ADHD Attention Deficit and Hyperactivity Disorders (2019) 11:31–45
https://doi.org/10.1007/s12402-018-0269-6

ORIGINAL ARTICLE

The impact of successful learning of self-regulation on reward processing in children with ADHD using fMRI

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Received: 28 June 2018 / Accepted: 10 September 2018 / Published online: 17 September 2018

Abstract

Neurofeedback (NF) is a non-pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) that is targeting self-regulation, is efficacious when standard protocols are used and induces partly specific neurophysiological changes in the inhibitory network. However, its effects on reward processing, which is also considered an important aspect of ADHD and has been linked to neurophysiological deficits, remain unknown. Children with ADHD ($N = 15$, mean age 11.8, SD 1.52) were randomly assigned to either slow cortical potential NF ($n = 8$) or EMG biofeedback control training ($n = 7$) and received 20 sessions of training under comparable conditions. Learning was defined as the slope of successful training runs across all transfer sessions. Whole brain analysis, region-of-interest analysis of anticipatory ventral striatal (VS) activation, and analysis of behavioral data were performed. Clinically, the NF group improved more than the EMG group. Whole brain analysis indicated increased activation in the left superior frontal gyrus in the control group only, and in medial prefrontal cortex and dorsolateral prefrontal gyrus (DLPFC) after treatment across all groups. Only successful learners of self-regulation ($n = 8$) showed increased left inferior frontal gyrus and DLPFC activation after treatment. Left VS activation was increased after treatment and showed a significant time*medication-status interaction. Specific treatment effects were found in left frontal regions for the control treatment and successful learners. Also, unmedicated participants, irrespective of treatment type or successful learning, showed treatment-induced improvement in reward processing. The results suggest no prominent specific effect of NF on reward processing. However, cautious interpretation is warranted due to the small sample.

Keywords Self-regulation · Neurofeedback · fMRI · Reward processing · Ventral striatum · ADHD

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable early-onset mental disorder characterized by a persistent pattern of inattention, hyperactivity and impulsiveness, which is impairing and developmentally inappropriate and often affects patients across the life span. Although stimulant medication is most widely used to treat severe ADHD, medication is not always effective or acceptable to patients and their parents, and side effects may occur. As a consequence, non-pharmacological treatments with potential long-term effects such as neurofeedback (NF) are of great interest. NF is intended to directly target neuronal dysfunctions by presenting physiological measures of the brain to the subject (Holtmann et al. 2014b). Through trial-and-error learning, subjects learn to regulate their brain activation in a desired direction. NF effects have been a focus of meta-analyses, showing medium-to-large effects on ADHD

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symptoms if mainly rated by those most proximal to the treatment (e.g., parents poorly or not blinded to treatment type) (Arns et al. 2009; Cortese et al. 2016; Sonuga-Barke et al. 2013). However, as the effects for probably blinded raters were reduced to a trend (Sonuga-Barke et al. 2013), limited to the inattention subscale (Micoulaud-Franchi et al. 2014) or eliminated except in an exploratory analysis of three studies using standard NF protocols (Cortese et al. 2016), the current evidence for reliable effects remains insufficient. Importantly, the neuronal processes underlying successful NF treatment in ADHD have not been fully understood. A number of studies have been able to show effects of NF on brain activation, such as a normalization of oscillatory activity in the theta band and in the theta/beta ratio (Doehnert et al. 2008; Gevensleben et al. 2009) as well as normalization of event-related potentials (ERPs) such as the anticipatory contingent negative variation (CNV) (Wangler et al. 2011) or the inhibitory NoGo N2 (Holtmann et al. 2009), and more recent studies have shown partly specific effects of NF using functional magnetic resonance imaging (fMRI) (Baumeister et al. 2018; Beauregard and Levesque 2006). Further, most recently, the fast transfer and analysis of fMRI data enabled the use of these signals for NF (real-time fMRI NF). Consequently, Alegria et al. (2017) were able to show in a first proof-of-concept study that successful real-time fMRI NF is feasible in adolescents with ADHD and associated with ADHD symptom reductions. However, while these studies provide important insight into beneficial effects of NF on executive functions in ADHD, its potential effects on motivation and reward processing remain unknown to date. In the context of the current work, NF will refer to EEG-NF.

While it has been convincingly demonstrated that the behavioral symptoms in ADHD are partly attributable to impairments in higher cognitive control processes, such as performance monitoring, response conflict and error processing, working memory and attentional control which are associated with dysfunctions in fronto-striatal dopaminergic networks (Banaschewski et al. 2005; Sagvolden et al. 2005), current models of ADHD also suggest abnormal reward processing as an important factor, causal to the disorder via malfunctions in reinforcement learning and motivation (Sagvolden et al. 2005; Sonuga-Barke 2011). A number of neuroimaging studies underline these theories, consistently showing reduced ventral striatal (VS) activation during anticipation of rewards in ADHD (for review, see Plichta and Scheres (2014)). Reduced VS activation has further been linked to lifetime ADHD symptoms in healthy subjects (Boecker et al. 2014). While some studies fail to replicate VS hypoactivation during reward anticipation in ADHD (Paloyelis et al. 2012; van Dongen et al. 2015; von Rhein et al. 2015), this is likely due to task design (Plichta and Scheres 2015). In contrast, VS activation during reward delivery has been less frequently studied and yielded more inconsistent results, with VS hyperactivation (Kohls et al. 2014; Paloyelis et al. 2012; von Rhein et al. 2015) as well as no VS deviation (Scheres et al. 2007; Strohle et al. 2008; van Dongen et al. 2015) reported in ADHD.

Although most studies have focused on VS as the core reward-related region, the reward circuit extends beyond this region (Haber and Knutson 2010; Oldham et al. 2018). In ADHD patients, deviations have been demonstrated in other areas beyond the VS such as hypoactivation of the left dorsolateral prefrontal cortex (DLPFC), putamen, thalamus, precuneus, posterior cingulate cortex (PCC), superior temporal lobe/inferior frontal gyrus (IFG)/insula and medial prefrontal cortex (mPFC) (Chantiluke et al. 2014; Hauser et al. 2014; Metin et al. 2018; Rubia et al. 2009b; Stoy et al. 2011; van Dongen et al. 2015) and hyperactivation of the anterior cingulate cortex (ACC), temporal pole, lingual gyrus, cerebellum, occipital cortex and orbitofrontal cortex (OFC) (Chantiluke et al. 2014; Kohls et al. 2014; Rubia et al. 2009b; von Rhein et al. 2015).

Stimulant medication, the gold-standard pharmacotherapy for ADHD, has been shown to increase reward-related activation in the right mPFC and ACC as well as the caudate head and reduce OFC and STG hyperactivation compared to placebo (Rubia et al. 2009a) and to compensate striatal dysfunction (Aarts et al. 2015). When investigating stimulant treatment trajectories, ADHD patients that started medication later and on lower doses showed reduced supplementary motor area (SMA) and ACC activation during reward delivery when compared to those that started medication early and with higher doses (Schweren et al. 2017).

Importantly, learning and motivation are functions directly targeted by NF. Specifically, training of slow cortical potentials (SCPs) is expected to functionally impact reward processing, as simultaneous EGG–fMRI imaging has demonstrated that CNV as a negative SCP is correlated with the reward circuit (Plichta et al. 2013). On the other hand, impacts on reward processing have also been discussed as factors contributing to unspecific training effects in NF shared with partly active control groups such as biofeedback (Holtmann et al. 2014b). However, as the impact of NF on reward processing remains unknown, our study investigated the effects of SCP EEG neurofeedback training on motivational circuits (reward processing) on the behavioral as well as neurophysiological level. In line with the previously reported impact of successful learning of self-regulation on inhibitory control (Baumeister et al. 2018), we hypothesized that reward function, and particularly reward anticipation in the VS, improves more in patients that successfully learned self-regulation (learners) than in those that did not (non-learners) across both treatment groups. Regarding effects of training type, we hypothesize that reward function improves

after treatment in both the active control group and the NF group, but with more pronounced effects for the NF group.

Methods and materials

Subjects

The full sample consisted of 26 ADHD patients (6 females) aged between 9 and 14 years. Participants were recruited through the outpatient clinic of the Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, as well as via local pediatricians and child psychiatrists. All participants met diagnostic criteria for ADHD based on the K-SADS-PL (Delmo et al. 2000) semi-structured clinical interview. Exclusion criteria were contraindications for MRI measurements, left-handedness and comorbid disorders other than oppositional defiant disorder, conduct disorder or reading disorder.

Due to extensive motion artifacts, four patients had to be excluded from further analysis. An additional seven patients did not complete treatment and were also excluded. Out of these seven patients, four dropped out prior to randomization, and three dropped out after randomization (due to start of medication use during the study or lack of time for regular training). The final sample therefore consisted of 15 subjects (4 females). For study sample characteristics, please see Table 1.

As a result of the randomization process, medication status was imbalanced in the NF and EMG groups. Thus, all analyses were conducted with medication status as covariate. However, all subjects who received medication underwent at least 48 h of medication washout prior to fMRI scanning. Due to missing post-training questionnaires, two subjects were excluded from the analysis of treatment outcome.

All subjects and their legal representatives gave written informed consent prior to their participation and had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University Heidelberg and registered at the German clinical trials register (https://drks-neu.uniklinik-freiburg.de/drks_web/), DRKS-ID: DRKS00003513.

Intervention

Subjects were randomly assigned to either SCP-NF training ($n=8$) or control electromyogram (EMG, $n=7$) feedback training. Except for shortening the treatment to 20 sessions, the training protocol was following a previously established protocol (Holtmann et al. 2014a; Strehl et al. 2017) and is described in more detail elsewhere (Baumeister et al. 2018). All subjects received 20 sessions of training, with each session consisting of three training blocks and one transfer block comprising 50% transfer trials where feedback was not visible during the feedback phase. Both NF and EMG training included a token plan for successful performance and training compliance. In an attempt to keep pre- and post-training ratings as unaffected as possible, subjects and their parents were not informed about the type of training they received.

As previously described (Baumeister et al. 2018), subjects were classified as learners and non-learners based on the slope of their success rates across the transfer blocks of all 20 training sessions. Subjects with positive slopes were classified as learners ($n=8$), while subjects presenting negative slopes were considered non-learners ($n=7$), irrespective of the type of training they received.

Experimental procedures

In the reward task (Boecker et al. 2014), modified from versions by Kirsch et al. (2003) and Knutson et al. (2001) that has been shown to reliably activate the ventral striatum (Plichta et al. 2012), subjects have to respond sufficiently fast to a flash target. Targets followed a cue indicating the possibility to win money (laughing smiley, 0.50 Euros) or receive verbal feedback (scrambled smiley, "fast reaction!"). After every trial, the participants were informed about the current account balance. Boost trials with an unexpected monetary reward of 2 Euro instead of 0.50 Euro were given about every eighth win trial to improve the participants' motivational level. In total, 50 monetary and 50 verbal trials were presented in a pseudo-randomized order. The cue duration was jittered (3–5 s) to cover the whole hemodynamic response function (HRF). Reaction time windows were adaptively tailored to account for inter-individual differences

Table 1 Study sample characteristics

	N	Age (mean/SD)	Male/female	IQ (mean/SD)	Medication (y/n)	Learner/non-learner
Overall	15	11.8/1.52	11/4	113.13/12.82	10/5	8/7
EMG	7	11.14/1.57	5/2	107.57/7.83	3/4	4/3
NF	8	12.38/1.30	6/2	118.00/14.78	7/1	4/4

and to yield comparable winnings across participants. The total duration of the task was 14 min 52 s.

fMRI data acquisition

Data were acquired recording EEG and fMRI simultaneously, but only fMRI data will be reported here. A 3-T Siemens Trio whole body scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard 12-channel head coil was used to obtain functional images via a BOLD-sensitive T2*-weighted echoplanar sequence (repetition time (TR) = 2210 ms, echo time (TE) = 28 ms, flip angle = 90°). A total of 277 volumes with 36 slices with a thickness of 3 mm were obtained, oriented approximately 20° steeper than the AC-PC plane (field of view: 220 mm; matrix: 64 × 64). Subject's positions in the scanner were axially shifted about 4 cm to reduce gradient artifacts in the simultaneously recorded EEG (Mullinger et al. 2011). The first four volumes were discarded to allow longitudinal magnetization to reach equilibrium. Functional measurement was followed by a T1-weighted anatomical MRI scan (192 sagittal slices, slice thickness 1 mm, FOV = 256 mm × 256 mm, matrix = 256 × 256) for each subject.

Performance analysis

Reaction times (RT) and standard deviation (SD) as a measure of reaction time variability (RTV) were analyzed using SPSS software package (Version 25, IBM Corp., Armonk, NY, USA). Separate analyses of variance (ANOVA) were conducted to test for expected behavioral effects and group differences. Mixed-model repeated-measures ANOVAs with the within-subject factors condition (win, no-win) and time (pre- and post-NF trainings) and between-subject factor of training type (NF, EMG) or learning (learners, non-learners) were used to assess training and learning effects in RT and RTV. Due to imbalanced medication status between the NF and EMG groups, and learners and non-learners, medication status is used as covariate in all models. Due to marginal age differences between groups, analyses comparing learners and non-learners will be additionally corrected for age.

Separate ANOVAs were performed for training type and learning due to the small groups.

fMRI data analysis

FMRI data analysis was carried out using SPM12 software (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, University College London, London, UK). Preprocessing included slice time correction, realignment to correct for movement artifacts, spatial normalization into a standard stereotactic space (2 mm^3) and spatial smoothing with a three-dimensional Gaussian filter of 8-mm full-width half-maximum using standard SPM12 methods. Spatial normalization was performed via direct normalization of the realigned mean image to the EPI template, and subsequent application of the obtained parameters to the time series.

Low-frequency temporal trends were minimized through high-pass filtering with a cutoff of 128 s, and intrinsic autocorrelations were modeled.

We constructed a general linear model, containing the experimental conditions of the task as regressors of interest, and further regressors of no interest. Regressors of interest were formed using onsets of the win and verbal cues, as well as onsets of the feedback of successful win trials, unsuccessful win trials, successful verbal trials and unsuccessful verbal trials, and convolved with the standard hemodynamic response function. Two regressors of no interest contained the onsets of flash targets and responses. Six further regressors contained the motion parameters obtained during realignment.

First-level results were calculated for two contrasts of interests: reward anticipation (cue of the win condition vs. cue of the verbal condition) and reward delivery (feedback of all won trials vs. feedback of all lost trials). Separate repeated-measures ANOVAs were conducted using first-level contrasts to investigate main effects of time (pre-training, post-training), training type (EMG, NF) or learning (learners, non-learners) and their interactions in the framework of the SPM flexible factorial design. In line with Beauregard and Levesque (2006) and Baumeister et al. (2018), paired T tests were conducted subsequently to compare activation in the contrasts of interest before training and after training for both training types as well as for learners and non-learners separately. Due to the small sample size, whole brain fMRI data are reported at an uncorrected level of $p < .001$ with a cluster threshold of $k = 10$.

In addition to whole brain analyses, a region-of-interest (ROI) analysis was conducted by extracting contrast estimates in the left and right ventral striatum from first-level reward anticipation contrast and performing subsequent analyses in SPSS software. ROI data mixed-model repeated-measures ANOVAs with the within-subject factor time (pre- and post-NF training) and between-subject factor of training type (NF, EMG) or learning (learners, non-learners) were used to ROI data in the left and right VS.

Treatment outcome analysis

Primary outcome was quantified using the ADHD questionnaires of the German diagnostic system for mental disorders (DISYPS-II, Döpfner et al. (2008)) rated by the patient's parents.

Treatment outcome was analyzed using SPSS Software package (Version 25, IBM Corp., Armonk, NY, USA) by

means of separate mixed-model ANOVAs with the within-subject factor of time (pre-training, post-training) and the between-subject factor of training type (EMG, NF) or learning (learners, non-learners) and medication status as covariate. Separate ANOVAs were performed for training type and learning due to the small groups, and the ANOVA for learning was additionally including age as covariate.

Correction for multiple testing

All results are reported uncorrected for multiple testing based on the small sample size. Partial eta squared (ηp^2) is reported where appropriate for categorization into small ($\eta p^2 > .0099$), medium ($\eta p^2 > .0588$) and large ($\eta p^2 > .1379$) effects (Richardson 2011) based on Cohen's benchmarks (1969).

Results

Behavioral data

The patients in the EMG and NF groups showed no significant differences regarding age ($t_{(13)} = 1.66$, $p = 0.121$), IQ ($t_{(10.90)} = 1.74$, $p = 0.110$) ADHD symptom severity ($t_{(13)} = 1.39$, $p = 0.188$) and gender distribution ($X^2_{(1)} = 0.02$, $p = 0.876$). However, there was a trend for unbalanced samples regarding medication status ($X^2_{(1)} = 3.35$, $p = 0.067$).

Learners and non-learners also showed no significant differences regarding IQ ($t_{(13)} = 0.35$, $p = 0.733$) ADHD symptom severity ($t_{(13)} = 0.046$, $p = 0.964$), medication status ($X^2_{(1)} = 0.02$, $p = 0.876$) or gender distribution ($X^2_{(1)} = 0.02$, $p = 0.876$). However, there was a trend for non-learners ($M = 12.57$) to be older than learners ($M = 11.13$, $t_{(13)} = -2.03$, $p = 0.063$).

Training dynamics for NF and EMG groups as well as learners and non-learners are reported elsewhere (Baumeister et al. 2018).

Reward task performance

Comparison of training types Analysis of training type effects on RTs yielded a significant effect of the covariate medication status ($F_{(1,12)} = 6.8$, $p = 0.023$, $\eta p^2 = 0.326$, see Fig. 1a.) with faster responses overall in unmedicated ($M = 191.40$ ms) compared to medicated patients ($M = 237.99$ ms). Further, the main effect of training type was borderline significant ($F_{(1,12)} = 4.7$, $p = 0.051$, $\eta p^2 = 0.282$, see Fig. 1b.) with faster responses overall in the NF ($M = 204.16$) compared to the EMG group ($M = 240.77$).

Analysis of RTV yielded a significant main effect of condition ($F_{(1,12)} = 9.26$, $p = 0.010$, $\eta p^2 = 0.436$, see Fig. 1c), with higher variability overall in the verbal ($M = 92.77$) compared to the win condition ($M = 49.47$). There was no significant effect of training type regarding RTV.

Comparison of learners and non-learners Analysis of RTV yielded a significant main effect of time ($F_{(1,11)} = 6.17$, $p = 0.030$, $\eta p^2 = 0.359$), with increased variability after ($M = 70.52$) when compared to before treatment ($M = 69.61$). A significant main effect of condition ($F_{(1,11)} = 5.88$, $p = 0.034$, $\eta p^2 = 0.348$) showed reduced variability in the win ($M = 48.81$) compared to the verbal condition ($M = 91.31$). Further, there were significant two-way interactions between time*age ($F_{(1,11)} = 7.41$, $p = 0.020$, $\eta p^2 = 0.403$), time*learning ($F_{(1,11)} = 5.73$, $p = 0.036$, $\eta p^2 = 0.343$) and time*condition ($F_{(1,11)} = 10.37$, $p = 0.008$, $\eta p^2 = 0.485$). Post hoc comparisons revealed significantly reduced variability in non-learners ($M = 53.04$) compared to learners ($M = 86.17$, $p = 0.010$) before treatment but not after treatment (learners: $M = 74.66$, non-learners $M = 66.38$, $p = 0.549$). Similarly,

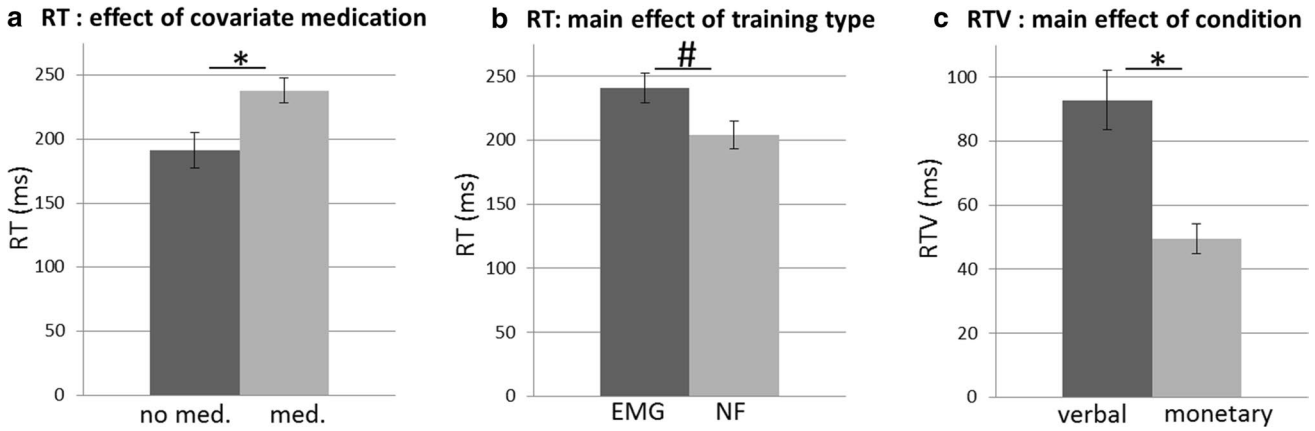

Fig. 1 Behavioral data results for comparison of training types. $^*p < 0.05$, $^\#p = 0.051$ Error bars indicate standard error of the mean

RTV was reduced in the win compared to the verbal condition before (win: $M=90.37$, verbal $M=48.85$, $p<0.001$) as well as after treatment (win: $M=92.26$, verbal $M=48.78$, $p=0.001$). Following up the interaction of time and covariate age with linear regressions, higher age was associated with reduced RTV after treatment ($F_{(1,13)}=10.40$, $R^2=0.444$, $b=-0.667$) but not before treatment ($F_{(1,13)}=3.02$, $R^2=0.188$, $b=-0.434$). Finally, significant three-way interactions between time*condition*learning ($F_{(1,11)}=5.52$, $p=0.039$, $\eta p^2=0.334$, see Fig. 2a) and time*condition*age ($F_{(1,11)}=11.13$, $p=0.007$, $\eta p^2=0.503$, see Fig. 2b) emerged. Post hoc analysis revealed that RTV differed significantly between conditions in non-learners after treatment (win: $M=41.02$, verbal $M=91.74$, $p=0.006$) and in learners before (win: $M=54.32$, verbal $M=118.03$, $p<0.001$) as well as after treatment (win: $M=56.54$, verbal $M=92.78$, $p=0.024$). RTV was further reduced in non-learners ($M=62.71$) compared to learners ($M=118.03$, $p=0.004$) in the verbal condition before treatment. Finally, non-learners showed a significant increase in RTV after ($M=91.74$) treatment compared to before treatment ($M=62.71$, $p=0.023$) in the verbal condition, while learners showed a decrease in RTV after treatment ($M=92.78$) compared to before treatment ($M=118.03$, $p=0.031$) in the verbal condition. Linear regressions showed that higher age was associated with reduced RTV in the verbal condition after ($F_{(1,13)}=16.87$, $R^2=0.565$, $b=-0.752$), but not before treatment ($F_{(1,13)}=1.51$, $R^2=0.104$, $b=-0.322$), while in the win condition there was a trend for reduced RTV with age only before treatment ($F_{(1,13)}=3.95$, $R^2=0.233$, $b=-0.483$).

Treatment outcome

The global ADHD score of the DISYPS questionnaires as rated by the parents showed a significant time *training type interaction ($F_{(1,10)}=5.87$, $p=0.036$, $\eta p^2=0.370$), with decreased scores after training ($M=1.05$) compared to before training ($M=1.52$, $p=0.018$) only in the NF group, but not in the EMG group (pre: $M=0.97$, post: $M=1.12$, $p=0.427$). There were no significant main effects or interactions regarding learning.

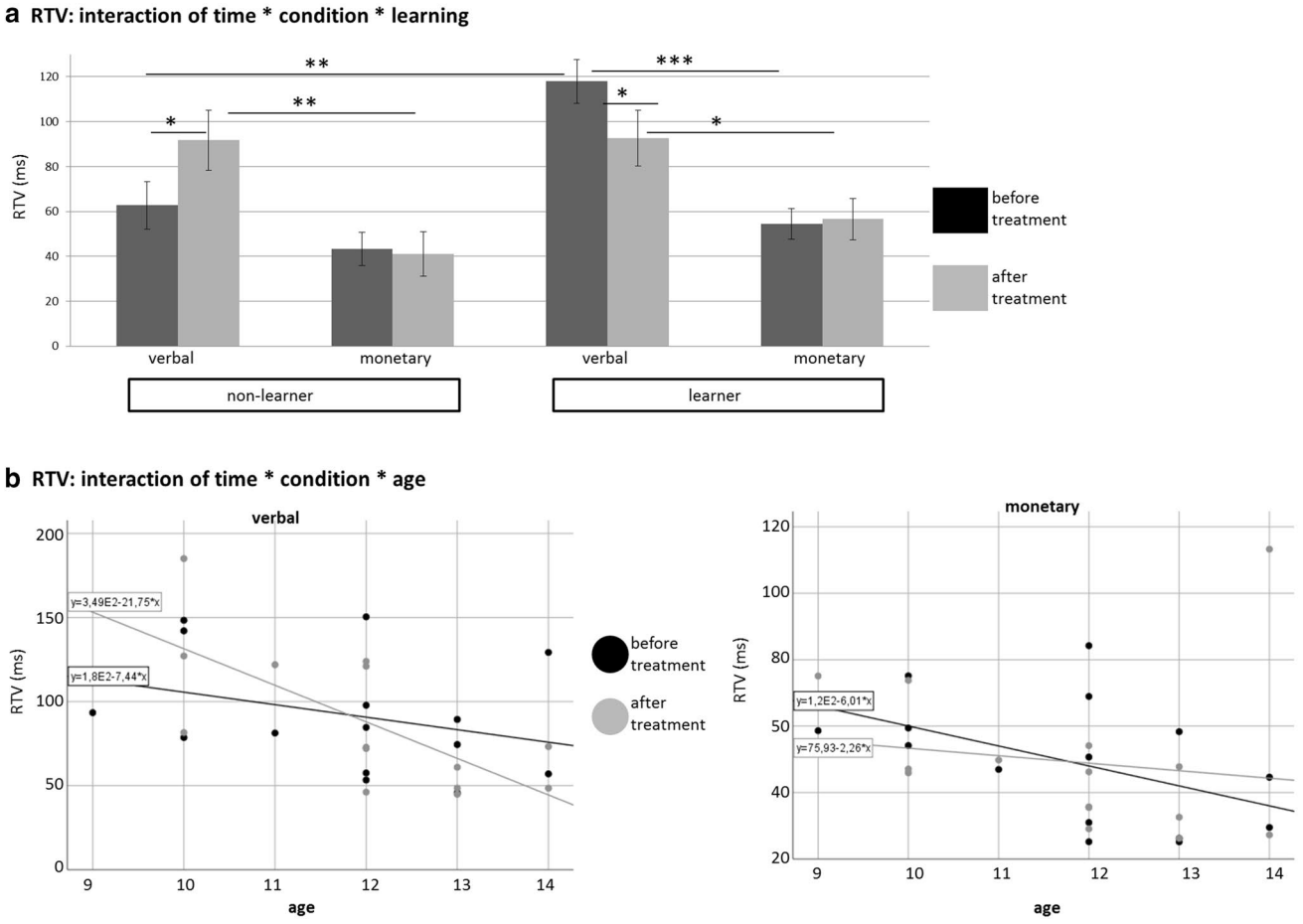

Fig. 2 Behavioral data results for comparison of learners and non-learners. *$p<0.05$, **$p<0.01$, ***$p<0.001$. Error bars indicate standard error of the mean

fMRI results

Comparison of training types

During reward anticipation, the whole brain analysis yielded a significant main effect of time in the right mPFC as well as a significant main effect of training type in a number of regions comprising frontal, temporal, occipital and limbic structures as well as the cerebellum (see Table 2 for complete list of regions and Fig. 3a, b). Subsequent t tests revealed the direction of the effect with increased activation after treatment compared to before treatment and increased activation in the NF compared to the EMG group, respectively. A significant effect of the covariate medication emerged in the

Table 2 Peak activations for the flexible factorial design with the within-subject factor time, between-subject factor treatment type and covariate medication status

Region	Hemisphere	Label	*F*	*p*(unc)	*x*	*y*	*z*
Reward anticipation							
Main effect time							
Frontal	r	Medial Frontal Gyrus (mPFC)+	45.14	0.000	12	56	−7
Frontal	r	Medial Frontal Gyrus (mPFC)+	24.17	0.000	3	53	−4
Main effect treatment							
Cerebellum	l	Declive*	54.09	0.000	−30	−70	−19
Cerebellum	r	Culmen*	35.54	0.000	6	−37	−4
Cerebellum	r	Culmen*	26.41	0.000	0	−46	−4
Cerebellum	r	Cerebellar Tonsil*	25.42	0.000	18	−55	−43
Frontal	l	Middle Frontal Gyrus*	53.89	0.000	−33	47	14
Limbic	l	Posterior Cingulate*	41.65	0.000	−6	−40	11
Limbic	r	Posterior Cingulate	22.83	0.000	6	−40	11
Limbic	r	Cingulate Gyrus*	33.69	0.000	0	−4	29
Occipital	r	Middle Occipital Gyrus*	67.06	0.000	36	−76	5
Occipital	r	Fusiform Gyrus*	45.77	0.000	36	−76	−19
Occipital	l	Middle Occipital Gyrus	33.4	0.000	−24	−76	−1
Occipital	l	Lingual Gyrus*	26.28	0.000	−15	−88	−4
Occipital	l	Middle Occipital Gyrus*	20.26	0.001	−36	−85	−4
Parietal	l	Postcentral Gyrus*	27.34	0.000	−24	−40	71
Parietal	l	Inferior Parietal Lobule*	25.8	0.000	−63	−43	23
Sublobar	l	Calcarine*	27.4	0.000	−21	−55	8
Sublobar	l	White Matter*	34.02	0.000	−27	−52	20
Sublobar	l	White Matter*	25.04	0.000	−24	−22	8
Temporal	r	Fusiform Gyrus*	27.51	0.000	42	−55	−16
Temporal	r	Inferior Temporal Gyrus*	20.28	0.001	48	−61	−13
Temporal	r	Superior Temporal Gyrus	26.85	0.000	39	−46	8
White Matter	r	Corpus Callosum*	28.68	0.000	12	−37	23
White Matter	r	Corpus Callosum*	26.3	0.000	15	−43	17
Effect of medication							
Cerebellum	r	NA	23.39	0.000	0	−37	−7
Occipital	l	Lingual Gyrus†	28.23	0.000	−24	−73	−1
Temporal	l	Superior Temporal Gyrus†	29.37	0.000	−66	−40	17
Reward receipt							
Main effect treatment							
Limbic	r	Cingulate Gyrus*	51.1	0.000	3	−19	29
Limbic	r	Cingulate Gyrus*	46.71	0.000	0	−31	23
Effect of medication							
Parietal	r	Inferior Parietal Lobule†	36.28	0.000	54	−49	50
Temporal	r	Middle Temporal Gyrus†	52.61	0.000	63	−28	−10

Results reported at $p_{\text{uncorr.}} < .001$, $k = 10$. Regions marked * show greater activation in the NF compared to the EMG group. Regions marked + show greater activation before compared to after treatment. Regions marked† show greater activation in unmedicated compared to medicated patients. *mPFC* medial prefrontal cortex

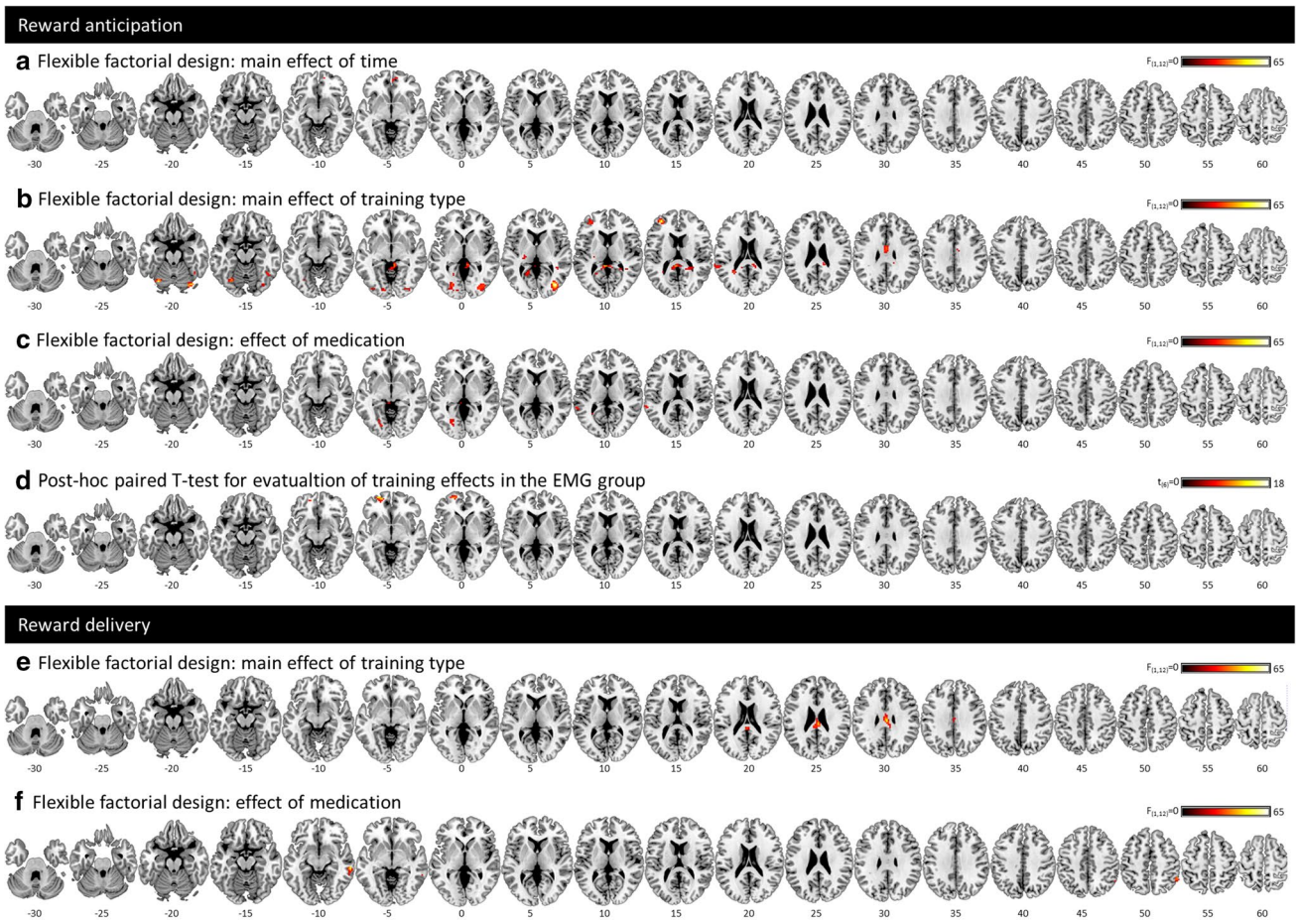

Fig. 3 Brain activations for the flexible factorial design with the within-subject factor time, between-subject factor training type and covariate medication status. **a**–**d** Reward anticipation and **e**, **f** reward receipt. All results reported at $p_{\text{uncorr.}} < .001$, $k = 10$

left superior temporal gyrus (STG), cerebellum and lingual gyrus with increased activation in unmedicated compared to medicated patients (see Fig. 3d). There was no significant interaction of group and training type.

During reward delivery, a significant main effect of training type yielded a cluster in the right cingulate gyrus and corpus callosum with increased activation in the NF compared to the EMG group.

Subsequent paired t tests showed increased activation in the left superior frontal gyrus (SFG) after training compared to before training in the EMG group only (see Fig. 3d and Table 4). Activation in clusters in the inferior parietal lobule (IPL) and middle temporal gyrus (MTG) was increased in unmedicated patients (Fig. 3f). There was no significant interaction of group and training type.

The ROI analysis of the VS yielded a borderline significant main effect of time ($F_{(1,12)} = 4.580$, $p = 0.053$, $\eta p^2 = 0.278$, see Fig. 4a) in the left VS during reward anticipation with increased activation after treatment ($M = 1.79$) compared to before treatment ($M = 1.16$). Activation in the right VS showed the same pattern, but was not significant ($F_{(1,12)} = 3.2$, $p = 0.099$, $\eta p^2 = 0.211$). There was no significant effect of training type on VS activation and no significant interactions.

Comparison of learners and non-learners

During reward anticipation, a significant main effect of time emerged in the left middle frontal gyrus (MFG)/DLPFC as well as a main effect of learning in a number of regions comprising frontal, temporal, occipital and limbic structures as well as subcortical structures such as the left thalamus, left (dorsal) caudate and putamen (see Table 3 for complete list of regions and Fig. 5). Subsequent t tests revealed the direction of the effect with increased activation in non-learners compared to learners. A significant time * learning interaction yielded a significant cluster in the left inferior frontal gyrus. Subsequent paired *t* test showed that the effect in this region was due to increased activation after treatment compared to before treatment in learners only (see Fig. 5e and

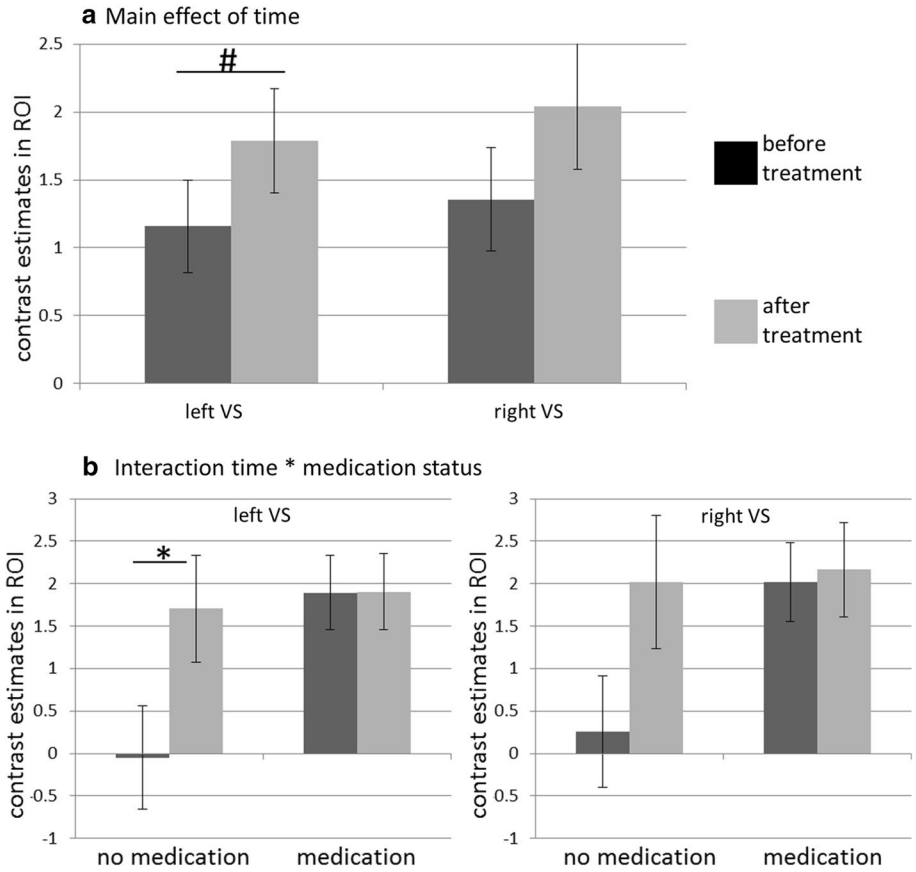

Fig. 4 ROI ventral striatum (VS) data **a** main effect of time and **b** interaction of time * medication status. *$p < 0.05$, #$p = 0.053$ Error bars indicate standard error of the mean

Table 4). Medication was associated with increased activation in the left pre- and postcentral gyri, IPL, STG, occipital gyrus and left temporal pole (Fig. 5d).

There were no main effects or interactions regarding reward delivery; however, activation was significantly reduced after treatment in learners only in the cerebellum, right caudate and left middle frontal gyrus (see Table 4 and Fig. 5f).

The ROI analysis of the VS yielded a significant time*medication interaction ($F_{(1,11)} = 5.40$, $p = 0.047$, $\eta p^2 = 0.312$, see Fig. 4b) in the left VS during reward anticipation. Post hoc analysis revealed that this interaction was based on a significant increase in activation in the left VS after treatment ($M = 1.71$) compared to before treatment ($M = -0.50$, $p = 0.021$) in unmedicated patients only, but not in medicated patients (pre: $M = 1.90$, post: $M = 1.90$, $p = 0.987$). There was no significant effect of learning on VS activation.

Discussion

The present study is the first to investigate the effects of NF or learning on neural reward processing in ADHD.

ROI analysis of the VS during reward anticipation showed a large effect with an overall increase in left VS activation after compared to before treatment irrespective of treatment type. Thus, this could suggest that ADHD patients improved in both treatment groups. However, when investigating learning effects, an interaction with the covariate medication status indicated that VS activation only increased in unmedicated patients. In contrast, medicated patients exhibited no increase in VS activation after treatment. As stimulant medication has been shown to compensate striatal dysfunction in ADHD (Aarts et al. 2015), one could speculate that medicated patients do not show neurophysiological deficits in VS activation and thus no room for improvement by other therapy forms such as NF remains. Interestingly, medicated patients overall exhibited slower RTs compared to unmedicated patients, suggesting that the neurophysiological normalization of VS activation not necessarily led to an increase in performance.

In whole brain analyses, we found increased activation during reward anticipation after treatment irrespective of treatment type in the right mPFC and left DLPFC. For both of these regions, decreased activation has been reported in ADHD compared to controls (Chantiluke et al. 2014; Hauser et al. 2014; van Dongen et al. 2015). Thus, an increase in activation in these regions can be interpreted as

Table 3 Peak activations for the flexible factorial design with the within-subject factor time, between-subject factor learning and covariates age and medication status

Region	Hemisphere	Label	*F*	*p*(unc)	*x*	*y*	*z*
Reward anticipation							
Main effect time							
Frontal	l	Middle Frontal Gyrus (DLPFC)+	22.16	0.001	−30	20	50
Main effect learning							
Frontal	r	Superior Frontal Gyrus/OFC*	41.22	0.000	18	53	−10
Frontal	r	Superior Frontal Gyrus/OFC*	25.32	0.000	30	59	−4
Frontal	l	White Matter*	28.57	0.000	−36	17	20
Limbic	r	Posterior Cingulate*	37.85	0.000	3	−40	5
Occipital	r	Cuneus*	45.39	0.000	9	−97	20
Occipital	r	Lingual Gyrus*	39.54	0.000	18	−79	−4
Occipital	r	Lingual Gyrus*	36.47	0.000	0	−76	−4
Occipital	r	Lingual Gyrus*	24.84	0.000	6	−79	−10
Occipital	r	Precuneus*	35.45	0.000	12	−91	38
Occipital	r	Cuneus*	26.97	0.000	24	−91	32
Occipital	r	Cuneus*	20.99	0.001	24	−88	23
Occipital	r	Middle Occipital Gyrus*	33.5	0.000	39	−73	8
Occipital	l	Middle Occipital Gyrus*	29.67	0.000	−48	−79	−1
Parietal	r	Paracentral Lobule*	28.96	0.000	6	−40	68
Sublobar	l	Caudate*	44.44	0.000	−24	−1	20
Sublobar	l	Extra-Nuclear*	30.87	0.000	−3	−4	8
Sublobar	r	Extra-Nuclear*	26.28	0.000	12	−1	11
Sublobar	l	Thalamus*	22.89	0.001	−3	−16	8
Sublobar	l	Putamen*	30.3	0.000	−24	2	−1
Temporal	l	Temporal Pole*	45.96	0.000	−36	5	−28
*Interaction learning*time*							
Frontal	l	Inferior Frontal Gyrus	34.88	0.000	−33	35	11
Effect of medication							
Frontal	l	Precentral Gyrus†	22.5	0.001	−48	−13	59
Occipital	r	Middle Occipital Gyrus†	33.18	0.000	33	−88	14
Parietal	l	Postcentral Gyrus†	34.44	0.000	−51	−22	56
Parietal	l	Inferior Parietal Lobule†	32.52	0.000	−51	−46	53
Parietal	l	Inferior Parietal Lobule†	29.37	0.000	−48	−55	50
Parietal	r	White Matter	21.01	0.001	36	−49	23
Temporal	r	Superior Temporal Gyrus†	41.97	0.000	33	17	−31
Temporal	l	Temporal Pole†	26.84	0.000	−36	5	−28
Temporal	r	Superior Temporal Gyrus†	26.71	0.000	39	−52	14

Results reported at $p_{\text{uncorr.}} < .001$, $k = 10$. Regions marked * show greater activation in learners compared to non-learners. Regions marked + show greater activation before compared to after treatment. Regions marked† show greater activation in medicated compared to unmedicated patients. *OFC* orbitofrontal cortex, *DLPFC* dorsolateral prefrontal cortex

an improvement of deficient brain function irrespective of treatment type. While an increase in activation could potentially also be explained by repletion effects, the prefrontal cortex activation during reward processing has high internal consistency (Luking et al. 2017) and has yielded activation decrease, not increase in a test–retest design (Balodis et al. 2016).

A specific, treatment-induced increase in brain activation was found for the EMG group during reward anticipation in the left SFG/OFC. This region receives more than 30% of the projections from the ventral tegmental area (Coenen et al. 2018), a region responding to appetitive and aversive stimuli (Hayes et al. 2014). Increased activation has been demonstrated in the SFG/OFC in subjects with internet addiction disorder compared to healthy controls during reward delivery (Dong et al. 2013). It has been further linked to increased self-efficacy to abstain from alcohol and showed a correlation of activation changes during reward processing after cue exposure training with increased baseline striatal reward sensitivity (Becker et al. 2018).

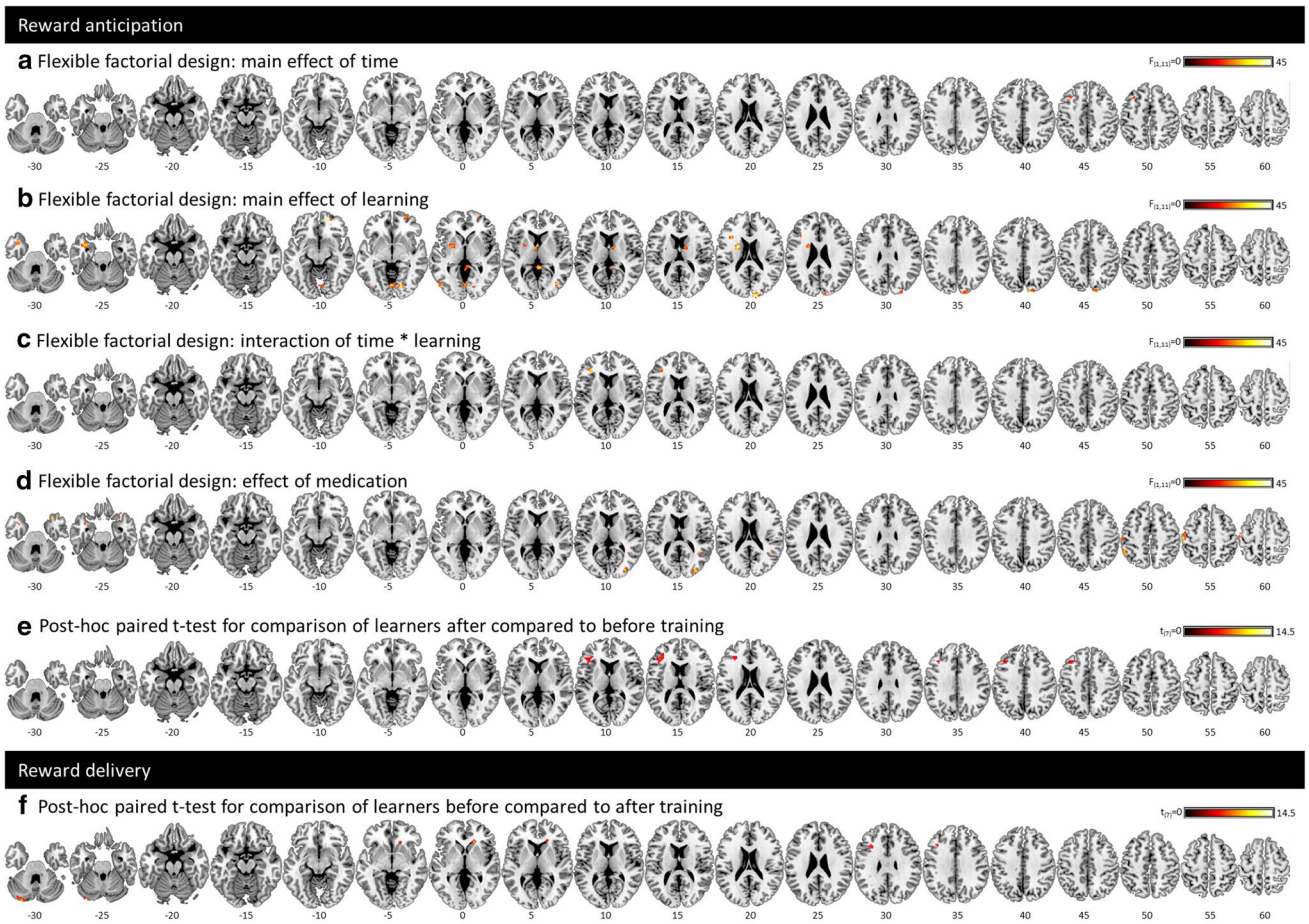

Fig. 5 Brain activations for the flexible factorial design with the within-subject factor time, between-subject factor learning and covariates medication status and age. **a**–**e** Reward anticipation and **f** reward receipt. All results reported at $p_{\text{uncorr.}} < .001$, $k = 10$

Table 4 Peak activations for the paired *T* tests for comparisons of patients in EMG group before and after training as well as learners before and after training

Region	Hemisphere	Label	*T*	*p*(unc)	*X*	*y*	*z*
Reward anticipation							
EMG group post-treatment > pre-treatment							
Frontal	l	Superior Frontal Gyrus/OFC	19.03	0.000	−21	56	−7
Learner post-treatment > pre-treatment							
Frontal	l	Inferior Frontal Gyrus	6.88	0.000	−39	29	14
Frontal	l	Inferior Frontal Gyrus	6.57	0.000	−33	35	14
Frontal	l	Inferior Frontal Gyrus	5.27	0.001	−45	23	17
Frontal	l	Middle Frontal Gyrus (DLPFC)	5.58	0.000	−39	26	38
Reward receipt							
Learner pre-treatment > post-treatment							
Cerebellum	l	Declive	14.56	0.000	−33	−85	−25
Cerebellum	l	Declive	9.96	0.000	−27	−88	−31
Sublobar	r	Caudate	10.07	0.000	18	29	−1
Frontal	l	Middle Frontal Gyrus (DLPFC)	7.67	0.000	−33	17	32

Results reported at $p_{\text{uncorr.}} < .001$, $k = 10$. *OFC* orbitofrontal cortex, *DLPFC* dorsolateral prefrontal cortex

Similarly, a specific, treatment-induced increase in brain activation was found in learners during reward anticipation in the left IFG and DLPFC, while during reward delivery activation decreased after treatment in the cerebellum, right caudate and left DLPFC. Increases in activation in IFG and DLPFC during reward anticipation may be interpreted as functional improvement in these regions, given that these have been shown to be hypoactive in ADHD (Chantiluke et al. 2014; Rubia et al. 2009b; van Dongen et al. 2015). Likewise, the decrease in activation during reward delivery in the left caudate head as part of the ventral striatum might be interpreted as beneficial on the neurophysiological level, as VS hyperactivation during reward delivery has been reported in ADHD (Kohls et al. 2014; Paloyelis et al. 2012; von Rhein et al. 2015). On the behavioral level, the interaction between time, condition and learning indicated that learners showed significantly reduced RTV after treatment in the verbal condition, while non-learners showed an increase in RTV. RTV in the monetary condition was not affected by treatment. As it has been demonstrated that task performance in ADHD patients is particularly sensitive to rewards (Luman et al. 2005; Uebel et al. 2010), the lacking impact of treatment on RTV in the monetary condition might be explained by subjects already performing at maximum under this condition. In contrast, reduced RTV in the verbal condition after treatment in learners may be viewed as a behavioral improvement, as responding more slowly and variably than healthy controls is consistently associated with ADHD (Kofler et al. 2013; Sjowall et al. 2013; Uebel et al. 2010).

Overall differences between groups emerged with patients in the NF group showing increased activation compared to the EMG group during reward anticipation in a number of regions where ADHD patients commonly exhibit deficits, such as middle and posterior parts of the cingulate cortex (extending into the posterior part of the corpus callosum), MFG, STG, occipital regions, cerebellum as well as the lingual gyrus. Further, patients in the NF group showed on average increased activation in the fusiform gyrus, a region associated with face processing (Muller et al. 2018), which is possibly due to improved discrimination of the cue smileys. Finally, greater IPL and postcentral activation likely reflect attentive control and reaction to the alerting (cue) stimuli (Singh-Curry and Husain 2009) and somatosensory processing, respectively. During reward delivery, patients in the NF group showed increased activation compared to the EMG group in middle and posterior parts of the cingulate cortex. While in most of these regions, hyperactivation is associated with ADHD (Chantiluke et al. 2014; Kohls et al. 2014; Rubia et al. 2009b; von Rhein et al. 2015), this is not the case for PCC (Rubia et al. 2009a).

Similarly, non-learners also exhibited increased activation in a number of reward-related regions, such as the PCC, OFC, lingual gyrus, precuneus, temporal pole, occipital regions, as well as (dorsal) caudate, thalamus (medial dorsal nucleus) and putamen. Again, hyperactivation has been demonstrated in ADHD for most of these cortical regions (Chantiluke et al. 2014; Kohls et al. 2014; Rubia et al. 2009b; von Rhein et al. 2015), while hypoactivation in ADHD has been shown in PCC, dorsal caudate, thalamus and putamen (Metin et al. 2018; Norman et al. 2018; Rubia et al. 2009a; Stoy et al. 2011). Based on these results, it cannot be concluded that the groups (NF and EMG or learners and non-learners) differ in terms of a general neurophysiological impairment. Instead, they seem to exhibit deviating patterns of activation with some enhanced and some diminished neurophysiological deficits. This is partly in line with behavioral data, showing no difference in ADHD symptom severity between groups. However, there was a difference in RT between the NF and the EMG groups, suggesting a better overall performance in the NF group.

Medication status affected activation in the right STG, with increased activation in medicated compared to unmedicated patients. This is in contrast to previous research, where STG hyperactivation was reduced by stimulant medication (Rubia et al. 2009a). Additionally, receiving stimulant medication was associated with increased activation in IPL, left pre- and postcentral gyrus as well as temporal pole and middle occipital gyrus.

Behavioral data yielded significant differences between the verbal and monetary condition in RTV (when investigating training types) and RT (when investigating learning). In line with the previous findings, RTs were faster and less variable when money was at stake (Demurie et al. 2011; van Dongen et al. 2015; von Rhein et al. 2015). Also in line with the literature and as previously described (Baumeister et al. 2018), the specific positive effect of NF training on parent-rated ADHD symptom severity was confirmed in this study with a significant decrease in symptoms after NF but not after EMG feedback.

While similar positive effects of both treatment types and of successful learning have been shown for inhibitory control (Baumeister et al. 2018), the results of the current study need to be considered carefully due to the small sample size. Most results presented in the current manuscript do not survive correction for multiple testing, thereby underlying increased risk of false-positive findings. However, effect sizes were large across the board, suggesting that this is indeed due to lack of power owed to the small sample size. Further, functional imaging effects also did not survive whole brain correction for multiple testing as often recommended for fMRI studies. However, uncorrected data are still commonly published when dealing with small patient groups. Moreover, the effect of learning was specific and robust across two paradigms despite the small groups. Importantly, the small sample size made it impossible to further subdivide

the groups of learners and non-learners according to training type. Thus, the present study is unable to answer the question whether learning of control over brain (NF) or muscular (EMG) activity yields differential results.

In summary, the present study suggests overall improvement in key reward processing regions (VS, mPFC, DLPFC) irrespective of treatment type and particularly for unmedicated patients. These effects most likely reflect the fact that both treatment types were employing a reward-based training protocol with additional reinforcement (token plan) (Holtmann et al. 2014a; Strehl et al. 2017). Additional, specific treatment effects were found for patients in the EMG group in the SFG/OFC and for learners in the IFG and DLPFC, indicating additional improvement in these regions of the reward circuit within these groups. Successful learning of self-regulation (irrespective of treatment type) was further linked to behavioral improvements (reduced RTV), combined with the fMRI results yet again highlighting the importance of successful learning for biofeedback studies. Despite the explorative nature of the present study due to its small sample size, this first study investigating NF effects on reward processing provides important first insights, suggesting no specific effects of NF on the level of brain activation. But future larger studies are needed to validate these results as well as further disentangle impacts of successful learning, medication status and treatment type on reward processing.

Acknowledgements This research was supported by the Deutsche Forschungsgemeinschaft (SFB 636). The authors thank Katharina Heubach, Elise Jezycki and Alexander Kraut for their assistance with data collection as well as administration of biofeedback training sessions, and Pascal Aggensteiner for fruitful discussions.

Compliance with ethical standards

Conflict of interest Tobias Banaschewski has served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM Scientific, Shire and Viforpharma. He received conference support or speaker's fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire and Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. Daniel Brandeis serves as an unpaid scientific consultant for an EU-funded neurofeedback trial. The present work is unrelated to the above grants and relationships. All other authors report no potential conflict of interest. The present work is unrelated to the above grants and relationships.

Ethics approval and consent to participate All subjects and their legal representatives gave written informed consent prior to their study participation. The study was approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University, Heidelberg.

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