10	.76	0.72	.40
MCT commission errors	5.99	0.70	5.13	0.66	4.63	0.69	4.36	0.67	0.34	.56	0.10	.76	0.001	.97	0.28	.60	0.22	.64
WCST perseverative errors	6.22	0.54	7.7	0.51	6.07	0.53	7.23	0.52	0.27	.61	8.93	**.004**[c]*	0.17	.68	0.03	.86	0.42	.52
WCST non-perseverative errors	7.14	0.81	9.64	0.78	7.72	0.80	8.63	0.78	0.02	.89	8.81	**.004**[d]*	0.34	.56	0.05	.83	0.18	.67
Working memory total score	28.2	1.94	26.5	1.83	30.5	1.91	27.5	1.85	0.56	.46	2.47	.12	0.18	.67	0.56	.46	2.47	.12
Composite response prematurity	2.63	0.35	3.5	0.33	2.97	0.34	2.7	0.33	1.34	.25	2.69	.11	5.58	.02	5.65	**.019***	0.18	.68
Composite processing speed	375.0	4.88	382.6	4.63	362.5	4.81	381.5	4.68	1.16	.29	16.9	**<.001**[e]*	4.25	.04	0.002	.97	3.60	.06

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Composite response variability	0.28	0.01	0.29	0.01	0.28	0.01	0.28	0.01	0.49	.48	1.35	.25	3.82	.05	3.00	.09	0.27	.60

Abbreviations. EMM = estimated marginal mean; M = mean; SE = standard error; ADHD-RS = ADHD Rating Scale; ARI = Affective Reactivity Index, MEWS=Mind Excessively Wandering Scale, CIS = Columbia Impairment Scale; WREMB-R = Weekly Rating of Evening and Morning Behavior-Revised; (P/C) = (Parent/Children); CPT=continuous performance task; MCT=Mackworth clock vigilance task; WCST=Wisconsin card sorting task. All *p*-values are presented uncorrected for multiple comparison. False discovery rate correction for multiple comparison on the fixed effects yielded p_{FDR} = [a].028; [b].048; [c].024; [d].016; [e].012. Simple-effect *p*-values were uncorrected.

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Table 2: Whole-brain analysis results. A. Group effect from the Group×Session ANCOVA. B. Comparing baseline and final fMRI-NF runs brain activation differences within-groups

Cluster #	Region(s)	Side	BA	Size (voxel)	*z*	*p*	Peak MNI Coordinates		
							x	y	z
	A. Group effect								
	Active > Sham								
1	Middle/superior temporal gyrus	R	21/37/22	891	5.93	.00001	66	-54	4
2	Middle/inferior occipital gyrus/ middle temporal gyrus	R	19/37	572	6.81	.0004	42	-88	4
3	Middle frontal gyrus/ precentral gyrus	L	46/44/9/6	413	5.25	.003	-32	16	38
4	Inferior frontal gyrus	R	45/44	375	5.3	.004	56	40	14
5	Cerebellum/lingual gyrus/inferior occipital gyrus/fusiform gyrus	L	19/18	363	5.82	.005	-42	-78	-20
6	Middle occipital gyrus	L	37/39	347	5.7	.006	-44	-70	10
7	Dorsomedial frontal gyrus	R	8/9/32	302	5.08	.011	6	36	52
8	Cerebellum/lingual gyrus	R	30	280	4.96	.016	12	-38	-10
9	Middle temporal gyrus	R	21	276	5.17	.017	70	-34	-2
	Sham > Active								
1	Middle/posterior cingulate cortex/precuneus	R	23	206	5.18	.034	14	-32	40
	B. Baseline and final run								
	(i) Active group								
	Baseline > Final run								
1	Thalamus/putamen	R	-	430	4.48	.002	14	0	6
2	Precentral gyrus	R	6/44	288	4.25	.012	48	4	32
3	Insula	L	48/47	260	4.38	.019	-36	16	-4
4	Insula	R	47	260	4.08	.019	34	20	-12
	Final > Baseline run								
1	Precuneus	L	7/23	729	4.74	.00001	-6	-54	36
	(ii) Sham group								
	Baseline > Final run								
1	Inferior frontal gyrus	R	44/45	426	4.24	.002	58	18	18

Abbreviation. L/R=left/right; BA=Brodmann Area

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2 weeks | 1 week | 6 months

Visit 1: Baseline

Screening measures:
- K-SADS
- SCQ
- WASI-II
- Conners 3-P

Parent-rated
- ADHD-RS*
- Conners 3-P
- WREMB-R
- CIS
- ARI
- Side Effects
- Medication Status

Participant-rated
- ARI
- MEWS

Cognitive tasks
- MARS Go/No-go
- MARS CPT
- MARS SIMON
- Vigilance task
- WCST
- WM task

Visit 2: Scan A

- Structural scans
- fMRI Stop-signal task
- 2 fMRI-NF runs
- Mood Questionnaire
- Medication Status

Visit 3 & Visit 4: Scan B & C

- 5 fMRI-NF runs
- Mood Questionnaire
- Medication Status

Visit 5: Scan D

- 3 fMRI-NF runs
- Transfer run
- fMRI Stop-signal task
- Mood Questionnaire
- Medication Status

R S R S R S R S R S R S R

Structural scans: ~7 min
fMRI-NF run: 7.5 min
fMRI Stop task: ~6 min

Visit 6: Post-treatment

Parent-rated
- ADHD-RS*
- Conners 3-P
- WREMB-R
- CIS
- ARI
- Side Effects
- Medication Status
- Adverse Effects
- Neurofeedback Effectiveness Questionnaire
- Blindness Questionnaire

Participant-rated
- ARI
- MEWS
- Neurofeedback Questionnaire
- Blindness Questionnaire

Cognitive tasks
- MARS Go/No-go
- MARS CPT
- MARS SIMON
- Vigilance task
- WCST
- WM task

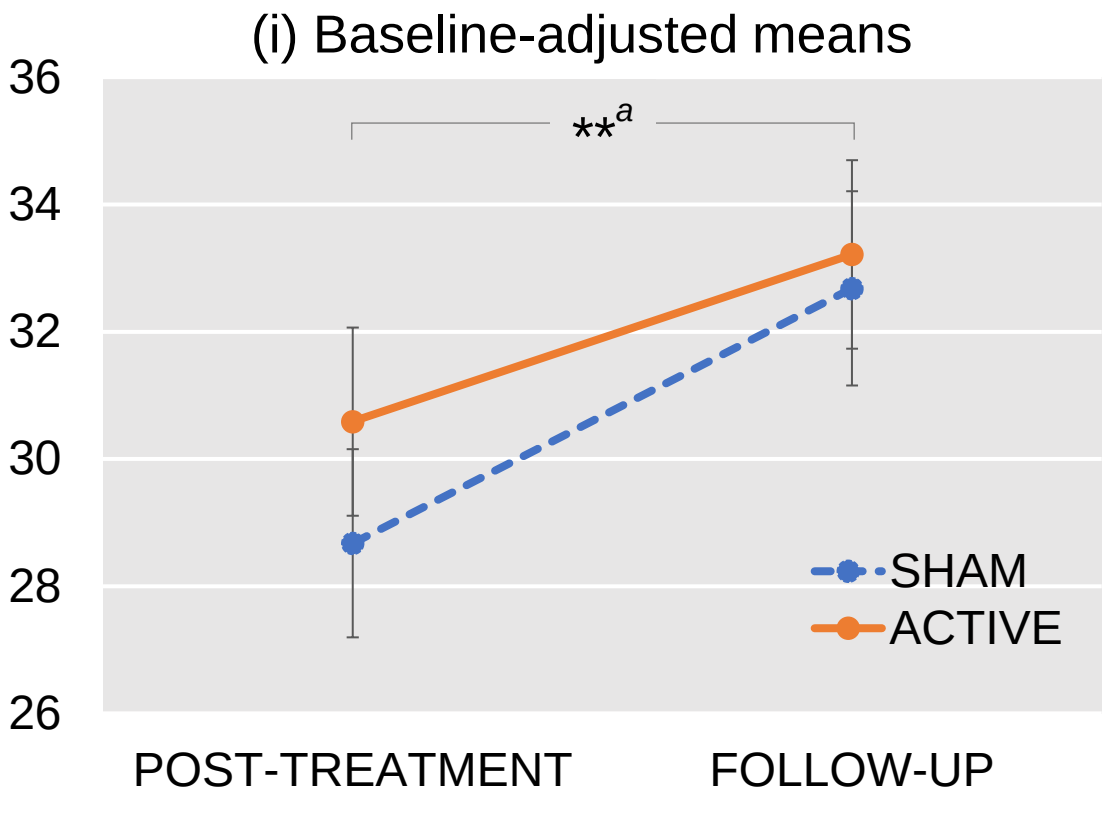
Visit 7: Follow-up

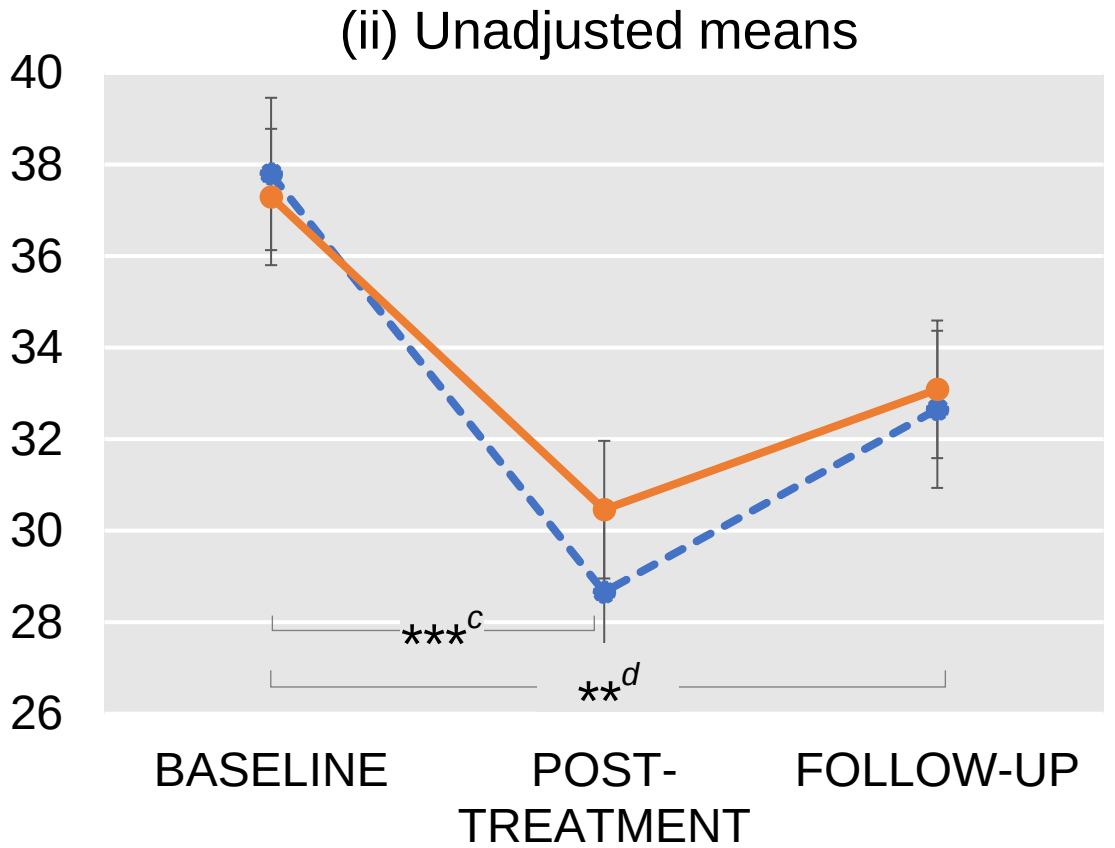
Parent-rated
- ADHD-RS*
- Conners 3-P
- ARI
- Medication Status

Participant-rated
- ARI
- MEWS

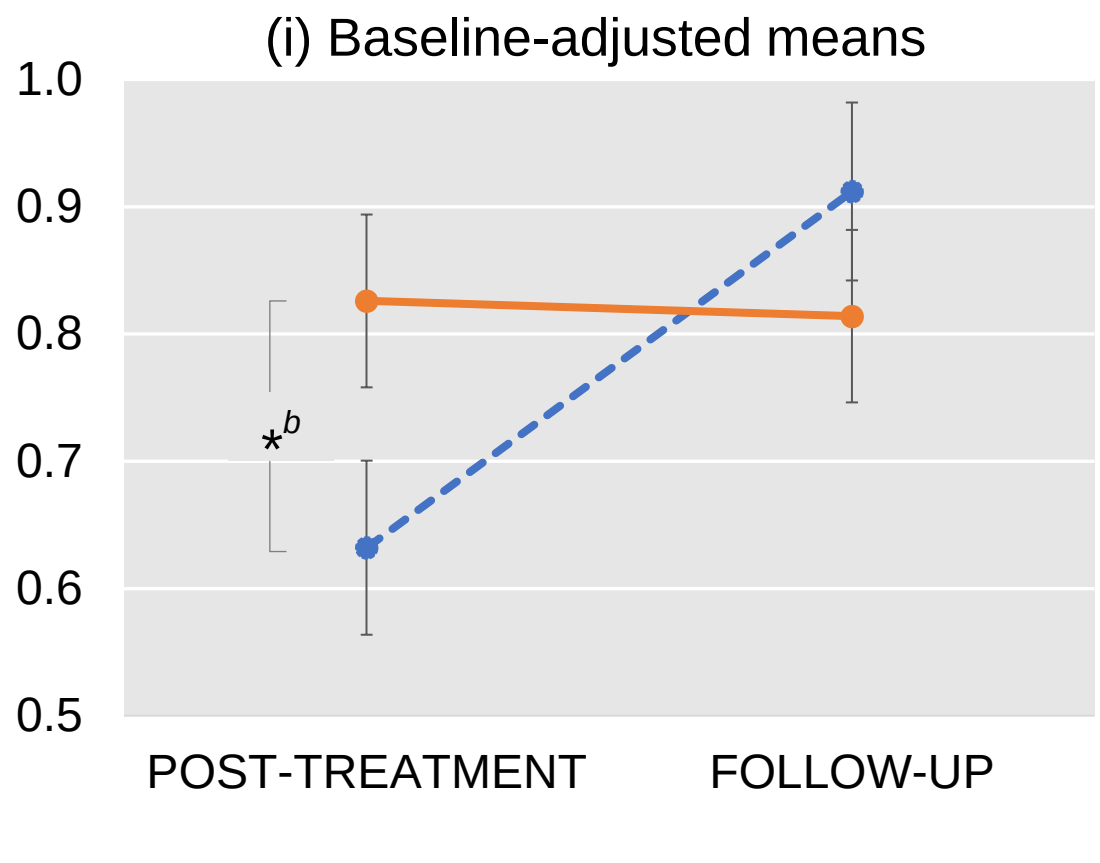
Cognitive tasks
- MARS Go/No-go
- MARS CPT
- MARS SIMON
- Vigilance task
- WCST
- WM task

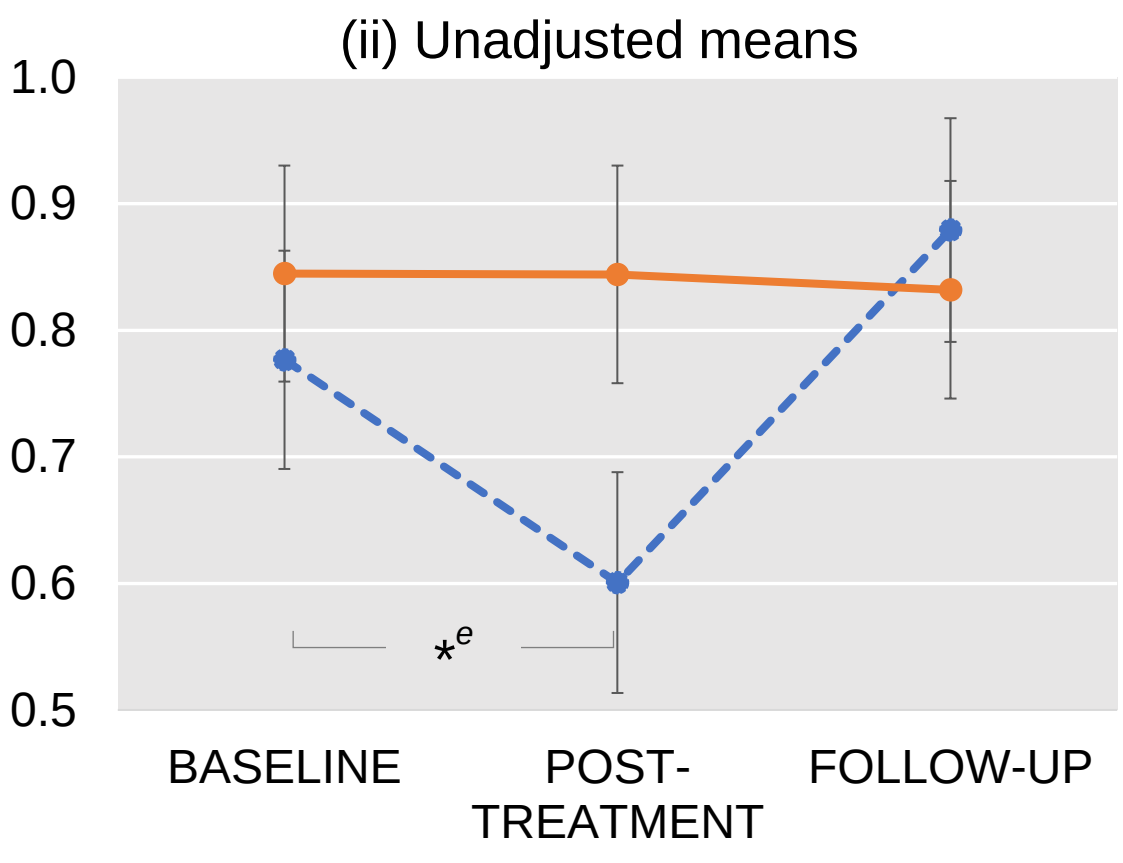
A. ADHD-rating scale total score



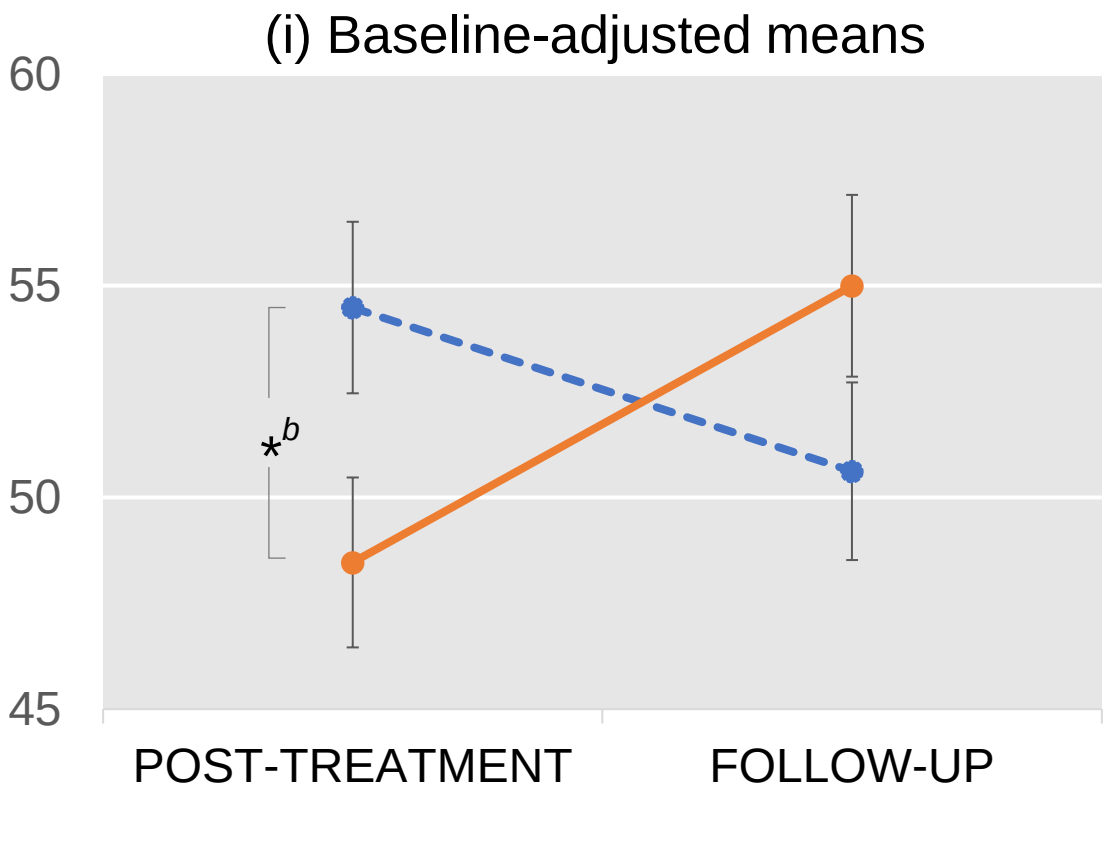


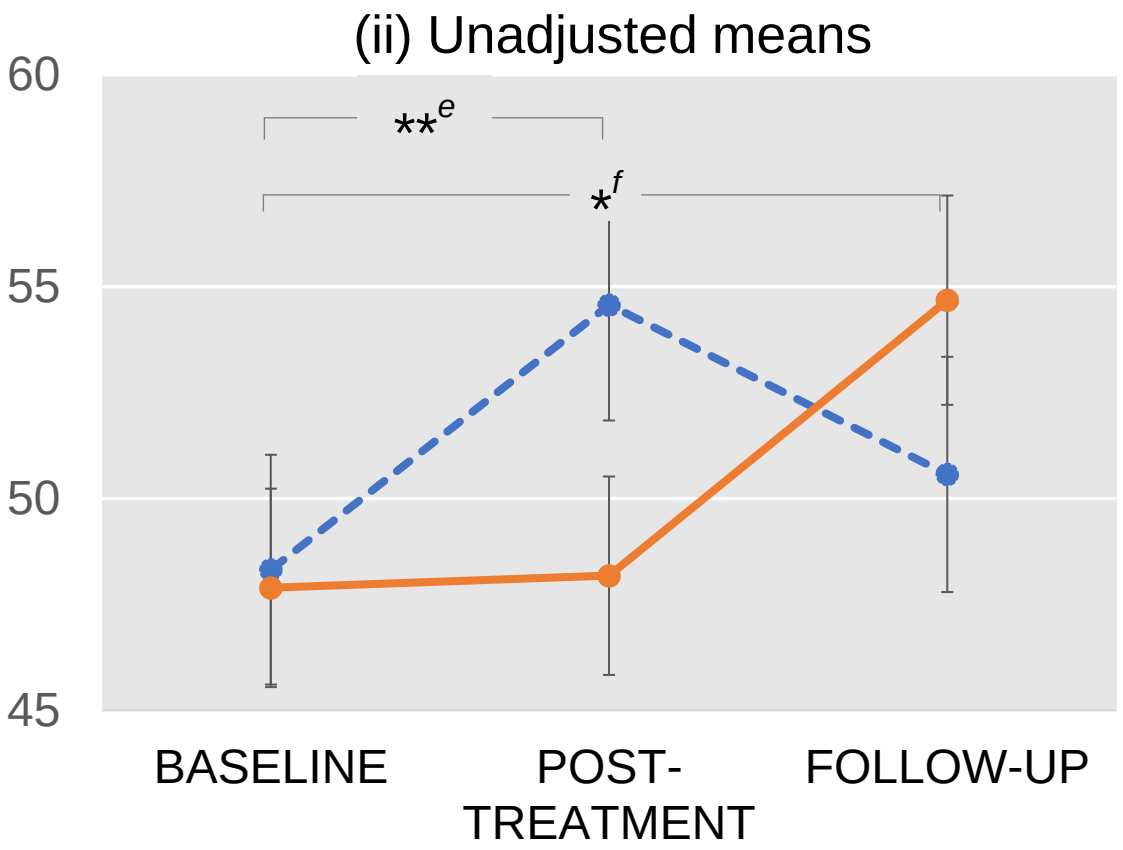
B. Parent-rated affective reactivity index



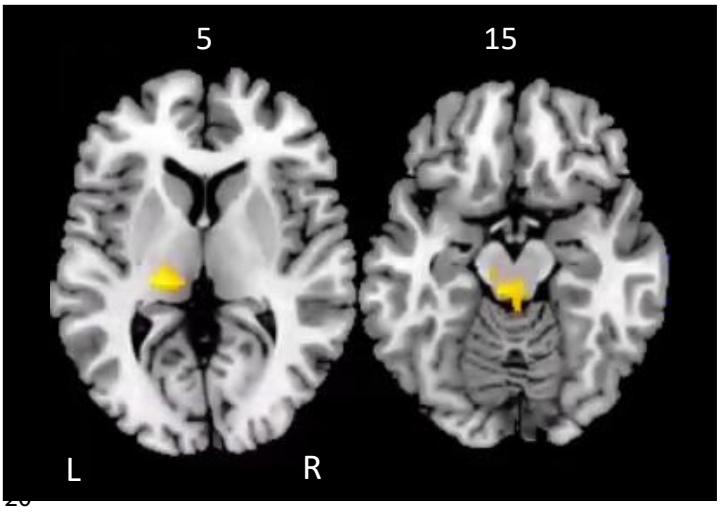


C. Go/no-go probability of inhibition





A. Group x Session



Active > Sham

0 2 4 6

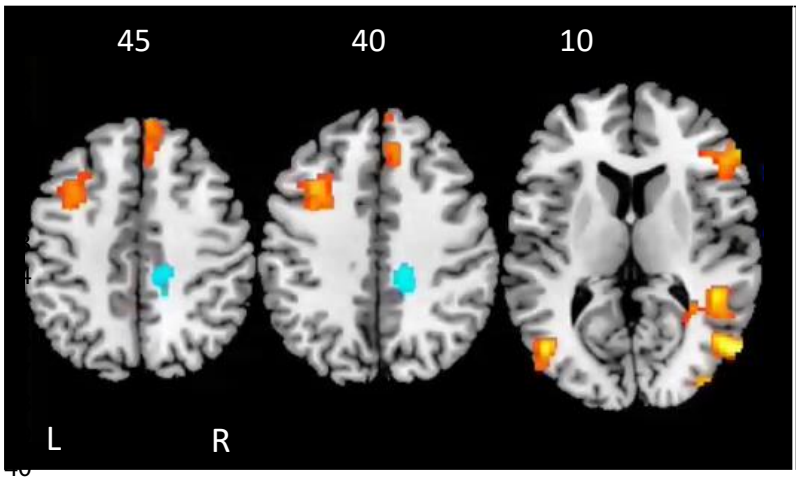
Sham > Active

0 1 2 3 4 5

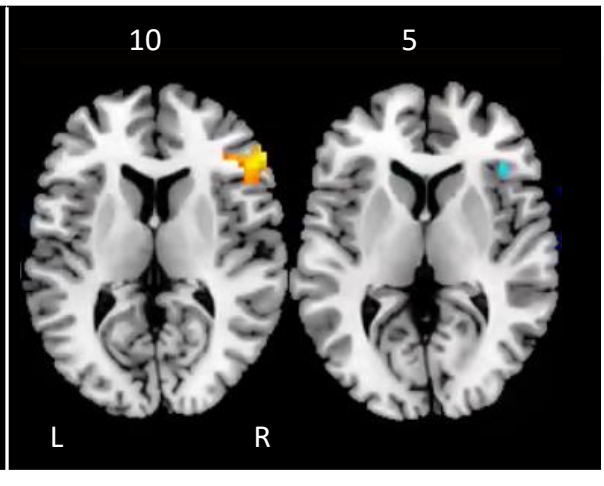
Z-score

B. Group effect

Whole Brain



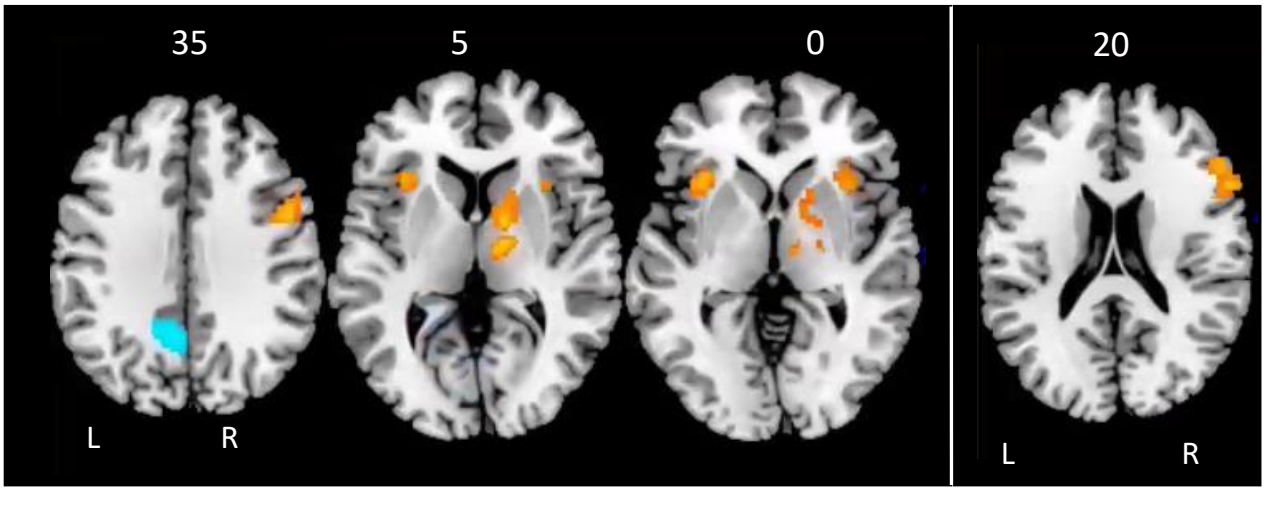
ROI



C. Baseline and Final run (Within-Group)

Active

Sham



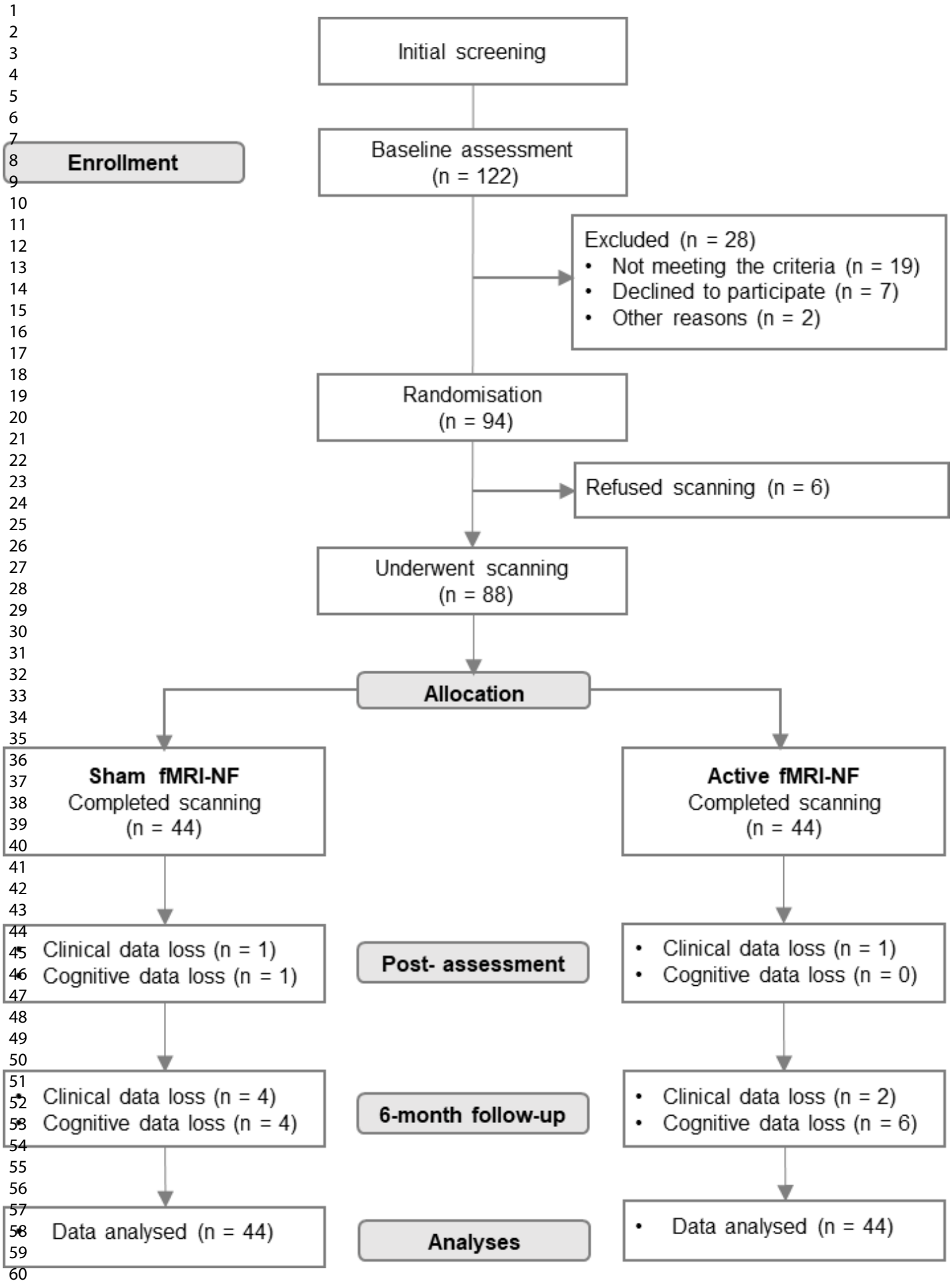
Baseline run > Final run

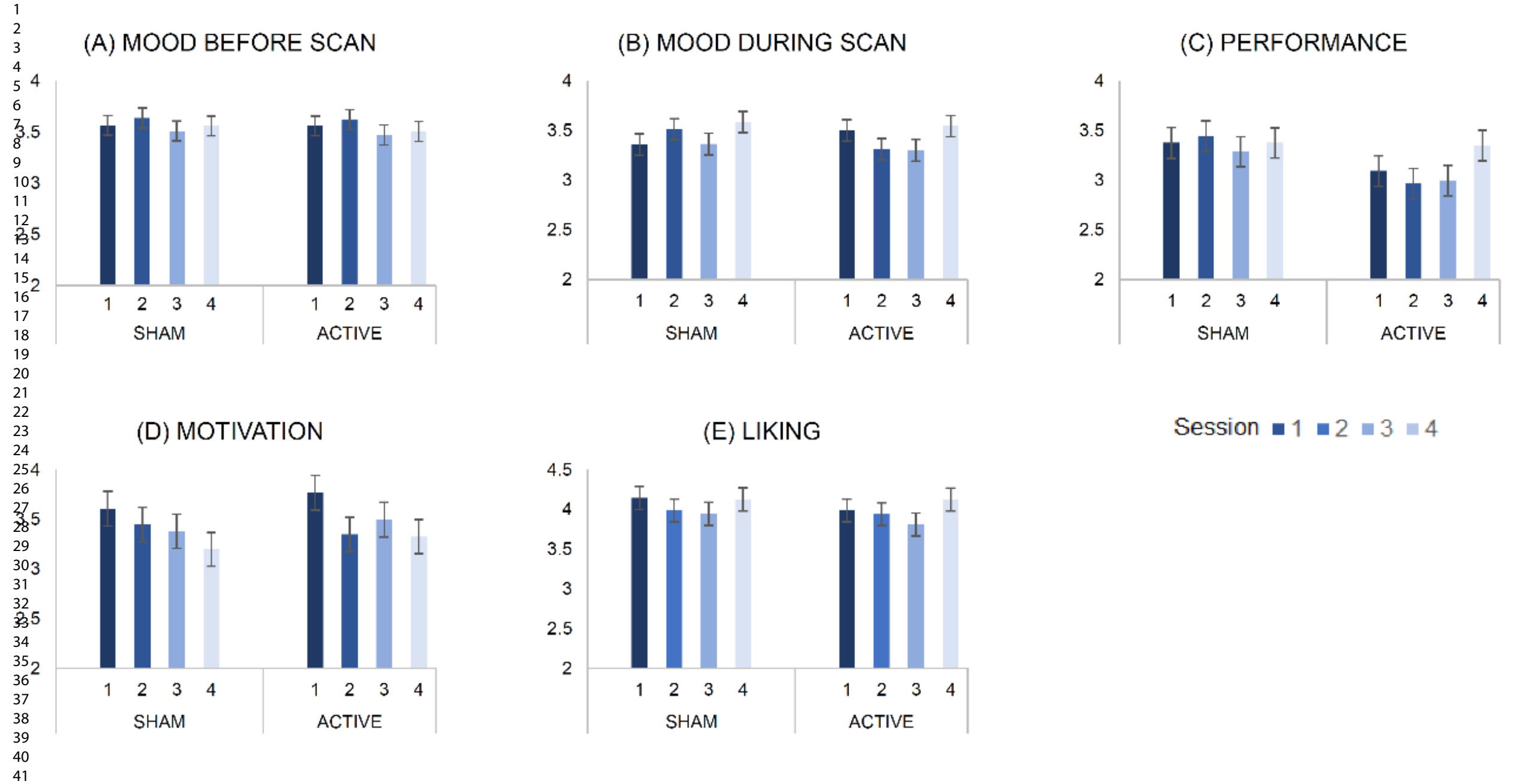
0 2 4 6

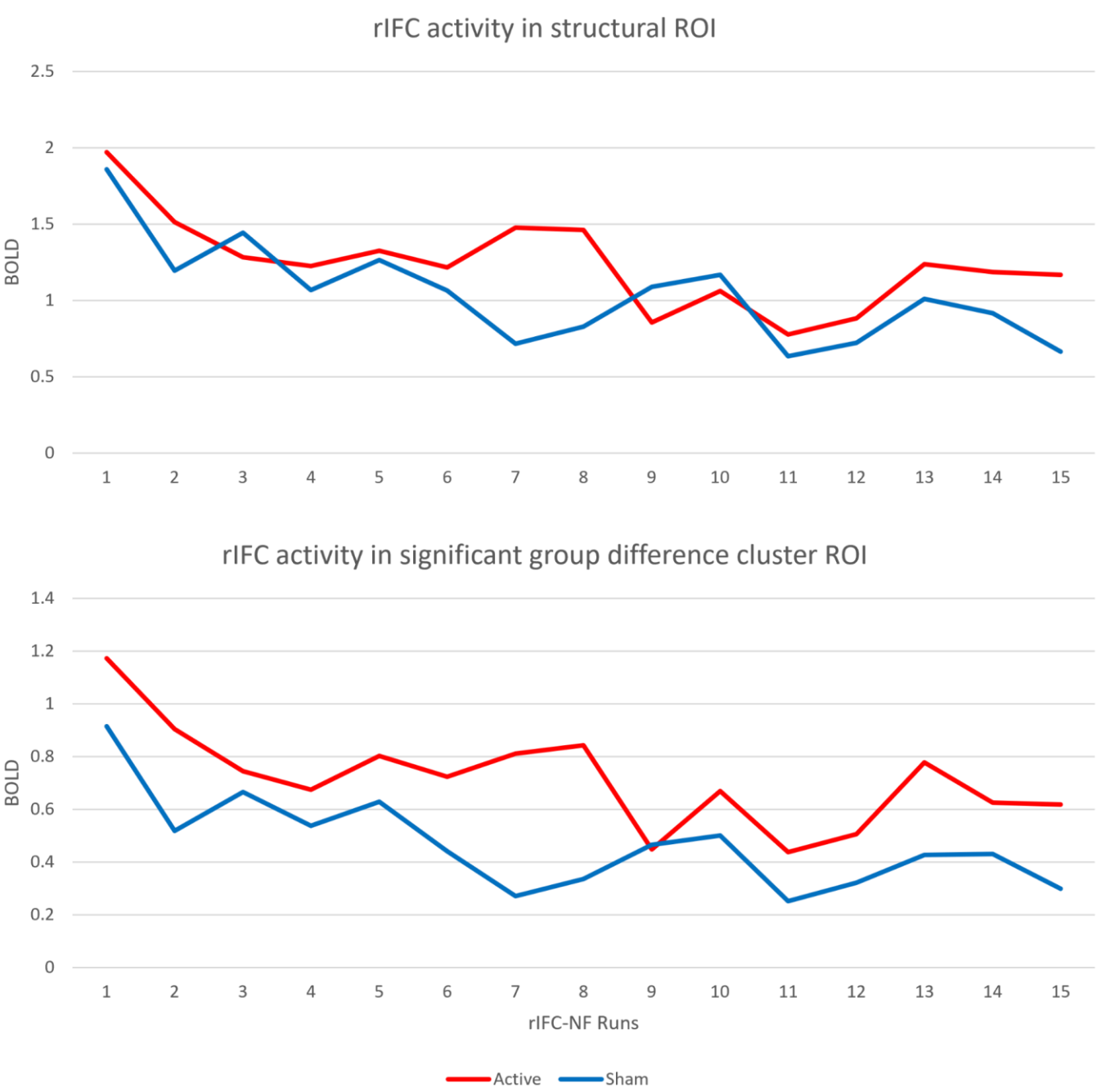
Final run > Baseline run

0 1 2 3 4 5

Z-score


Initial screening
Enrollment
Baseline assessment
(n = 122)
Excluded (n = 28)
• Not meeting the criteria (n = 19)
• Declined to participate (n = 7)
• Other reasons (n = 2)
Randomisation
(n = 94)
Refused scanning (n = 6)
Underwent scanning
(n = 88)
Allocation
Sham fMRI-NF
Completed scanning
(n = 44)
Active fMRI-NF
Completed scanning
(n = 44)
Clinical data loss (n = 1)
Cognitive data loss (n = 1)
Post- assessment
• Clinical data loss (n = 1)
• Cognitive data loss (n = 0)
Clinical data loss (n = 4)
Cognitive data loss (n = 4)
6-month follow-up
• Clinical data loss (n = 2)
• Cognitive data loss (n = 6)
Data analysed (n = 44)
Analyses
• Data analysed (n = 44)


(A) MOOD BEFORE SCAN
(B) MOOD DURING SCAN
(C) PERFORMANCE
(D) MOTIVATION
(E) LIKING
SHAM
ACTIVE
Session 1 2 3 4


rIFC activity in structural ROI
BOLD
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
rIFC activity in significant group difference cluster ROI
BOLD
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
rIFC-NF Runs
Active
Sham