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Original article

Transcranial magnetic stimulation in children with fetal alcohol spectrum disorder: A randomised, crossover pilot-trial

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1. Introduction

Fetal Alcohol Spectrum Disorders (FASD) is a term that encompasses the congenital disorders fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS) and alcohol-related neurodevelopmental disorder (ARND) resulting from prenatal alcohol exposure (PAE) [1]. FASD is one of the most common congenital disorders with a prevalence of 1.98 % in Europe [2], where 25.2 % of mothers consume alcohol during pregnancy [3]. PAE can irreversibly damage all organ systems [4] and impair cognitive and behavioural development [5], resulting in growth retardations (FAS), phenotypic facial dysmorphic features (FASD, pFAS) and heterogeneous functional and/or structural abnormalities of the central nervous system (FASD, pFAS, ARND) [1].

Within the heterogeneous group of functional impairments [6], executive functions (EF), attention and social-emotional regulation are essential for self-regulation [7] and crucial for adaptive behaviour and an independent everyday life [8–13]. Thus, early interdisciplinary treatments (e.g. occupational therapy, psychotherapy and pharmacotherapy) are crucial to compensate for developmental deficits and treat comorbidities [14,15]. However, pharmacotherapy is often associated with undesirable side effects [16], highlighting the need for treatment approaches with little to no systemic side effects, such as targeted non-invasive brain stimulation [17].

In repetitive transcranial magnetic stimulation (rTMS) neurons in superficial cortex areas are inductively depolarised by a changing magnetic field [18]. As a result, cortical excitability can be modulated, with changes persisting even beyond stimulation [19]. Observations of neuropsychological changes in addition to antidepressant effects in patients with treatment-resistant depression drew attention to modulation of neurocognitive domains via TMS [20,21].

A first clinical study conducted by our research group demonstrated the feasibility but no significant effects of 1Hz-rTMS in children with FASD [22]; a detailed investigation of neurocognitive effects including different rTMS protocols is still pending. In children with disorders showing overlapping symptoms – but differing pathogeneses – such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), TMS-effects on cognitive domains have already been observed.

Following 30 sessions of 10Hz-rTMS at 100 % resting motor threshold (RMT) over the right DLPFC, an open-label study in children with ADHD by Cao et al. (n = 64) demonstrated improvement in the domains of inattention, hyperactivity, oppositional defiance, and EF [23]. As a measure for stimulation intensity, the resting motor threshold is defined as the minimum stimulus intensity necessary to produce a minimal motor evoked response (about 50 μV in at least 5 of 10 trials) of the right abductor pollicis brevis at rest [24]. By applying 15 sessions of intermitted Theta Burst Stimulation (iTBS) at 100 % RMT over the right DLPFC in children with ASD, Abujadi et al. (n = 10) found an improvement in repetitive behaviour, obsessive compulsions, and EF [25].

In FASD, PAE disrupts network formation, visible as globally or locally decreased grey and white matter volume [26,27] and reflected by dysfunction in connectivity with prolongated signalling pathways and reduced functional connectivity of resting-state networks [28–30].

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Embedded in the frontoparietal network (FPN), functional considerations make the DLPFC a promising stimulation area for modulating EF, attention and social behaviour, as the FPN facilitates these higher cognitive processes, amongst others, via the adaptive activation and flexible coordination of other networks [31,32].

In this crossover study, we evaluated the feasibility and effects of high-frequency 10Hz-rTMS and iTBS over the left and right DLPFC, respectively, in children with FASD. Real low-frequency 1Hz-rTMS – expected to have no effect on FASD-symptoms – was used as control. The protocols chosen were based on current safety recommendations for TMS [17] and adapted from previously published protocols in children with ADHD and ASD, which were shown to be safe, feasible, and effective [23,25,33]. We assessed the feasibility of each stimulation protocol in terms of recruitment, acceptability, tolerability, and safety. Furthermore, we examined potential effects of rTMS on performance in executive functioning, attention, and social-emotional regulation as well as on participants' quality of life and everyday functioning. Finally, caregivers' quality of life and stress were also examined.

We hypothesized that the use of high-frequency 10Hz-rTMS and iTBS in children with FASD is feasible, well tolerated and safe. Our second hypothesis was that the use of high-frequency 10Hz-rTMS and iTBS in children with FASD leads to a significant improvement in attention, social-emotional regulation and executive functions. Furthermore, we hypothesized that the use of high-frequency 10Hz-rTMS and iTBS in children with FASD provides significant relief for families in terms of stress and quality of life of caregivers.

2. Methods and materials

2.1. Study design

This prospective crossover study took place at the Department of Paediatric Neurology, Dr. von Hauner Children's Hospital, LMU-University-Hospital, Munich, Germany, in cooperation with the Centre for Noninvasive Brain Stimulation at the Department of Psychiatry and Psychotherapy, LMU-University-Hospital, Munich, Germany.

The participants underwent three stimulation protocols of weekday stimulation for two weeks each. The order was randomised and counterbalanced (see Fig. 1). Each stimulation condition was followed by a break of at least two weeks, serving as a washout phase, to prevent any potential residual effects from influencing the subsequent protocol.

The participants were not blinded to the type of stimulation condition but to the intended effects. Seven of the participants were TMS-naïve, three had experienced 1Hz-rTMS.

The study was approved by the Ethics Committee of the Medical Faculty of LMU Munich (project number 21–0256). Written informed consent was obtained from participants and guardians.

2.2. Participants

Study participants were recruited from the "TESS outpatient clinic" (at-risk children with toxin exposure during pregnancy) at the iSPZ (interdisciplinary social-paediatric centre) of the Dr. von Hauner Children's Hospital of the LMU-University-Hospital Munich, Bavarian Social-Paediatric Centres (SPZ), and in FASD support groups.

Inclusion and exclusion criteria were formulated according to current guidelines by Rossi et al. [17] and are listed in Fig. 1a. Medication intake during the study was allowed if deemed necessary by the clinical team. Drugs associated with a reduction in seizure threshold were not administered. Before inclusion and at the end of the study period, a paediatric neurologist performed a neurological examination to rule out co-disorders and TMS-associated changes.

2.3. Intervention

2.3.1. Stimulation setup

A PowerMag Stimulator Clinical 100 with a maximum output of 160 J connected to a PMD70 pCool figure-of-eight coil (both MAG&More) was used. RMT was measured according to the standard relative frequency method [34]. The coil was placed tangentially, with the handpiece rotated 45° dorsally. The DLPFC was located using the Beam F3 method. Here, the corresponding electrode in the international 10–20 electroencephalography system that coincides with the projection of the DLPFC on the scalp gets calculated via three head measurements [35, 36].

2.3.2. Stimulation conditions

For lack of previous literature on different rTMS regimen in children with FASD, the choice of rTMS regimen was justified with existing studies on children with ADHD and ASD, as these clinical pictures differ in pathophysiology but overlap in neurocognitive symptoms:

The first stimulation condition (A) was a low-frequency 1Hz-rTMS over the left DLPFC at a stimulus intensity of 90 % RMT adapted from a study by Gómez et al. in children with ASD [33]. Per session, a total of 1500 stimuli were delivered within 27 min, containing 4 stimulation trains of 375 stimuli each with a 60s-intertrain interval (ON-time 375s, OFF-time 60s). While sham stimulation with a sham coil was not possible with our setup, real 1Hz-rTMS served as an implicit control due to its good feasibility and lack of significant effects in children with FASD [22].

The second stimulation condition (B) was a high-frequency 10Hz-rTMS over the right DLPFC at a stimulus intensity of 80 % RMT adapted from a study by Cao et al. in children with ADHD [23]. The intensity was lowered from 100 % RMT to 80 % RMT for better tolerability. Per session, a total of 2000 stimuli were delivered within 25 min, containing 50 stimulation trains of 4s ON-time and 26s OFF-time.

The third stimulation condition (C) was an iTBS protocol over the right DLPFC at a stimulus intensity of 70 % RMT, originally published by Huang et al. [37] and adapted from a study by Abujadi et al. in children with ASD [25]. Here, a theta burst stimulation pattern of 3 pulses at 50 Hz was repeated every 200 ms. Per session, a total of 600 stimuli were delivered within 3 min, containing 20 stimulation trains with 2s ON-time and 8s OFF-time. Due to setup-limitations, the stimulation intensity was adapted from 80 % AMT to 70 % RMT, guided by a study protocol by Enticott et al. [38].

2.3.3. Involving environment

TMS-effects have been demonstrated to depend on the state of baseline cortical activity and combining TMS with cognitive tasks suited to the stimulated area is suspected to have additional synergistic effects [39]. Therefore, participants played developmentally appropriate app-based games [40–43], challenging attention and planning skills during stimulation.

2.4. Outcomes

Feasibility was evaluated by investigating recruitment, acceptability, tolerability, and safety. Treatment response was assessed by comparing the effects of rTMS on EF, attention, social-emotional regulation, everyday functioning, and quality of life (QOL) of participants and caregivers.

2.5. Clinical and cognitive assessments

2.5.1. Feasibility

Safety, tolerability, acceptability and recruitment were evaluated as part of feasibility. The adherence rate was defined as % of participants with completion of $\geq$ two stimulation conditions with 8 out of 10 stimulation sessions. Detailed information on the methods used to assess

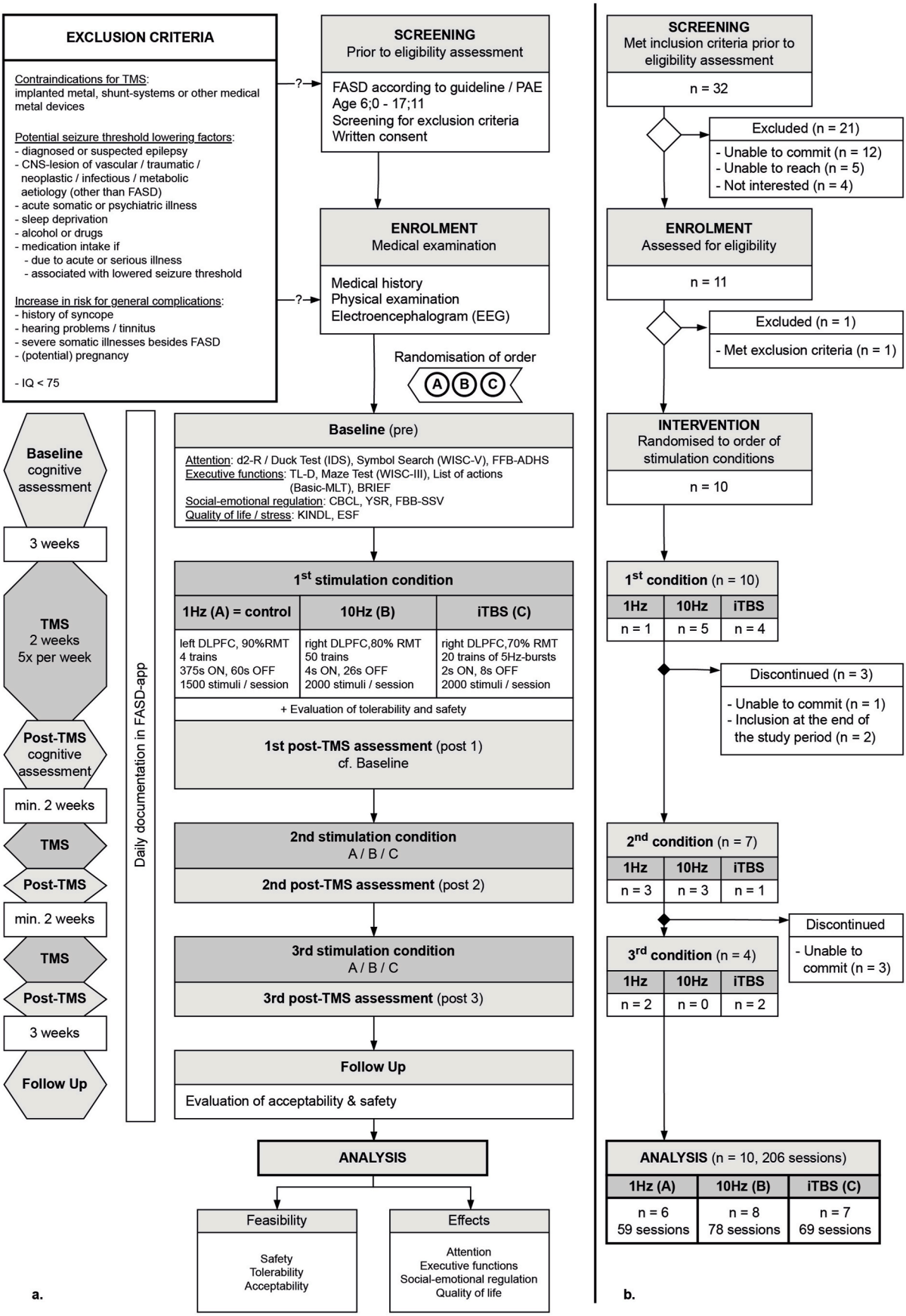

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Fig. 1. Flow diagram of recruitment and course of the study (**a**); number of participants, randomisation of stimulation conditions and reasons for exclusion and discontinuation in each study phase (**b**). Abbreviations: Basic-MLT = test battery on memory and learning; BRIEF = Behaviour Rating Inventory of Executive Function; CBCL = Child Behaviour Checklist; d2-R = d2 Test of Attention – Revised; DLPFC = Dorsolateral Prefrontal Cortex; ESF = Parental Stress Questionnaire (German); FASD = Fetal Alcohol Spectrum Disorders; FBB-ADHS = questionnaire on ADHD symptoms (subtest of DISYPS-III); FBB-SSV = questionnaire on conduct disorders (subtest of DISYPS-III); IDS = Intelligence and Developmental Scales; IQ = Intelligence quotient; iTBS = Intermittent Theta Burst Stimulation; KINDL = questionnaire on Health-Related Quality of Life of Children and Adolescents (German); PAE = Prenatal Alcohol Exposure; RMT = Resting Motor Threshold; TL-D = Tower of London (German version); rTMS = Repetitive Transcranial Magnetic Stimulation; WISC = Wechsler Intelligence Scales for Children; YSR = Youth Self-Report (children's version of the CBCL).

safety, tolerability, and acceptability, is provided in the previous paper by our research group [22] (for documentation forms and questionnaires see documents supp. 1–4 in the e-supplement).

2.5.2. Neurocognitive effects

At baseline (pre) and within one week after each stimulation condition (post 1, 2, 3), we performed age-adjusted cognitive assessments (see Fig. 1a). The BRIEF external (BRIEF = Behaviour Rating Inventory of Executive Function [44]) for caregivers was also repeated two weeks after completion of stimulation. The results attained at baseline were used as reference for all following protocols, and all results were transferred into T-values.

In addition, caregivers completed the German FASD parents' app daily during the study [45].

2.5.2.1. Attention. Sustained attention was directly assessed via performance in "go/no-go"-tasks. The revised d2 Test of Attention (d2-R [46]) or the Duck Test (subtest of the Intelligence and Development Scales – IDS [47]) were administered according to age, and all participants completed the Symbol Search (subtest of Wechsler Intelligence Scales for Children Fifth Edition – WISC-V [48]). For external assessment of ADHD symptoms, the German FBB-ADHS questionnaire (subtest of DISYPS-III [49]) was used.

2.5.2.2. Executive functions (EF). EF were tested via performance in the Tower of London (TL-D, German version [50]), the Maze Test (subtest of HAWIK III – German version of WISC-III [51]) and the subtest "list of actions" (subtest of Basic-MLT [52]).

For children ≥11 years, the BRIEF SBB was administered for self-assessment of executive function impairment in everyday life. For external assessment, the BRIEF for caregivers was used [44].

2.5.2.3. Social-emotional regulation. For children ≥11 years, the Youth Self-Report (YSR) was administered as a self-assessment, and caregivers completed the CBCL (Child Behavior Checklist [53]) as a tool for general behavioural problems. For external assessment of conduct disorders, the German FBB-SSV questionnaire (subtest of DISYPS-III [49]) was used.

2.5.2.4. Participants' everyday functioning and QOL. Caregivers evaluated the participants' everyday functioning by answering five Likert-scaled questions on the German FASD parents' app daily [45]. Participants' QOL was assessed via the KINDL questionnaire [54].

2.5.2.5. Caregivers' stress and QOL. Subjective caregivers' stress was evaluated via the Parental Stress Experience (subscale of ESF – parental stress questionnaire, German only [55]). Caregivers' quality of life was documented via the FASD parents' app.

2.6. Statistical analysis

Statistical analysis was performed using SPSS (Version 29) and R (Version 4.3.3) in RStudio (Version 2023.12.1 + 402) with a significance level of $\alpha = 0.05$. Distributions of continuous variables were tested for normality with Shapiro-Wilk test with $p < 0.05$: not normally distributed and $p > 0.05$: normally distributed. In this crossover study, due to the explorative character of the analysis in a small sample with repeated measurements no adjustment for multiple testing was performed. Graphs were created using ggplot2 in RStudio.

Feasibility: To examine the independence of categorical explanatory variables (stimulation conditions/units/weeks) and dependent variables (adverse events/impressions during stimulation/acceptability), Pearson's chi-square test and – in case of not fulfilling χ^2 requirements – Fisher's exact test were performed. Due to lack of clinical relevance, the comparison of means in VAS-scores (severity of AEs/pain sensations) between groups was not carried out. Regarding acceptability, Kruskal-Wallis and Friedman test were applied to compare mean grades for satisfaction and everyday practicability between groups.

Treatment response: To compare the means in T-scores of neurocognitive assessments, two-sided paired *t*-test or one-way repeated measures ANOVA were applied in case of normal distribution. In case of violation of the normal distribution assumption, Wilcoxon signed rank test or Friedman rank sum test were performed. To account for possible cumulative effects of repeated TMS over several weeks or practice effects, means of baseline and following each stimulation condition were compared in case of significant changes in a neurocognitive domain.

3. Results

3.1. Feasibility

3.1.1. Recruitment and patient collective

Fig. 1b illustrates the study timeline. Between March 2022 and February 2023, 10 of 32 potentially eligible patients could ultimately be included in the study (31.3 % recruitment rate; FAS n = 4, pFAS n = 4, ARND n = 1, PAE n = 1). The child with confirmed PAE was included because of relevant neurocognitive impairments, though not all were at least two standard deviations below the mean and therefore according to the German guideline without FASD-diagnosis. The main reasons for not participating in the study were high time expenditure, a long journey to the clinic or difficult family circumstances. 206 of 210 planned stimulation sessions were carried out.

Adherence rate was 70 % (≥2/3 stimulation conditions, 8/10 stimulation sessions), and retention rate was 100 % (until follow-up). In total, the 1Hz-rTMS condition (control) was completed 6 times (59 sessions), the 10Hz-rTMS condition 8 times (78 sessions) and the iTBS condition 7 times (69 sessions). On average, the time between the individual stimulation conditions was 52.2 days (7.5 weeks, SD: 31.9 days). Table A1 summarises the demographic characteristics of participants and caregivers as well as stable medication during stimulation.

3.1.2. Safety

Average RMT was 58.9 % (SD: 10.7 %, Range: 43.0–80.0 %), leading to a mean stimulation intensity of 55.4 % (SD: 11.8 %) for 1 Hz rTMS, 49.6 % (SD: 8.2 %) for 10 Hz rTMS and 43.4 % (SD: 8.5 %) for iTBS.

A total of 45 AEs were detected during or after stimulation, all of which were classified as mild and self-limiting, with no intervention needed (see Table A2 and Fig. 2A). The overall per-session risk was 21.8 %. Most AEs occurred with the 10Hz-rTMS condition (n = 27; 34.6 % per-session risk), followed by the iTBS (n = 12; 17.4 % per-session risk) and 1Hz-rTMS (n = 6; 10.2 % per-session risk), resulting in a significant difference in per session risks ($p = 0.002$) between protocols.

Among AEs, discomfort during the stimulation was rated mild on the Visual Analogue Scale (VAS). (See Tables e-A1-2 in e-supplement for

Table A1
Demographic characteristics and medication intake.

Participants (n = 10)		Caregivers (n = 10)	
Age (at study entry)	N	**Age**	N
Average age = 11; 11 years (SD = 2; 10 years)			
6; 0–10; 11 years	4 (40.0 %)	41–60 years	9 (90.0 %)
11; 0–14; 11 years	4 (40.0 %)	> 60 years	1 (10.0 %)
15; 0–17; 11 years	2 (20.0 %)		
Gender		**Gender**	
Female	4 (40.0 %)	Female	8 (80.0 %)
Male	6 (60.0 %)	Male	2 (20.0 %)
Diagnosis		**Kind of caregiver**	
FAS	4 (40.0 %)	Adoptive parent	2 (20.0 %)
pFAS	4 (40.0 %)	Foster parent	7 (70.0 %)
ARND	1 (10.0 %)	Grandparent	1 (10.0 %)
PAE	1 (10.0 %)		
School			
Special school	6 (60.0 %)		
Anthroposophic school (Steiner/ Waldorf)	2 (20.0 %)		
Secondary school	2 (20.0 %)		
Medication			
One stimulant per day (Aripiprazole/ Lisdexamfetamine/Methylphenidate)	4 (40.0 %)		
Two medications per day (Lisdexamphetamine & Risperidone)	1 (10.0 %)		
No medication	5 (50.0 %)		

Table A1: ARND = Alcohol-related neurodevelopmental disorder; FAS = Fetal Alcohol Syndrome; PAE = confirmed Prenatal Alcohol Exposure; pFAS = partial Fetal Alcohol Syndrome.

Table A2
Types and severity of adverse events per stimulation condition.

	Total	1 Hz	10 Hz	iTBS	p
Adverse Events					
N/percentage of total [%]	45 [100]	6 [13.3]	27 [60.0]	12 [26.7]	****0.002**[a]
Per session risk [%]	21.8	10.2	34.6	17.4	
Severity on VAS – mean (SD)	1.9 (1.4)	1.5 (0.5)	2.1 (1.7)	1.8 (0.4)	-[c]
Missing	6	0	3	3	
Local pain/paraesthesia over DLPFC					
N/percentage of condition [%]	26 [57.8]	4 [66.7]	19 [70.4]	3 [25.0]	*****< 0.001**[a]
Severity on VAS – mean (SD)	2.0 (1.7)	1.3 (0.5)	2.3 (1.9)	1.3 (0.6)	-[c]
Pain radiating from DLPFC					
N/percentage of condition [%]	3 [6.7]	1 [16.7]	–	2 [16.7]	0.384[b]
Severity on VAS – mean (SD)	2.0 (0.0)	2.0 (–)	–	2.0 (0.0)	–
Headache					
N/percentage of condition [%]	4 [8.9]	–	3 [11.1]	1 [8.3]	0.461[b]
Severity on VAS – mean (SD)	1.4 (0.8)	–	1.2 (0.8)	2.0 (–)	–
Tiredness					
N/percentage of condition [%]	3 [6.7]	–	2 [7.4]	1 [8.3]	0.779[b]
Severity on VAS – mean (SD)	1.7 (0.6)	–	1.5 (0.7)	2.0 (–)	–
Dizziness					
N/percentage of condition [%]	3 [6.7]	1 [16.7 %]	–	2 [16.7]	0.384[b]
Severity on VAS – mean (SD)	2.0 (0.0)	2.0 (–)	–	2.0 (0.0)	–
Sleep Disturbance (problems falling or staying asleep)					
N/percentage of condition [%]	5 [11.1]	–	2 [7.4]	3 [25.0]	0.325[b]
Severity on VAS – mean (SD)	n.a.	–	n.a.	n.a.	–
Sweating at night					
N/percentage of condition [%]	1 [2.2]	–	1 [3.7]	–	1.000[b]
Severity on VAS – mean (SD)	n.a.	–	n.a.	–	–

Table A2: Count of adverse events, per-session risks and severity of adverse events per stimulation condition. Data is presented either as count [percentage] or mean (standard deviation). a = Pearson Chi^2; b = Fisher's exact test; c = No significance testing due to lack of clinical relevance. Abbreviations: n.a. = no answer; VAS = Visual Analogue Scale. Statistical significance: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Non-significant comparisons are not marked.

additional information on the onset and duration of AEs.)

3.1.3. Tolerability

Patients' impressions during stimulation are summarized in Fig. 2B (for additional information see Tables e-A3-4 in e-supplement). The sounds of the stimulation device were mostly considered perceptible (87.4 %), the scalp sensations as slight pinching (77.7 %). In general, sessions were rated as pleasant by 65.0 %. When ranked within eight potentially pleasant or unpleasant everyday events, a total of 44.2 % of the sessions achieved positions 1 to 4. The severity of painful sensations during or after stimulation was rated very low on VAS ($mean_{pre} = 0.26$, $SD = 0.90$; $mean_{post} = 0.02$, $SD = 0.17$).

3.1.4. Acceptability

81.0 % of caregivers were willing to re-participate, 90.5 % would recommend the treatment to other patients with FASD. For additional information see Table e-A5 in the e-supplement. None of the inter-condition differences reached significance.

3.2. Neurocognitive effects

3.2.1. Attention

For pre- and post-scores in the assessment of attention, see Table B1/ Fig. 3A. There was a significant improvement in D2-R and Symbol Search (WISC-V) T-scores in both the 10Hz (D2R: mean = 41.3 to mean = 50.9, $p < 0.001$; Symbol Search: mean = 40.8 to mean = 45.8, $p = 0.036$) and iTBS stimulation condition (D2R: mean = 40.0 to mean = 53.6, $p = 0.005$; Symbol Search: mean = 41.4 to mean = 49.5, $p = 0.042$). No significant changes were found in the FBB-ADHS in all three different stimulation forms. All tests showed no pre/post-difference in the 1Hz-control.

When evaluating performance in attention over the course of the study (see Table e-B1 in e-supplement) - regardless of stimulation protocol – a significant increase of ≥1 SD between baseline and the third stimulation unit was found for D2-R T-scores ($mean_0 = 43.0$ to $mean_3 = 57.3$; Friedman rank sum test, $p = 0.007$, Chi^2 (3) = 12.0, $p_{03} < 0.001$) and an increase for Symbol Search T-scores did not reach statistical significance ($mean_0 = 40.8$ to $mean_3 = 49.2$; Friedman rank sum test, $p = 0.092$, Chi^2 (3) = 6.44).

3.2.2. Executive functions

For pre- and post-scores in the assessment of EF, see Table e-B2 in e-supplement. There were no significant changes in the neurocognitive assessment. Although non-significant, TL-D T-scores for the iTBS stimulation condition improved by > 1 SD ($mean_{pre} = 51.5$ to $mean_{post} = 61.7$, two-sided paired *t*-test, $p = 0.084$, t (6) = −2.07). Additionally, there was an increase of >1 SD in TL-D T-scores ($mean_0 = 50.6$ to $mean_3 = 61.7$) over the study period (see Table e-B3 in e-supplement). The

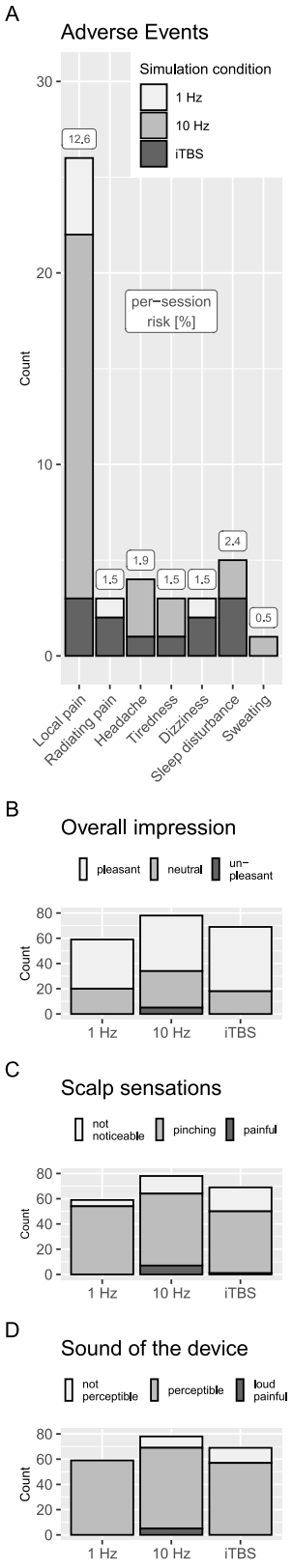

Fig. 2. Adverse Events per stimulation condition – count and per-session risk– (**A**) and tolerability of each stimulation condition regarding the overall impression (**B**), scalp sensations (**C**) and sound of the stimulation device (**D**).

Table B1
Attention and social-emotional regulation – comparison of pre- and post-rTMS means in neurocognitive assessment per stimulation condition.

Attention					
	Stimulation condition	N	Pre Mean (SD)	Post Mean (SD)	p
D2-R	Total	6	41.3 (10.0)	52.7 (8.5)	
	1 Hz (control)	4	43.0 (9.5)	54.2 (6.7)	p = 0.050[a]; t (3) = −3.19
	10 Hz	6	41.3 (10.0)	50.9 (8.4)	***p < 0.001[a]; t(5) = −7.11; d = 3.31
	iTBS	5	40.0 (10.6)	53.6 (11.1)	**p = 0.005[a]; t(4) = −5.72; d = 5.32
Symbol Search (WISC-V)	Total	10	42.0 (6.7)	47.8 (8.9)	
	1 Hz (control)	6	42.2 (4.5)	48.3 (8.9)	p = 0.089[a]; t (5) = −2.10
	10 Hz	8	40.8 (6.1)	45.8 (8.3)	*p = 0.036[b]
	iTBS	7	41.4 (6.3)	49.5 (10.4)	*p = 0.042[a]; t (6) = −2.57; d = 8.35
FFB-ADHS (DISYPS-III)	Total	10	63.5 (4.1)	62.9 (5.8)	
	1 Hz (control)	6	63.3 (5.2)	63.3 (7.5)	p = 1.000[b]
	10 Hz	8	63.1 (4.6)	62.5 (4.6)	p = 0.773[b]
	iTBS	7	62.1 (3.9)	62.9 (6.4)	p = 0.773[b]
Social-emotional regulation	**Stimulation condition**	**N**	**Pre** Mean (SD)	**Post** Mean (SD)	**p**
YSR Self-assessment	Total	6	57.3 (8.0)	51.7 (7.8)	
	1 Hz (control)	4	59.8 (6.8)	51.8 (9.1)	p = 0.100[b]
	10 Hz	6	57.3 (8.0)	51.7 (8.6)	*p = 0.015[a]; t (5) = 3.62; d = 3.83
	iTBS	5	56.8 (8.8)	51.6 (7.6)	*p = 0.025[a]; t (4) = 3.47; d = 3.35
CBCL External assessment	Total	10	69.6 (11.6)	68.3 (10.0)	
	1 Hz (control)	6	73.2 (10.4)	72.7 (10.1)	p = 0.807[a]; t (5) = 0.26;
	10 Hz	8	68.8 (12.9)	66.6 (11.6)	p = 0.216[a]; t (7) = 1.36;
	iTBS	7	66.7 (9.4)	66.6 (8.2)	p = 0.930[a]; t (6) = 0.09;
FBB-SSV (DISYPS-III)	Total	10	65.0 (5.3)	65.2 (4.9)	
	1 Hz (control)	6	65.8 (6.7)	66.7 (4.1)	p = 1.000[b]
	10 Hz	8	64.4 (5.6)	65.0 (6.0)	p = 1.000[b]
	iTBS	7	64.3 (6.1)	64.3 (4.5)	p = 1.000[b]

Table B1: Comparison of pre (baseline) and post (following each stimulation condition) mean T-scores in the neurocognitive assessment of attention and social-emotional regulation per stimulation condition. Data is presented as mean (standard deviation). a = two-sided paired *t*-test; b = Wilcoxon signed rank test. Abbreviations: CBCL = Child Behaviour Checklist; d2-R = d2 Test of Attention – Revised; FBB-ADHS = questionnaire on ADHD symptoms (subtest of DISYPS-III); FBB-SSV = questionnaire on conduct disorders (subtest of DISYPS-III); WISC-V = Wechsler Intelligence Scales for Children, Version V; YSR = Youth Self-Report (children's version of the CBCL). Statistical significance: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Non-significant comparisons are not marked.

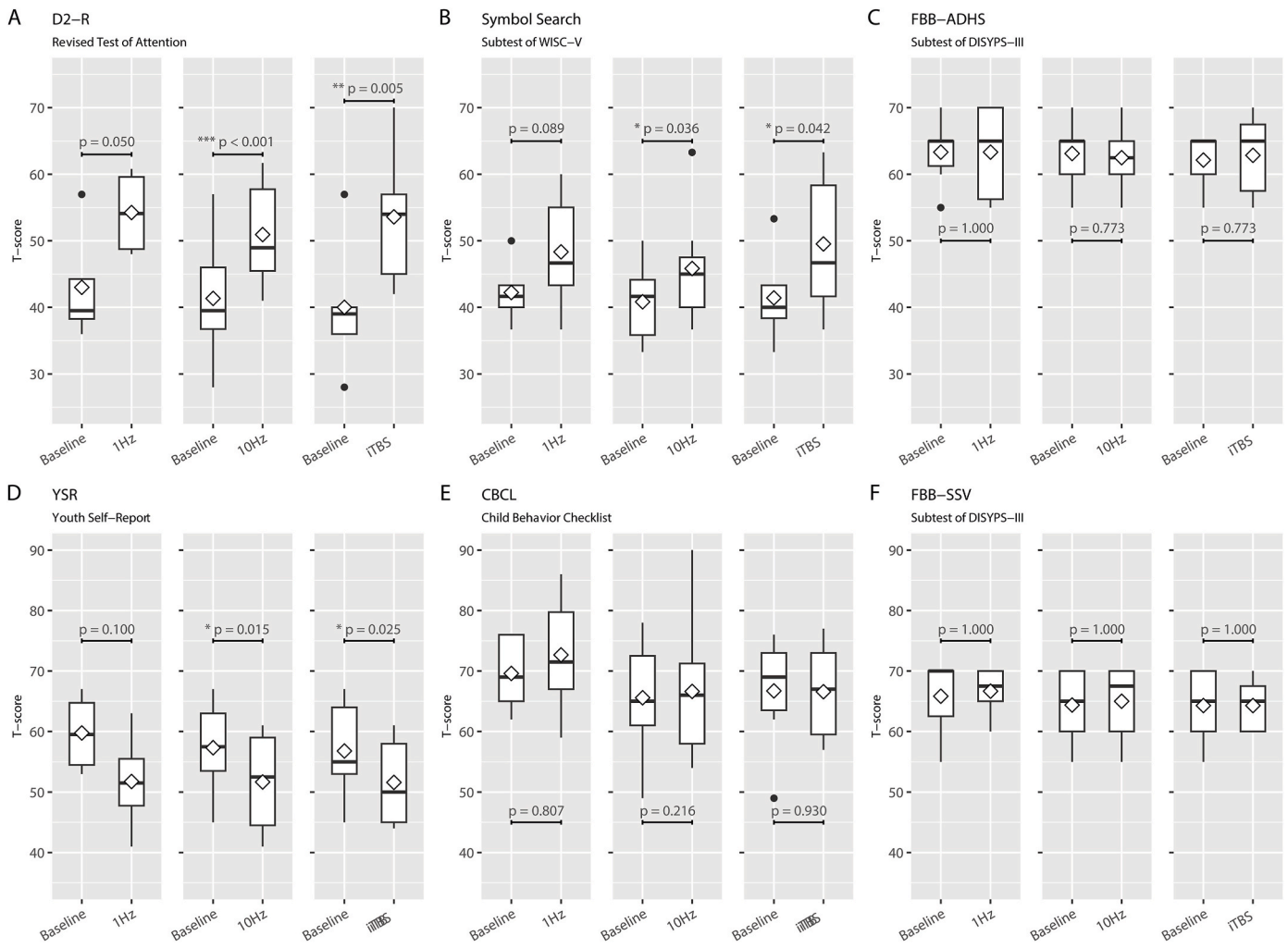

Fig. 3. Comparison of pre (baseline) and post (following each stimulation condition) mean T-scores in the neurocognitive assessment of attention (**A, B, C**) and social-emotional regulation (**D, E, F**) per stimulation condition (1Hz-rTMS (control), 1Hz-rTMS, iTBS). Statistical significance: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Non-significant comparisons are not marked.

parents' external assessment consistently indicated a clinically significant impairment of EF (BRIEF external, $mean_0 = 73.1$ to $mean_{3\text{-}2} = 72.8$), whereas EF in the children's self-assessment improved by almost one SD over the course of the study and were not perceived as impaired (BRIEF self-assessment, $mean_0 = 52.8$ to $mean_3 = 43.8$).

3.2.3. *Social-emotional regulation*

For pre- and post-scores in the assessment of social-emotional regulation, see Table B1/Fig. 3B. There was a significant improvement in YSR T-scores in 10Hz-rTMS (mean = 57.3 to mean = 51.7, p = 0.015) and iTBS (mean = 56.8 to mean = 51.6, p = 0.025). No significant changes were found in the corresponding external assessment via CBCL and the FBB-SSV (here scores ≥65 indicate clinically significant conduct disorders) in all three stimulation conditions. All tests showed no pre/post-difference in the 1Hz-control.

When evaluated over time (see Table e-B4 in e-supplement), YSR T-scores decreased significantly by > 1 SD ($mean_0 = 59.8$ to $mean_3 = 51.2$; Friedman rank sum test, $p = 0.039$, $Chi^2\ (3) = 8.38$, $p_{03} = 0.026$). In the self-assessment no general behavioural problems were present, which was not reflected in the corresponding external assessment (CBCL). Stable mean T-scores >63 indicated a clinically significant impairment ($mean_0 = 69.6$ to $mean_3 = 67.5$).

3.2.4. *Participants' everyday functioning and QOL*

For pre- and post-scores in the assessment of children's QOL and everyday functioning, see Table e-B5 in e-supplement. There were no significant changes in self- or external assessment of children's QOL or daily behaviour during the stimulation period graded via the FASD parents' app.

Over the course of the study (see Table e-B6 in e-supplement), the participants reported an above-average QOL ($mean_0 = 76.7$ to $mean_3 = 80.1$), while their caregivers rated it lower by about one SD ($mean_0 = 63.8$ to $mean_3 = 68.3$). The evaluation of behaviour alternated between 2 "good day" and 3 "medium day" ($mean_0 = 2.81$ to $mean_{3\text{-}3} = 2.47$).

3.2.5. *Caregivers' stress and QOL*

For pre- and post-scores in the assessment of caregivers' stress and QOL, see Table e-B7 in e-supplement. There were no significant changes in ESF-scores or parental QOL as part of the FASD parents' app. ESF T-scores indicated constant borderline parental stress ($mean_0 = 61.5$ to $mean_3 = 61.3$, see Table e-B8 in e-supplement), caregivers rated their daily QOL steadily as "medium" ($mean_0 = 2.73$ to $mean_{3\text{-}3} = 2.83$).

4. Discussion

As a first in children with FASD, this crossover study investigated the feasibility and possible therapeutic effects of neuromodulation via high-

frequency rTMS over the DLPFC compared to 1Hz-stimulation as control.

All three protocols (1Hz, 10Hz, iTBS) proved to be safe, tolerable, acceptable and therefore feasible with small differences between stimulation conditions. Regarding adherence throughout the study, the majority (70 %) of participants completed at least 2/3 of the protocols and 100 % of protocols started were completed.

AEs were mild and self-limiting without intervention, with local pain/paraesthesia over the stimulation area accounting for the majority of AEs (57.8 %) which is in line with existing literature [56,57]. The observed per-session risk (21.8 %) was lower in comparison to 53.3 % in a previous study conducted by our group in children with FASD [22] but higher compared to a recent review on safety in children with other disorders (3.8 %) [56]. This might be due to a reporting bias, as most of the existing literature focuses on the TMS effects rather than equally addressing feasibility. From a clinical perspective, children with FASD are also known to experience tactile hypersensitivity and to have strong reactions to unfamiliar situations, reflected in the stimulation setting, the noise of the coil and the scalp sensations.

This crossover study is the first to show a positive effect of high-frequency rTMS on attention and social-emotional regulation in children with FASD. The low-frequency rTMS that served as a control condition did not have an effect, which is consistent with our group's previous findings [22] and makes positive effects of high-frequency rTMS all the more relevant. This is in contrast to Gómez et al. who demonstrated improved behaviour and social interaction on parent-reported clinical scales when applying 1Hz-rTMS over the left DLPFC in children with ASD [33].

Regarding attention, the 10Hz and iTBS stimulation conditions demonstrated improved performance in go/no-go-tasks (D2-R, Symbol Search of WISC-V). For 10-Hz-rTMS over the right DLPFC, Cao et al. [23] also described an improvement in inattention/hyperactivity in children with ADHD. However, attention was not assessed by task performance but only by symptom severity via an ADHD symptom questionnaire (SNAP-IV), so changes in task performance may have been overlooked. At present, no literature is available on the effects of iTBS on attention in children with FASD or other disorders.

Regarding social-emotional regulation, an improved self-assessment of internalizing and externalizing problem behaviour (via YSR) could be observed in the 10Hz and iTBS stimulation conditions. These positive changes on the self-assessment (YSR, BRIEF self) were not reflected in the external assessment of the caregivers via parallel forms (CBCL, BRIEF external). For iTBS over the right DLPFC, Abujadi et al. [25] also described an improvement of emotional regulation in children with ASD reflected in reduced repetitive behaviour externally evaluated via a symptom questionnaire for parents (Repetitive Behaviour Scale Revised). However, no self-assessment was carried out that could be used for comparison. To our knowledge, our study is the only so far to record an improvement in behaviour in children through high-frequency rTMS in the self-report. This is relevant as all therapy should be patient-centred and positive success experienced by the child has an impact on their motivation for therapy. Currently, no studies are available on the effects of 10Hz on social-emotional regulation in children with FASD or other disorders.

Regarding EF, there were no significant effects. However, in the iTBS stimulation condition, an improvement of more than one standard deviation was found in the test for EF (Tower of London) [58]. In accordance with our results, Abujadi et al. [25] demonstrated a significantly improved EF performance (Wisconsin Card Sorting Test; Stroop test) applying iTBS over the right DLPFC in children with ASD [58]. In contrast, Ameis et al. found no significant effects of high frequency rTMS on EF (BRIEF questionnaire (external and self-assessment); CANTAB spatial working memory task) [59] using not iTBS but 20Hz-rTMS over both DLPFC. This study therefore also supports our results of no effect of non-iTBS-high-frequency rTMS for EF. However, a study by Cao et al. [23] found an add-on effect of 10Hz-rTMS over the right DLPFC on EF (Iowa gambling task [60]); subtests of WISC) when combined with atomoxetine.

As to why a statistically significant improvement was observed in the performance tasks for attention but not for EF, the following explanations should be considered: we assume EF to be a much more complex process requiring more sophisticated networks and thus is more difficult to influence and it might be more difficult to spot small changes [32]. Additionally, practice effects might be more easily attained in tests for attention rather than EF, as learning effects in the TL-D are small [61, 62]. It could also be speculated that rTMS simply cannot influence EF deficits in children with FASD because of the complexity of involved CNS networks.

Our results showed no significant effects of high-frequency rTMS on QOL of the caregivers or participants. This could, in part, be due to confounders independent of the intervention (e.g. workplace stress, health-related worries, worries about siblings not participating in the study) also influencing the scores in the FASD parents' app and the parent stress questionnaire. To our knowledge, all other rTMS studies in children didn't measure QOL of both participants and caregivers, even if this item is essential for participation and personal outcome.

Currently, there are many different experimental approaches aimed at improving neuroplasticity, but also neurocognitive symptoms in general [63]. Epigallocatechin Gallate is a promising antioxidant therapy shown to attenuate consequences of PAE in a mouse model [64]. Other pharmacological interventions under research include dihydromyricetin, choline, and Omega-3 fatty acids among others [63].

Neurocognitive stimulation tools are being researched in different variations, including in combination with transcranial Direct Current Stimulation [65] or in the context of serious gaming. A study by Kerns et al. utilizing the game "The Caribbean Quest" showed positive effects on working memory, attention and reading fluency in children with FASD and ASD [66]. In the future, there is a need for comparing these interventions with rTMS but also possibly for trials combining them with rTMS to explore synergistic effects.

4.1. Limitations

The small sample size (n = 10), participants' heterogeneity and differently sized comparison groups may have led to reduced representativeness and potentially impeded the interpretation of results with only large alterations becoming statistically significant and subtle changes staying concealed. As mainly children with FAS or pFAS were included, the sample was additionally skewed towards more severe spectrum disorders, although all children had significant CNS-dysfunctions (at least 2 SD below the mean).

Given the lack of prior research or recommendations on effective rTMS protocols for FASD, the stimulation regimen was chosen based on protocols used for disorders with overlapping clinical symptoms (ASD, ADHD). Instead of a sham stimulation, real 1Hz-rTMS – that was expected to have no significant effects on neuropsychological outcomes – was used to control for the placebo-effect. Thus, replicating our previous negative findings of 1Hz-rTMS on neuropsychological functions, the significant results of 10Hz-rTMS and iTBS are less likely caused by a placebo effect alone. The washout period between protocols and their randomised and counterbalanced order accounted for cumulating effects by repeated active rTMS. However, the methodological limits of a crossover design do not allow to completely rule them out. Although the performance tests used for attention and EF show good overall retest reliability and adequate to good internal consistency, the same limitations apply to practice effects due to repeated neurocognitive testing, as study participants who completed all protocols were assessed four times within a few months [46,48,50].

In addition, the nature of the study and of the neuropsychological constructs make it difficult to draw comparisons with previous studies: Comparisons are made with other disorders similar in symptoms but not in pathophysiology (e.g. ADHD, ASD) which may account for the

mentioned discrepancies. The wide variety of test methods used in previous studies (as seen for EF) also makes comparison difficult. Therefore, performance tasks and symptom checklists were combined in our study to ensure a comprehensive assessment of the cognitive domains.

5. Conclusion

The present study demonstrates low- and high frequency rTMS over the right DLPFC to be well feasible and provides first preliminary evidence of positive effects of high-frequency rTMS on attention and social-emotional regulation in children with FASD. Non-invasive neuromodulation via rTMS could potentially complement the therapy of heterogeneous deficits in children with FASD by providing a brain-targeted and biologically focused approach. Larger, randomised, and placebo-controlled trials with more homogenous groups are urgently needed to further investigate the neuromodulatory effect of high-frequency rTMS on cognitive domains.

7. CRediT authorship contribution statement

Jasmin Hubert: Conceptualization, Investigation, Data Curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing; **Vivien Schmidt:** Conceptualization, Investigation, Data Curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing; **Esther Wittmann:** Conceptualization, Data Curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing; **Anja Melder:** Conceptualization, Investigation, Writing – review & editing; **Anna Lomidze:** Investigation, Writing – review & editing; **Nancy Smit:** Investigation, Writing – review & editing; **Lucia Bulubas:** Conceptualization, Writing – review & editing, Resources; **Mattia Campana:** Conceptualization, Writing – review & editing, Resources; **Ulrike Vogelmann:** Conceptualization, Writing – review & editing, Resources; **Beate Dornheim:** Conceptualization; **Prof. Frank Padberg MD:** Conceptualization, Writing – review & editing, Resources, Supervision; **Prof. Florian Heinen MD:** Conceptualization, Writing – review & editing, Resources, Supervision; **Prof. Mirjam N. Landgraf MD:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Project administration, Resources.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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