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Personalized at-home neurofeedback compared to long-acting methylphenidate in children with ADHD: NEWROFEED, a European randomized noninferiority trial

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Background: Neurofeedback is considered a promising intervention for the treatment of attention-deficit hyperactivity disorder (ADHD). NEWROFEED is a prospective, multicentre, randomized (3:2), reference drug-controlled trial in children with ADHD aged between 7 and 13 years. The main objective of NEWROFEED was to demonstrate the noninferiority of personalized at-home neurofeedback (NF) training versus methylphenidate in the treatment of children with ADHD. **Methods:** The NF group (n = 111) underwent eight visits and two treatment phases of 16 to 20 at-home sessions with down-training of the theta/beta ratio (TBR) for children with high TBR and enhancing the sensorimotor rhythm (SMR) for the others. The control group (n = 67) received optimally titrated long-acting methylphenidate. The primary endpoint was the change between baseline and endpoint in the Clinician ADHD-RS-IV total score in the per-protocol population (90 NF/59 controls). Trial registration: US National Institute of Health, ClinicalTrials.gov #NCT02778360. **Results:** Our study failed to demonstrate noninferiority of NF versus methylphenidate (mean between-group difference 8.09 90% CI [8.09; 10.56]). However, both treatment groups showed significant pre–post improvements in core ADHD symptoms and in a broader range of problems. Reduction in the Clinician ADHD-RS-IV total score between baseline and final visit (D90) was 26.7% (SMD = 0.89) in the NF and 46.9% (SMD = 2.03) in the control group. NF effects increased whereas those of methylphenidate were stable between intermediate and final visit. **Conclusions:** Based on clinicians' reports, the effects of at-home NF were inferior to those of methylphenidate as a stand-alone treatment. **Keywords:** Attention-deficit hyperactivity disorder; neurofeedback; methylphenidate; randomized clinical trial.

Background

Attention-deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by developmentally inappropriate levels of either inattention, hyperactivity/impulsivity or a combination of both. Treatments of ADHD include parent programmes, school-based interventions and psychostimulant and nonstimulant medications (Daley et al., 2018; National Institute for Health & Care Excellence [NICE], 2018).

As ADHD impairs self-regulation of behaviour and attention, targeting cognitive control and its neurobiological substrates is a promising field of intervention. NF is a computer-based training where brain activity is measured with electroencephalography (EEG) while continuous or discrete rewards reinforce neural changes. Standard NF protocols in ADHD aim at decreasing the theta/beta ratio (TBR) or at increasing the sensorimotor rhythm (SMR; 12–15 Hz; Arns, Heinrich, & Strehl, 2014).

Conflict of interest statement: See Acknowledgements for full disclosures.

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The efficacy of NF for the treatment of ADHD is a current focus of research and debate. Previous studies used a variety of NF protocols in small samples, and although meta-analyses show significant clinical effects on parents' assessments of ADHD symptoms, they also report a lack of robust effects for 'probably blinded' measures (Cortese et al., 2016; Sonuga-Barke et al., 2013). Another factor possibly diluting NF effects lies in the heterogeneity of the neurocognitive profiles associated with ADHD. For example, elevated theta/beta ratios seem to occur only in 26–38% of subjects with ADHD (Bussalb, Collin, et al., 2019). Accessibility of NF is another obstacle, as standard protocols require extensive training and high-quality equipment (Bussalb, Congedo, et al., 2019). Finally, the specificity of NF treatment effects is questionable since the relationship between clinical efficacy and NF learning (e.g. the subjects' ability to modify the relevant EEG parameter) has not been consistently investigated (Zuberer, Minder, Brandeis, & Drechsler, 2018) and is not supported by a recent double-blind, placebo-controlled trial of TBR NF (Arnold et al., 2020).

This context provided the rationale for the NEWROFEED study that uses a novel NF class IIa medical device (Mensia Koala™ developed by Mensia Technologies, Chantepie, France) matching the NF protocol to individual EEG characteristics and allowing at-home treatment with online monitoring after a short training phase at the clinic.

The main objective of NEWROFEED was to demonstrate the noninferiority of this personalized NF versus optimally titrated methylphenidate (Medikinet®; MPH) in the treatment of children with ADHD. According to the previous evidence about NF and the well-documented large effect size of MPH, we did not expect to reach superiority. Nevertheless, by improving technical aspects and personalizing the NF protocols, we aimed to show noninferiority.

The primary endpoint was the change from baseline (inclusion visit) to end of treatment (last visit) in the clinician-rated ADHD-RS-IV total score (DuPaul, 1998). We hypothesized that the decrease in the clinician-rated ADHD–RS-IV total score between baseline and end of treatment was not significantly larger in the MPH group compared with the NF group. Secondary exploratory analyses were included to assess treatment effects across informants, type of measures and symptom domains, and explore response over time (D 60 assessments) and differences across centres as well as safety.

Methods

Study design

NEWROFEED is a prospective, multicentre, randomized, reference drug-controlled trial in children with ADHD. Participants were recruited between August 2016 and September 2017 in nine centres across five European countries and randomized in two groups: Neurofeedback training (NF group) and methylphenidate (MPH group) using a 3:2 randomization ratio that maximized exposure to NF without impacting power. The Research Ethics Boards at each of the participating sites approved the study registered in the US National Institute of Health ClinicalTrials.gov under number #NCT02778360 (https://clinicaltrials.gov/ct2/show/NCT02778360). Bioulac et al., (2019) reported details of the NEWROFEED protocol, including personalized NF implementation. Additional information about EEG feature extraction, brain activity variables, artefact correction and data quality are available in the Appendix S1

The 'CRED-nf checklist' (Ros et al., 2020) summarizes individual neurofeedback study design (see Appendix S2).

Study population

The study population included children diagnosed with an inattentive or combined presentation of ADHD, aged between 7 and 13 years. Diagnosis of ADHD was made by a clinician using Kiddie-SADS (K-SADS; Kaufman et al., 1997), a semi-structured interview with the child and his/her parents. Eligible children had already received corrective actions for ADHD (i.e. psychoeducation) and had a wireless Internet connection at home and their parents and themselves gave signed informed consent (or children's assent according to local requirements) after adequate time to reflect on study information (Bioulac et al., 2019). Details about study population and data sets can be found in the Appendix S3.

Randomization and masking

Investigators used an eCRF to collect clinical data. At the end of the inclusion visit, after the investigator confirmed the patient's eligibility and signed the eCRF, the eCRF displayed a randomization number and the corresponding assigned treatment. The allocation sequence was computer-generated with randomization performed with SAS software (v9·4). The investigator, the clinician rating the scales and the parents were unblinded; the clinical research organization, and the team performing the statistical analysis were blinded.

Study interventions

There were eight visits over three months: pre-inclusion visit, inclusion visit (D0), four discovery (NF group) or four titration visits (MPH group), an intermediate visit (D60) and a final visit (D90).

NF group. The Mensia Koala™ uses a medical-grade EEG device with 8 AgCl electrodes (Fpz, Fz, F3, F4, Cz, C3, C4 and Pz). For each participant, the investigator calibrated the device during an initial qEEG session that also identified individualized alpha peak frequency (iAPF) to determine individualized EEG frequency bands. If the participant's theta/beta ratio (TBR) was above 4.5 (Bussalb, Congedo, et al., 2019), the device assigned down-regulation of the TBR, whereas children with lower TBR ratio trained the individualized SMR. A NF training session consisted of five four-minute-long 'active' NF blocks (with real-time feedback) and two two-and-a-half-minute-long 'transfer' blocks (with only intermittent feedback). The investigator did not give any specific instructions to the participant during the sessions.

After initiation at the clinic, the family took the NF device home for a training period. Once they were able to use the device reliably, the first treatment phase of 16 to 20 sessions (4 per week) took place, followed by the mid-assessment visit (D60). The second treatment phase was of similar length and ended with the final assessment visit (D90). Further details about the study protocol, including the reinforcement schedule and content, are available elsewhere (Bioulac et al., 2019).

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MPH group. The MPH group received an open titration period of three weeks and a treatment period. Titration started with 10 mg of extended-release MPH per day. The maximum possible dose was 60 mg/day. The treatment period lasted two months (from Day 28 to Day 90). During this period, the optimal dose had to be maintained.

Study outcomes

Primary outcome. We used the clinician-rated *ADHD Rating Scale-IV* (*ADHD-RS-IV*; DuPaul, 1998; Zhang, Faries, Vowles, & Michelson, 2005). This 18-item scale has one item for each of the DSM-IV ADHD criteria.

Secondary and safety outcomes. Secondary outcomes included the parent- and teacher-rated *ADHD-RS-IV* (DuPaul, 1998; Zhang et al., 2005), the *Behavior Rating Inventory Executive Function* (*BRIEF;* Mahone et al., 2002), the *Strengths and Difficulties Questionnaire* (*SDQ*; Goodman, 1997), the *Sleep Disturbance Scale for Children* (*SDSC*; Bruni et al., 1996), the *Clinical Global Impression (CGI) scale* (Busner & Targum, 2007) and the Conners Continuous Performance Test 3 (CPT-3; Conners, 2014) that was done at D0 and D90 with a different device than the one used for NF sessions. Secondary outcomes also included EEG parameters with both individual alpha peak frequency and qEEG. As regards safety, investigators asked participants and parents about side effects and used the *Pediatric Adverse Event Rating Scale* (*PAERS*; March, Karayal, & Chrisman, 2007) for additional information. The investigator assessed the intensity of each adverse event. Suicidal ideation and behaviour were examined at each visit with the *Columbia–Suicide Severity Rating Scale* (*C-SSRS*; Posner et al., 2011), and quality of life was assessed with the *Child Health and Illness Profile-Child Edition (CHIP-CE,* Riley et al., 2004) at D0 and D90. Details about the schedule of events are described in our protocol paper (Bioulac et al., 2019) and in the supplements.

Statistics

Sample-size calculation. With a noninferiority bound estimated at 4.5 and a standard deviation at 11.5 for the primary endpoint, and using a 3:2 ratio, we estimated our initial sample size at 170 children. We chose an unequal randomization ratio to gain insight into NFs putative mechanisms in further analyses. With the anticipation of a 5% drop-out rate, we adjusted the total number of patients to 179, 72 in the MPH group and 107 in the NF group using either TBR or SMR protocols according to individual TBR values.

Analysis. We assessed the primary endpoint on both the Per Protocol population (PP) and the modified Intent-To-Treat Population (mITT) defined as all randomized patients from the total population who received at least one dose of methylphenidate for the MPH group or who participated in the first NF session (see supplements for details about the different study populations). We calculated the upper limit of the 90% confidence interval (2-sided) for the difference between the two groups in the primary endpoint and declared noninferiority if the upper limit was less than a 4.5-points difference on the primary outcome.

Exploratory analyses comprised an analysis of variance on the changes of the Clinician ADHD-RS-IV total score with the treatment group and the country as studied effects. We also compared groups with the chi-square test for categorical variables and the t-test for continuous variables (or the nonparametric Mann–Whitney test when the assumption of normal distribution was questionable). Response rates were compared with odds ratios of both clinician-rated ADHD-RS-IV total score and CGI, with odds ratio >1, indicating a higher probability to respond to NF than to MPH. As secondary outcomes were not the primary focus of the research question, we did not correct for multiple testing. A contract research organization handled eCRF data monitoring, and another performed the blind data analysis; a blind data review meeting solved additional queries. Statistical tests were 2-sided with a .05 significance level.

Results

Patient inclusion

We obtained informed consent for 190 children. The mITT population consisted of 67 patients in the MPH and 111 in the NF group; these children came from 5 countries (56.7% France, 22.4% Spain, 11.9% Switzerland, 6% Germany, 3% Belgium). The flow chart (Figure 1) shows details of patient screening, withdrawals and major deviations.

Baseline characteristics

In the PP population at D90, participants were male in 81% of cases and were 7 to 13 years old (mean: 10.1 ± 1.8, median: 9.8). Their mean clinician-rated ADHD-RS-IV total score at baseline was 35 (Minimal score 14 - Maximal score 54), and a majority of patients were 'markedly ill' or 'severely ill' (CGI-S of 5 or 6: 65.6% MPH vs 54.1% NF).

The PP population had a higher baseline hyperactivity score on the parent-rated ADHD-RS and a lower prosocial score on the teacher-rated SDQ. MPH patients had a slightly elevated baseline compared with NF patients on the following items (mITT): medical history, medical examination and TBR value. Baseline characteristics for clinical, neuropsychological and EEG variables for the PP population can be obtained from Table 1.

Noninferiority – primary efficacy analysis

Our primary analysis included 149 patients from the PP population at D90 (59 MPH / 90 NF) (see Table 2). We found that clinician-rated ADHD-RS-IV total score declined between baseline and D90 by 46.9% in the MPH group and 26.7% in the NF group.

The upper limit of the confidence interval (10.56) exceeded the noninferiority bound (4.5); therefore, we did not reject the null hypothesis and did not show the noninferiority of NF versus MPH. We also assessed the primary endpoint on the 156 patients from the mITT population who completed the visit at D90 (61 MPH / 95 NF). The upper limit of the confidence interval was 10.72 confirming the previous results.

Country effects

There was a significant interaction between country and treatment group ($F = 3.74$ $p = .006$) with details

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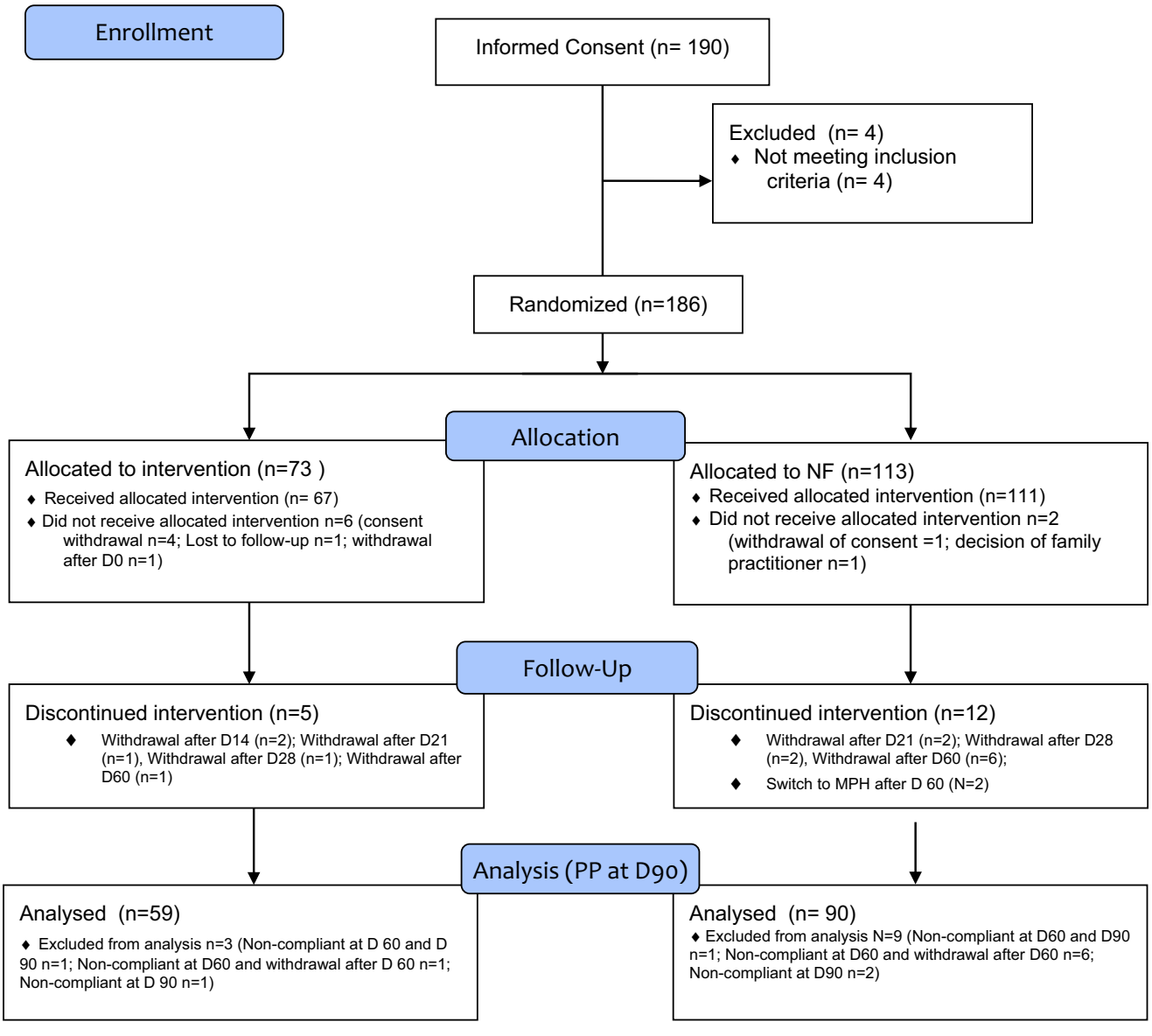

Figure 1 NEWROFEED-CONSORT study flow chart.

given in the supplementary section (Appendix S4 and Table S1). The mean dosage of MPH at the end of titration was 34.40 mg/day without significant between-countries differences.

Secondary exploratory outcomes

Table 3 shows raw values and group comparisons for secondary exploratory outcomes for the PP population. Changes from baseline for the primary and secondary outcomes are shown in Table S2.

Clinician-rated ADHD-RS subscores. Our results showed a significant decrease in the clinician-rated ADHD-RS-IV inattention score in both groups at D60 and D90 with group differences favouring MPH. We found similar results for the clinician-rated hyperactivity/impulsivity score and the total score. The total clinician-rated ADHD-RS score showed mean changes from baseline of 46% (Standardized Mean Difference SMD = 2.03) in the MPH group and 27% (SMD = 0.89) in the NF group at D90. Contrasts between the groups at both D60 and D90 showed lower total ADHD-RS scores in the MPH group.

Clinician ADHD-RS-IV: Total score Response rate. The comparisons between NF and MPH were significant both at D60 and D90. There were more responders in the MPH group than in the NF group for both 25% and 40% response rates in the clinician-rated ADHD-RS scale.

Teacher- and parent-rated ADHD-RS. For the teacher-rated ADHD-RS-IV total score, we found significant decreases from baseline to D90 in both groups with between-groups comparison at D90 in favour of MPH. The inattention score showed the same trend. For hyperactivity/impulsivity, significant decreases emerged only in the MPH group. The standardized mean of the pre–post difference (SMD)

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Table 1 Baseline clinical, neuropsychological and EEG characteristics (PP-D90 population)

	Group	*N* (%)	Mean (*SD*)	Min	Max	Test Estimate	*p*-value
Male Gender (*N*, %)	MPH	50 (84.7)				1.10 (chi-square)	.29
	NF	70 (77.8)					
Age	MPH	59	9.8 (1.8)	7	13	−1.61 (MW)	.11
	NF	90	10.3 (1.8)				
IQ	MPH	59	105.4 (14.9)	80	154		
	NF	90	109.8 (16.0)				
ADHD-RS-C – total	MPH	59	36.3 (8.6)	17	54	1.38 (MW)	.17
	NF	90	34.2 (8.5)	14	50		
ADHD-RS-C – inattention	MPH	59	20.3 (4.1)	10	27	0.65 (MW)	.52
	NF	90	19.9 (3.9)	9	27		
ADHD-RS-C hyperactivity/impulsivity subscale	MPH	59	16.0 (6.6)	4	27	1.61(MW)	.11
	NF	90	14.3 (6.7)	0	25		
ADHD-RS-P – total	MPH	59	35.3 (10.6)	7	53	1.95 (MW)	.05
	NF	89	31.90 (9.7)	5	52		
ADHD-RS-P – inattention	MPH	59	19.3 (5.3)	6	27	1.07 (MW)	.28
	NF	89	18.40 (5.2)	4	27		
ADHD-RS-P – hyperactivity/impulsivity	MPH	59	15.90 (7.1)	1	27	2.13 (MW)	**.03**
	NF	89	13.50 (6.6)	0	26		
ADHD-RS-T – total	MPH	50	27.00 (12.5)	5	54	−0.03 (MW)	.97
	NF	70	26.10 (11.3)	2	49		
ADHD-R-T – inattention	MPH	50	15.50 (6.0)	2	27	0.13 (MW)	.90
	NF	71	15.10 (6.0)	2	27		
ADHD-RS-T – hyperactivity/impulsivity	MPH	50	11.50 (8.0)	0	27	0.01(MW)	.99
	NF	71	11.20 (7.0)	0	25		
SDQ-P – total difficulties	MPH	58	18.40 (6.0)	5	30	1.49 (MW)	.14
	NF	90	17.00 (6.5)	3	36		
SDQ-P – emotional problems	MPH	58	3.90 (1.0)	0	9	0.48 (MW)	.62
	NF	90	3.70 (2.6)	0	10		
SDQ-P – conduct problems	MPH	58	4.10 (2.5)	0	9	1.31 (MW)	.19
	NF	90	3.60 (2.5)	0	10		
SDQ-P – hyperactivity	MPH	58	7.90 (1.9)	4	10	2.07 (MW)	**.04**
	NF	90	7.20 (2.2)	2	10		
SDQ-P – peer problems	MPH	58	2.4 (2.0)	0	8	0.06 (MW)	.94
	NF	90	2.6 (2.4)	0	9		
SDQ-P – prosocial	MPH	58	7.6 (2.3)	2	10	−0.52 (MW)	.60
	NF	90	7.9 (2.1)	2	10		
SDQ-T – total difficulties	MPH	50	14.70 (6.00)	4	27	1.17 (MW)	.24
	NF	71	13.50 (5.80)	3	30		
SDQ-T – emotional problems	MPH	50	2.80 (2.6)	0	9	0.14 (MW)	.88
	NF	72	2.70 (2.3)	0	10		
SDQ-T – conduct problems	MPH	50	2.50 (2.2)	0	4	1.29 (MW)	.20
	NF	73	2.10 (2.3)	0	3		
SDQ-T – hyperactivity	MPH	50	7.00 (2.5)	1	10	0.70 (MW)	.48
	NF	73	6.60 (2.7)	0	10		
SDQ-T – peer problems	MPH	50	2.4 (2.1)	0	8	0.30 (MW)	.76
	NF	71	2.3 (2.1)	0	7		
SDQ-T – prosocial	MPH	49	5.7 (2.9)	0	10	−2.18 (MW)	**.03**
	NF	70	6.9 (2.3)	1	10		
CGI-S mildly ill-3 (*N*, %)	MPH	2 (3.4)					
	NF	5 (5.6)					
CGI-S moderately ill-4 (*N*, %)	MPH	18 (31.0)					
	NF	36 (40.0)					
CGI-S markedly ill-5 (*N*, %)	MPH	27 (46.6)					
	NF	37 (41.1)					
CGI-S severely ill-6 (*N*, %)	MPH	11 (19.0)				0.003 (Fisher exact test)	.59
	NF	12 (13.3)					
BRIEF – total	MPH	58	191.80 (26.1)	122	247	0.92 (MW)	.36
	NF	89	187.30 (30.1)	108	251		
CPT – response style	MPH	59	56.60 (12.10)	35	90	0.88 (MW)	.38
	NF	89	54.70 (9.80)	37	90		
CPT – detectability	MPH	59	55.00 (9.10)	29	73	1.51 (MW)	.13
	NF	89	53.20 (9.00)	16	74		
CPT – omission	MPH	59	59.10 (16.10)	41	90	1.40 (MW)	.16
	NF	89	54.70 (12.60)	40	90		
CPT – commission	MPH	59	51.00 (9.10)	28	64	0.49 (MW)	.62
	NF	89	50.50 (8.60)	27	68		

(continued)

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Table 1 (continued)

	Group	*N* (%)	Mean (*SD*)	Min	Max	Test Estimate	*p*-value
CPT – perseverations	MPH	59	57.60 (12.50)	43	90	2.21 (MW)	**.03**
	NF	89	53.70 (11.20)	43	90		
CPT – hit reaction time	MPH	59	59.70 (11.50)	41	90	1.27 (MW)	.20
	NF	89	57.30 (12.60)	35	90		
CPT – hit reaction time *SD*	MPH	59	62.30 (13.20)	39	90	2.26 (MW)	**.02**
	NF	89	58 00 (12 60)	37	90		
CPT – variability	MPH	55	57.10 (11.20)	38	90	1.82 (MW)	.07
	NF	87	54.00 (10.20)	40	89		
CPT – hit reaction time block change	MPH	57	56.10 (11.40)	25	83	0.68 (MW)	.50
	NF	89	54.70 (12.20)	4	90		
CPT – hit reaction time ISI change	MPH	59	58.40 (12.00)	38	90	1 40 (MW)	.16
	NF	89	56.20 (13.00)	34	90		
qEEG-iAPF (Hz)	MPH	50	9.00 (1.00)	7.0	11.0	−0.22 (MW)	.82
	NF	90	9.10 (0.90)	7.0	11.5		
qEEG-TBR	MPH	50	4 (1.90)	1.0	10.1	1.69 (MW)	.09
	NF	90	3.4 (1.20)	1.4	7.1		
qEEG-SMR (μV^2)	MPH	50	266.4 (136.5)	84.1	882.2	−0.24 (MW)	.811
	NF	90	277.2 (156.3)	106.7	992.2		

p-values less than .05 are highlighted in bold.
CPT, continuous performance test; MPH, methylphenidate; MW, Mann–Whitney test; NF, neurofeedback.

Table 2 Primary criterion ADHD-RS clinician-rated total score (PP analysis)

	Group	*N*	Mean (*SD*)	95%CI	Min	Max
ADHD-RS-C total D0	MPH	59	36.27 (8.57)	[34.04; 38.50]	17	54
	NF	90	34.17 (8.48)	[32.39; 35.94]	14	50
ADHD-RS-C total D90	MPH	59	18.97 (8.49)	[16.75; 21.18]	6	36
	NF	90	24.96 (10.32)	[22.79; 27.12]	5	51

Noninferiority test

[NF: D90-D0] – [MPH: D90-D0]	Mean	90% CI mean
	8.09	[5.62; 10.56]

was 0.87 in the MPH group and 0.20 in the NF group. Parent-rated ADHD-RS yielded similar results.

CGI improvement. The comparisons between NF and MPH groups were significant at D60 and D90 with odds ratios <1, indicating a better CGI Improvement in the MPH group than the NF group at both D 60 and D90. At D90, 76.3% were much or very much improved with MPH and 21.1% with NF.

Parent-rated SDQ. We found significant decreases between baseline and D90 in the total difficulties score and the emotional, conduct problems, hyperactivity/inattention scores in both treatment groups. Total difficulties and hyperactivity/inattention scores showed between-group differences in favour of MPH.

Teacher-rated SDQ. Both treatment groups had significant decreases in total difficulties and at D90; this score was lower in the MPH group. We found a significant decrease in the emotional problems score and the internalizing score in the NF group without significant group differences at D90. Conduct problems and hyperactivity decreased in the MPH group with significant group differences in favour of MPH for hyperactivity.

Executive functions (BRIEF). Significant decreases in the total BRIEF score were identified in both groups. The comparison between MPH and NF showed greater effects in the MPH group.

Conners CPT-3. Detectability and Commission Error T-Scores decreased between baseline and endpoint in both groups with significant between-group differences at D90 in favour of the MPH group. Perseverations and Hit reaction time improved only in the MPH group. Hit reaction time standard deviation and interstimulus interval change improved in the MPH group and deteriorated in the NF group.

qEEG. The TBR values increased significantly from baseline to D60 and D90 only in the NF group. This change was in the unexpected direction.

Safety analyses

Columbia suicide severity rating scale (C-SSRS). Two patients in the MPH group described

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Table 3 Secondary criteria – raw values and group comparison (PP population)

	Group	*N*	Mean (*SD*)	*t* value	*p*-value
ADHD-RS-C inattention D60	MPH	60	10.20 (3.36)	7.25	<.0001
	NF	97	15.09 (4.84)		
ADHD-RS-C inattention D90	MPH	59	10.42 (3.94)	6.02	<.0001
	NF	90	14.36 (4.99)		
ADHD-RS-C hyperactivity/impulsivity score D60	MPH	60	9.43 (5.32)	4.09	<.0001
	NF	97	11.73 (6.43)		
ADHD-RS-C hyperactivity/impulsivity D90	MPH	59	8.54 (5.73)	4.43	<.0001
	NF	90	10.60 (6.76)		
ADHD-RS-P total D60	MPH	60	20.58 (10.10)	6.28	<.0001
	NF	90	28.20 (10.22)		
ADHD-RS-P total D90	MPH	58	20.05 (10.31)	5.83	<.0001
	NF	89	26.53 (11.22)		
ADHD-RS-P inattention D60	MPH	60	10.67 (4.66)	6.87	<.0001
	NF	95	15.62 (5.21)		
ADHD-RS-P inattention D90	MPH	58	11.02 (4.97)	5.73	<.0001
	NF	89	15.02 (5.54)		
ADHD-RS-P hyperactivity/impulsivity D60	MPH	60	10.01 (6.32)	4.81	<.0001
	NF	95	12.51 (6.49)		
ADHD-RS-P hyperactivity/impulsivity subscale D90	MPH	59	9.27 (6.77)	4.90	<.0001
	NF	89	11.51 (7.00)		
ADHD-RS-T total D90	MPH	38	16.26 (10.51)	4.24	<.0001
	NF	51	23.46 (11.81)		
ADHD-RS-T inattention D90	MPH	38	9.41 (5.35)	4.24	<.0001
	NF	52	13.57 (6.30)		
ADHD-RS-T hyperactivity/impulsivity D90	MPH	38	6.84 (6.21)	3.55	.0006
	NF	53	9.85 (7.04)		
BRIEF total score D90	MPH	56	164.91 (30.57)	3.12	.0022
	NF	85	175.91 (30.17)		
SDQ-P total difficulties D90	MPH	58	13.62 (6.29)	2.52	.0128
	NF	89	14.72 (5.91)		
SDQ-P emotional problems D90	MPH	58	2.81 (2.36)	0.01	.9935
	NF	89	2.72 (2.14)		
SDQ-P conduct problems D90	MPH	58	2.95 (2.12)	1.44	.1507
	NF	89	3.02 (1.86)		
SDQ-P hyperactivity D90	MPH	58	5.57 (2.10)	4.34	<.0001
	NF	89	6.51 (2.31)		
SDQ-P peer problems D90	MPH	58	2.29 (2.18)	0.47	.6421
	NF	89	2.47 (2.21)		
SDQ-P prosocial D90	MPH	58	7.69 (2.08)	−0.06	.9535
	NF	89	7.87 (1.86)		
SDQ-T total difficulties D90	MPH	39	10.72 (6.01)	2.64	.0097
	NF	53	12.60 (5.73)		
SDQ-T emotional problems D90	MPH	39	2.46 (2.43)	−0.84	.4056
	NF	53	2.21 (2.02)		
SDQ-T conduct problems D90	MPH	39	1.64 (1.97)	1.56	.1219
	NF	54	2.02 (2.20)		
SDQ-T hyperactivity D90	MPH	39	4.46 (2.08)	5.38	<.0001
	NF	56	6.18 (2.75)		
SDQ-T peer problems D90	MPH	39	2.15 (1.86)	0.17	.8630
	NF	53	2.21 (1.91)		
SDQ-T prosocial D90	MPH	37	6.57 (2.44)	−1.23	.2231
	NF	52	6.71 (2.42)		
CPT response style D90	MPH	59	56.27 (11.58)	0.56	.5793
	NF	89	56.15 (10.85)		
CPT detectability D90	MPH	59	48.14 (9.16)	4.26	<.0001
	NF	89	51.73 (9.67)		
CPT commission D90	MPH	59	45.47 (8.65)	3.31	.0012
	NF	89	48.62 (9.16)		
CPT perseverations D90	MPH	59	50.36 (8.70)	4.09	<.0001
	NF	89	55.51 (13.20)		
CPT hit reaction time D90	MPH	59	57.03 (12.36)	2.16	.0327
	NF	89	58.41 (12.46)		
CPT hit reaction time *SD* D90	MPH	59	53.86 (11.44)	5.89	<.0001
	NF	89	60.58 (12 91)		
CPT variability D90	MPH	54	50.59 (7.74)	3.67	.0004
	NF	85	54.90 (9.68)		

(continued)

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Table 3 (continued)

	Group	*N*	Mean (*SD*)	*t* value	*p*-value
CPT hit reaction time block change D90	MPH	57	53.74 (10.52)	1.02	.3111
	NF	89	55.62 (12.60)		
CPT hit reaction time ISI change D90	MPH	59	53.56 (11.72)	5.43	<.0001
	NF	89	61.73 (13.85)		
qEEG-iAPF (Hz) D90	MPH	56	9.02 (0.94)	0.21	.8340
	NF	89	9.08 (1.02)		
qEEG-TBR D90	MPH	56	4.01(1.89)	1.41	.1602
	NF	89	3.67 (1.49)		
qEEG-SMR (μV^2) D90	MPH	56	265.33 (165.12)	−0.77	.4434
	NF	89	266.99 (163.37)		

suicidal ideation, whereas in the NF group, one patient had suicidal ideation. No patient showed suicidal behaviour during the study.

Sleep quality with Sleep Disturbance Scale for Children (SDSC). The total score of the SDSC decreased significantly in both MPH and NF groups between baseline and endpoint ($t = -6.6$, $p < .0001$; $t = -6.02$, $p < .0001$) without significant group differences at D90.

Child Health and Illness Profile-Child Edition (CHIP-CE). Family involvement ($t = -2.96$, $p = .0036$), threats to achievement ($t = -3.30$, $p = .0012$), risk avoidance ($t = -3.00$, $p = .0032$) and academic performance were significantly better in the MPH group compared with the NF group at D90.

Adverse events (AEs) and severe adverse events (SAEs). Spontaneous reporting or PAERS yielded AEs in 94% of patients in the MPH group versus 66.7% in the NF group with a significant between-group difference (chi-square test (1) = 17.65, $p < .0001$). 91% of patients in the MPH group versus 21.6% in the NF group had at least one AE related to treatment with a significant between-group difference (chi-square test (1) = 80.71, $p < .0001$). Table S3 shows the AEs that occurred in >5% of patients.

In 9% MPH and 2.7% NF patients, AEs led to discontinuation of treatment (Fisher exact test = 0.055; $p = .08$). We found severe AEs in 20.9% of patients in the MPH versus 29.7% in the NF group without significant group difference (chi-square test (1) = 1.68, $p = .195$).

Observance analysis (PP population). Adherence to treatment with MPH defined as 50% or more days of treatment intake was 94% at D60 and 93.9% at D90. The mean number of NF sessions was 17.1 (*SD* = 1.9) at D60 and 17.6 (*SD* = 2.8) between D60 and D90. The total number of NF sessions in the treatment phase between D28 and D90 was 34.5 (*SD* = 3.1).

Discussion

This prospective, multicentre, randomized, reference drug-controlled trial in children with ADHD did not confirm our hypothesis of noninferiority for at-home personalized NF compared with optimally titrated MPH. Significant uncontrolled pre–post symptom reductions were found for the clinician-rated ADHD-RS-IV total score in both groups at intermediate (D60) and final (D90) assessments, but these were generally more prominent for MPH. This result is in line with a recent meta-analysis including 18 head-to-head studies that found MPH to be significantly more efficacious than NF in short-term trials (Yan, Wang, Yuan, & Zhang, 2019). Given that our study used an optimal titration procedure for MPH, smaller between-group differences may have been observed with fixed-dose regimens or in community services, in line with some previous studies comparing MPH and NF (Duric, Assmus, Gundersen, & Elgen, 2012; Monastra, Monastra, & George, 2002).

In both treatment groups, pre–post differences in core ADHD-symptom ratings were highest for clinicians, intermediate for parents and lowest for teachers, but clinical outcomes in core symptoms were superior for MPH regardless of the informant. Although teacher ratings improved significantly from baseline to endpoint in both treatment groups, the modest mean change in the NF group raises questions regarding the clinical significance of NF effects on core ADHD symptoms in the school setting. Contrary to clinicians and parents, teachers may be less affected by positive expectation effects related to treatments, and therefore, their ratings have been considered probably blinded (Sonuga-Barke et al., 2013). However, a recent study examining informant effects in ADHD confirmed larger treatment effects in parents but reported expectancy bias in both parents and teachers (Minder, Zuberer, Brandeis, & Drechsler, 2018). Treatment effects for NF were nonsignificant in meta-analyses when teacher-rated outcomes were used instead of parent ratings (Cortese et al., 2016; Sonuga-Barke et al., 2013). Rather than being more objective, teachers could be less sensitive to ADHD-symptoms variation than parents (Biederman,

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Faraone, Monuteaux, & Grossbard, 2004; Bussalb, Congedo, et al., 2019), particularly regarding subtle or slow changes (Cortese et al., 2016). However, this interpretation is challenged by results from a recent study comparing TBR NF to sham NF, showing that when blinded, parents were no more sensitive to treatment differences than teachers (Arnold et al., 2020). In our sample, teachers rated children as less affected at baseline. These lower baseline scores in teacher ratings could potentially contribute to the smaller within-group effects observed in our sample and in other studies (Strehl et al., 2017).

Our ADHD-RS total score within-group response rates at endpoint are at the upper end of previous findings regarding both MPH (Gazer-Snitovsky, Brand-Gothelf, Dubnov-Raz, Weizman, & Gothelf, 2019; Steele, Jensen, & Quinn, 2006) and NF (Gevensleben et al., 2009; Strehl et al., 2017). We also observed positive effects in parent-rated SDQ conduct and emotional problems in both treatment groups with significant between-group differences favouring MPH. In teacher ratings, emotional symptoms improved only in the NF group.

We also found that CPT-3 Detectability and Commission Errors improved in both groups, while some CPT-3 variables deteriorated in the NF group. This indicates that NF has weaker effects than MPH using an objective determination of treatment efficacy (Hall et al., 2016) on inhibitory control capacity and vigilance.

This pattern of a significant but weaker effect for NF, when compared to MPH, is also reflected by the results obtained for other secondary outcomes, such as BRIEF or SDQ mean score changes. However, the low rate of functional improvement in the NF group (21% vs 76% as measured by the CGI-I < 2) indicates these may be nonspecific effects.

Our study showed a time effect for NF with improvement in scores between D60 and endpoint, whereas the effects of MPH were stable. This could be explained by the fact that MPH dosage was unchanged between D60 and D90 whereas NF thresholds were adapted to performance. It could also indicate progressivity in the effects of NF during the study. A recent meta-analysis on follow-up data demonstrated that NF effects, unlike those of medication, take longer but increase over time (Van Doren et al., 2018). The fact that NF enables acquiring skills and strategies with long-term effects may be a possible explanation for this finding and emphasizes the importance of including follow-up measures in future studies.

We did not find that NF induced qEEG changes in the expected direction of training. This suggests that such potential changes did not transfer to the resting-state brain activity assessed by qEEG. Furthermore, participants in the NF group showed a significantly lower baseline TBR compared with the MPH group which may have influenced the current results (Ros, Baars, Lanius, & Vuilleumier, 2014). In the recent double-blind, placebo-controlled NF trial using a TBR protocol and sham control, both groups showed improvement from baseline to end and 13-month follow-up without evidence for a specific effect of NF (Arnold et al., 2020). The reported effect sizes (d = 1.51 in the NF group and d = 1.47 in the control group) and durability of effects at follow-up point to nonspecific effects such as reinforcement of on-task behaviour, sleep hygiene and mental effort that could also have played a role in our findings in addition to a placebo effect.

Of note, the pattern of withdrawal and nonadherence differed across treatment groups; early withdrawal and patients lost to follow-up after randomization were more frequent in the MPH group, whereas late withdrawal and nonadherence were more frequent in the NF group. The preference for NF in certain families participating in the study may explain early withdrawal in the MPH group as only two patients withdrew due to MPH-related adverse events. Late withdrawal or nonadherence to NF may instead be a result of difficulties in implementing repeated sessions, and limited efficacy.

The AE profile for MPH was similar to what has already been documented, whereas most AEs reported with NF were attributable to persistent ADHD symptoms. Notably, the NF group demonstrated a significantly lower number of reported AEs related to treatment (22% for NF vs 91% for MPH).

Overall, this randomized trial holds several strengths, including a large sample size and the inclusion of probably blinded raters and objective outcomes. It is also the first to show that at-home NF is an innovative and feasible technique. Limitations of our study include the absence of sham NF or another nonactive control group as well as non-blinded assessment by clinicians and parents. As we relied on a formal clinical diagnosis of ADHD with a semi-structured interview (K-SADS), we did not require a minimum cut-off on the ADHD-RS in the inclusion criteria. This may explain the low value of the minimum ADHD score in our sample (range 14–54). However, only a small proportion of children were minimally ill at baseline (3.4% in the MPH and 5.6% in the NF group). We also chose to use per-protocol analyses to ensure the population had a maximal exposure to NF; this may be a matter of debate but in our study the ITT and PP analyses yielded similar results. Another limitation is the absence of a follow-up study to assess NF outcomes after the end of active treatment. In addition, secondary analyses are exploratory and statistical tests are given for information purpose only.

Conclusion

Although inferior to the front-line therapeutic effect of MPH and possibly nonspecific when used as a stand-alone treatment, the short- and long-term effects of at-home NF should be further explored to define its place in the management of ADHD. NF

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could be studied in addition to medication as a recent study reported lesser medication needs in the NF group (Arnold et al., 2020). NF had a good tolerability profile, but nonadherence was an issue in some participants.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplements to the Methods section.
Appendix S2. CRED-nf checklist summary output.
Appendix S3. Details about the study population and data sets analysed.
Appendix S4. Country effects.
Table S1. Country Effects – change from baseline at D90.
Table S2. Secondary variables – change from baseline at D90.
Table S3. Adverse events occurring in >5% of patients.

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Access to data and Data sharing

- Pr. Diane Purper-Ouakil confirms that she has full access to all the data in the study and takes responsibility for integrity of the data and the accuracy of data analysis;
- Data collected for the study will be made available to others (e.g. deidentified participant data), and additional, related documents will be available (e.g. study protocol, statistical analysis plan, informed consent form);
- These data will be available with publication in a public data repository.

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Key points

- Neurofeedback (NF) is considered a promising treatment option for attention-deficit hyperactivity disorder (ADHD).
- The main objective of NEWROFEED was to demonstrate the non-inferiority of personalized at-home NF training versus methylphenidate within a prospective, multicentre, randomized (3:1), reference drug-controlled trial in children with ADHD aged between 7 and 13 years.
- Our study showed inferiority of NF when compared to methylphenidate but both treatment groups showed significant pre–post improvements in core ADHD symptoms and in a broader range of problems.
- Although results of our study do not support the use of NF as a stand-alone treatment for ADHD, further studies could explore adjunctive treatment effects.

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