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Feedback-Based Learning of Timing in Attention-Deficit/Hyperactivity Disorder and Neurofibromatosis Type 1

Astrid Prochnow[1], Annet Bluschke[1], Barbara Novotna[2], Maja von der Hagen[2] and Christian Beste[1,*]

[1]Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Faculty of Medicine of the TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany
[2]Abteilung Neuropädiatrie, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Fetscherstrasse 74, 01307 Dresden, Germany

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Abstract

Objective: Patients with Neurofibromatosis Type 1 (NF1) frequently display symptoms resembling those of Attention Deficit/Hyperactivity Disorder (ADHD). Importantly, these disorders are characterised by distinct changes in the dopaminergic system, which plays an important role in timing performance and feedback-based adjustments in timing performance. In a transdiagnostic approach, we examine how far NF1 and ADHD show distinct or comparable profiles of timing performance and feedback-based adjustments in timing. **Method:** We examined time estimation and learning processes in healthy control children (HC), children with ADHD with predominantly inattentive symptoms and those with NF1 using a feedback-based time estimation paradigm. **Results:** Healthy controls consistently responded closer to the correct time window than both patient groups, were less variable in their reaction times and displayed intact learning-based adjustments across time. The patient groups did not differ from each other regarding the number of in-time responses. In ADHD patients, the performance was rather unstable across time. No performance changes could be observed in patients with NF1 across the entire task. **Conclusions:** Children with ADHD and NF1 differ in feedback learning-based adjustments of time estimation processes. ADHD is characterised by behavioural fluctuations during the learning process. These are likely to be associated with inefficiencies in the dopaminergic system. NF1 is characterised by impairments of feedback learning which could be due to various neurotransmitter alterations occurring in addition to deficits in dopamine synthesis. Results show that despite the strong overlap in clinical phenotype and neuropsychological deficits between NF1 and ADHD, the underlying cognitive mechanisms are different.

Keywords: Time estimation, Interval timing, Pacemaker-accumulator model, Dopamine, Neurofibromatosis Type 1, Attention-deficit/hyperactivity disorder, Reaction time variability, Learning deficits

INTRODUCTION

Timing in the seconds-to-minutes range is a consciously controlled process and is therefore flexible but also open to influences such as attentional fluctuations (Buhusi & Meck, 2005; Coull, Cheng, & Meck, 2011; Merchant & de Lafuente, 2014). Attentional deficits occur in psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD; American Psychiatric Association & American Psychiatric Association, 2013; Bluschke, Zink, Mückschel, Roessner, & Beste, 2020) and also in genetic conditions such as Neurofibromatosis Type 1 (NF1; Coudé, Mignot, Lyonnet, & Munnich, 2007; Heimgärtner et al., 2019; Koth, Cutting, & Denckla, 2000). For more detailed insights into the processes underlying timing performance, it is useful to attempt a comparison of timing between these conditions which are phenotypically similar (Coudé et al., 2007; Koth et al., 2000) but differ significantly regarding the underlying neural mechanisms (Brown et al., 2010, 2011; Klein et al., 2017). According to the pacemaker-accumulator model (Buhusi & Meck, 2005; Gibbon, 1977; van Rijn, Gu, & Meck, 2014), the timing process is based on a pacemaker emitting pulses. At the clock stage, where these pulses are accumulated, attention is an important modulator (Coull et al., 2011; Merchant & de Lafuente, 2014), therefore particularly the dopamine system is important (Buhusi & Meck, 2005; Gibbon, Church, & Meck, 1984). For a correct evaluation of the passed duration, the attentional focus has to be directed towards the emitted pulses. Insufficient attention to the pacemaker pulses leads

*Correspondence and reprint requests to: Christian Beste, Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Faculty of Medicine of the TU Dresden, Schubertstrasse 42, D-01309 Dresden, Germany. E-mail: Christian.beste@uniklinikum-dresden.de

Astrid Prochnow and Annet Bluschke contributed equally to the manuscript.

to some pulses being missed, which results in an underestimation of the elapsed duration (Buhusi & Meck, 2009; Coull et al., 2011; Hwang, Gau, Hsu, & Wu, 2010). At the memory stage, the number of accumulated pulses is counted when receiving feedback. This number is stored in reference memory and updated when necessary so it can be used for current and future decisions (i.e. decision stage) (Buhusi & Meck, 2005; Gibbon et al., 1984). This memory-component in time estimation strongly depends on trial-by-trial feedback-based learning process and is mainly subject to cholinergic modulation (Buhusi & Meck, 2005; Gibbon et al., 1984; Sohn & Lee, 2012).

Altered dopaminergic functioning, deficits in interval timing and learning deficits are evident in ADHD, a disorder marked by the core symptoms of inattention, impulsivity, and hyperactivity (American Psychiatric Association & American Psychiatric Association, 2013; Klein et al., 2017; Mahone & Denckla, 2017; Ptacek et al., 2019; Swanson et al., 2000). ADHD is associated with deficient dopaminergic transmission due to an increased presynaptic dopamine transporter activity and alterations of dopamine receptors (Klein et al., 2017). Patients frequently show an increased variability in reaction times and cognitive performance (Bluschke, Chmielewski, Mückschel, Roessner, & Beste, 2017; Bluschke, Schreiter, et al., 2020; Kofler et al., 2013; Mahone & Denckla, 2017; Yordanova et al., 2011). Deficits in timing have been well described on the behavioural level (Bauermeister et al., 2005; Bluschke, Schuster, Roessner, & Beste, 2018; Hwang et al., 2010; Kerns, McInerney, & Wilde, 2001; Smith, Taylor, Rogers, Newman, & Rubia, 2002; Toplak & Tannock, 2005), and using neurophysiological methods (Bluschke et al., 2018; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013). However, it is not yet understood whether these impairments in timing are due to pure time perception deficits (Smith et al., 2002; Toplak & Tannock, 2005; Walg, Oepen, & Prior, 2015), or due to problems in attentional regulation (Bauermeister et al., 2005; Hwang et al., 2010; Kerns et al., 2001) affecting learning-related adjustments of processes important during time estimation.

The symptom of inattention is also evident in patients with NF1, a hereditary rare disease that exhibits close overlaps in the neurocognitive profile with ADHD (Coudé et al., 2007; Koth et al., 2000). NF1 is also associated with altered dopaminergic functioning, particularly as far as dopamine synthesis is concerned (Brown et al., 2010). Preliminary small clinical trials demonstrated that methylphenidate is effective in treating ADHD symptoms in children with NF1 (Mautner, Kluwe, Thakker, & Leark, 2002). Although the pattern of impairments shows strong inter-individual variability (Diggs-Andrews & Gutmann, 2013; Kayl & Moore, 2000; Soucy, Gao, Gutmann, & Dunn, 2012), many of the children with NF1 and their parents also report more general learning deficits (Descheemaeker, Ghesquière, Symons, Fryns, & Legius, 2005; Hyman, Shores, & North, 2005; Zimerman et al., 2015). Importantly, such deficits could potentially also influence time estimation abilities and evidence accumulation processes by the pacemaker. Thus, it can be hypothesised that time estimation processes are also deficient in NF1 patients, just like it is the case for ADHD. Since there is a strong overlap in cognitive dysfunctions in ADHD and NF1 patients that are relevant for timing processes, the current study pursues a transdiagnostic approach and compares time estimation processes in ADHD and NF1 patients in comparison to healthy controls. Since inattention is the most pronounced ADHD-like symptom in NF1 (Heimgärtner et al., 2019) and correlated with interval timing (Bluschke et al., 2018; Mullins, Bellgrove, Gill, & Robertson, 2005), we included children with the predominantly inattentive subtype of ADHD. We hypothesize that time estimation performance will be reduced both in patients with NF1 and those with ADHD compared to healthy controls. In addition, we expect to observe a successful learning process, that is an improvement in performance over time, in healthy controls. Based on the alterations in dopaminergic functioning, however, we expect altered learning curves compared to healthy controls in the two patient groups. Since there are differences between ADHD and NF1 in terms of dysfunctions in the dopaminergic system (Brown et al., 2010, 2011; Klein et al., 2017), we expect differential modulated processes between ADHD and NF1, particularly for learning processes.

METHOD

Sample

To determine the detectable effect size, a sensitivity analysis was conducted using G* Power (Faul, Erdfelder, Lang, & Buchner, 2007). With the total sample size of $n = 72$ subjects, given the three groups and three measurements (response type and block, respectively), a small to medium effect ($\eta^2 = .042$) can be detected with a power of 95%.

The group of NF1 patients was recruited from the Department of Neuropediatrics at the TU Dresden. In all of them, the diagnosis of NF1 had been determined according to ICD-10 criteria (Q85.0). IQ measures were not available for this sample, however, 74% of the NF1 patients attended regular school. Overall, $n = 26$ patients with NF1 (11.5 ± 2.9 years, 12 males, two sisters) were included in the study. All of them reported multiple neurological and physiological problems. Fourteen of the patients further were characterised by one or more comorbid diagnosis ($n = 3$ with an Axis III diagnosis (F70.9, F74.8, F79.9), $n = 12$ with an Axis II diagnosis (F80.1, F81.0, F81.3, F82.9, F83), $n = 1$ with ADHD (F90.0), $n = 6$ with psychological/emotional/behavioural problems (F98.0, F98.1, F40.2, F43.2, F54), for details see Table S1). None of the patients received psychopharmacological treatments.

The ADHD group was recruited from the outpatient clinic of the Department of children and adolescent psychiatry. Diagnoses had been determined according to established clinical guidelines and included interviews and questionnaires completed by parents, children, and teachers, testing of general IQ level using the Wechsler scales and attention

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as well as the exclusion of possible underlying somatic conditions (i.e. by EEG assessments, vision testing, audiometry, and blood tests). In order to achieve good matching between the two groups, ADHD patients were only included if they fulfilled diagnostic criteria for attention deficit disorder of the inattentive subtype as assessed by the ADHD Symptom Checklist (Döpfner, Görtz-Dorten, & Lehmkuhl, 2009; see below). 20 patients with ADHD (10.8 ± 2.4 years, IQ: 99 ± 11.2, 9 male) were included in the study. Eight of those patients received an additional psychiatric diagnosis (F95.2, F95.8, F43.2, F93.8, F94.1, F98.0, F98.9; for details see Table S1). None of the patients received psychopharmacological treatments.

A group of healthy control children (HC) was recruited from an in-house database and via advertisements. None of these children had previously taken part in a study with an interval timing task. Controls were only included if the parents reported no psychiatric or neurological disorders during a telephone interview. IQ levels in this group were measured using the short form of the WISC-IV (Waldmann, 2008). Overall, a group of $n = 26$ healthy control children participated in the study (12.1 ± 2.7 years, IQ: 105 ± 6.6, 12 male).

In all three groups, parents rated their children's behaviour on the ADHD Symptom Checklist (Döpfner et al., 2009) on the three scales inattention, hyperactivity, and impulsivity from 0 (no problems) to 3 (severe problems; see Figure 1). A mean score ≥1.5 indicates high symptom severity. Controls displayed no significant symptoms on any of the three scales (inattention: 0.36 ± 0.36, hyperactivity: 0.09 ± 0.23, impulsivity: 0.25 ± 0.36) and therefore differed significantly from the two patient groups on all three scales (all $p \leq .001$). Patients with NF1 and ADHD differed on the inattention scale (NF1:1.56 ± 0.62, ADHD: 2.01 ± 0.41), with more reported inattention in the ADHD group ($t(35.237) = 2.73$; $p = .010$). Differences in the domains of hyperactivity (NF1:0.49 ± 0.60, ADHD: 0.54 ± 0.42) or impulsivity (NF1:1.02 ± 0.82, ADHD: 0.91 ± 0.60) were not found ($t \leq .50$; $p \geq .617$). Furthermore, the three groups did not differ regarding age ($F(2,69) = 1.20$; $p = .308$) or gender distribution ($\chi^2(2, N = 72) = .01$; $p = .996$). Regarding the IQ levels, healthy controls and ADHD patients differed significantly ($t(44) = 2.19$, $p = .034$). However, comparability can still be assumed, as the difference of 6 IQ points is clinically negligible and both groups were within average bounds.

All subjects and their parents or legal guardians provided written informed consent before any study procedure was applied. The local ethics committee of the Medical Faculty of the TU Dresden approved the study.

Task

The task is identical to that used in previous publications on time estimation by our group (Beste et al., 2007; Bluschke et al., 2018; Wild-Wall, Willemssen, Falkenstein, & Beste, 2008). The procedure of the task is shown in Figure 2.

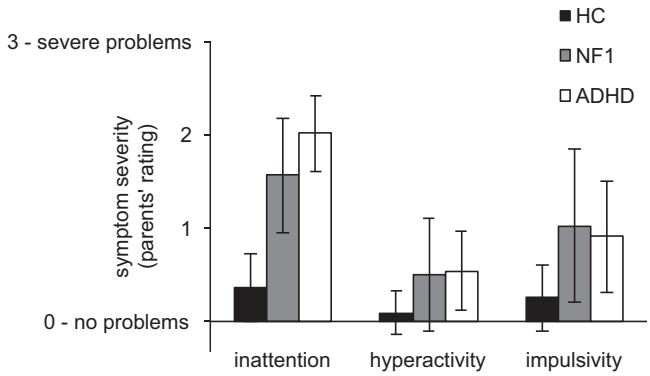

Fig. 1. Reported symptom severity according to the ADHD Symptom Checklist (Döpfner et al., 2009) on the three scales inattention, hyperactivity, and impulsivity for the three groups. Error bars show standard deviations of the mean.

Participants were seated in front of a 24″ TFT display. Each trial began with the presentation of a white fixation cross. After that, a white square on black background was presented and participants were asked to press the space key 1200 ms after the onset of this stimulus. Key presses occurring between 1000 and 1400 ms were accepted as in-time (correct) responses. Key presses given between 400 and 1000 ms after the stimulus onset were classified as early responses. Key presses occurring between 1400 and 2000 ms after the stimulus onset were classified as late responses. Key presses before 400 ms or after 2000 ms were classified as missed responses and were not included in further analyses. After every key press, participants received visual feedback; that is after in-time responses, a green happy smiley and the German word for "correct" were shown. After early/late responses (including trials later classified as misses), a red sad smiley and the German words for "too early"/"too late" were shown. The German words for "did not react" were displayed if there had been no response 3000 ms after cue onset. Overall, the participants performed 300 trials divided into three blocks with short breaks of self-chosen length in between. The intertrial interval was randomized between 800 and 2200 ms. For the analyses, the percentage of trials, the reaction times (RTs), and the standard deviation of reaction times (RT-SDs) separated for correct, early, and late responses were used.

Statistical Analysis

For the analysis of the data, we used mixed effects analyses of variance (ANOVAs). This included the within-subject factor *Response* (correct, early, late) and the between-subjects factor *Group* (NF1, controls, ADHD) for the general analyses. Bonferroni-adjusted correlations (three tests, $p = .017$) were calculated for timing performance measures and symptom severity separately for the three groups. For the analyses of learning processes, we included the within-subject factor *Block* (first, second, third) and the between-subjects factor *Group* (NF1, controls, ADHD). One-way ANOVAs and

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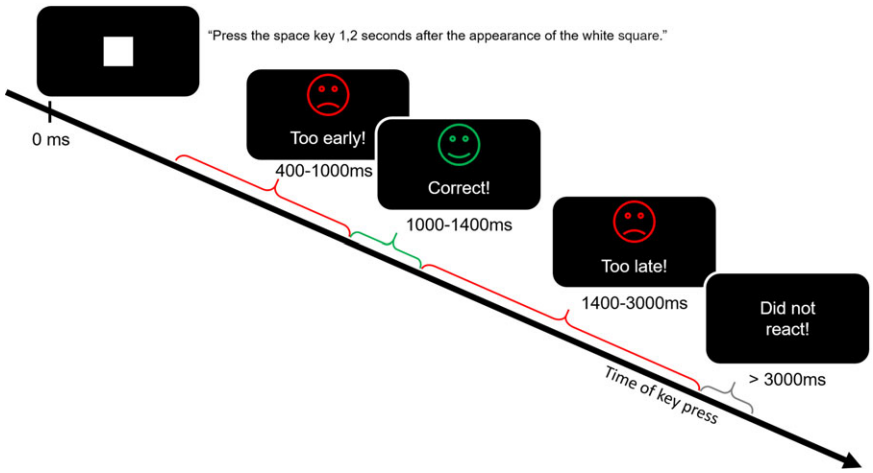

Fig. 2. Procedure of the applied time estimation task. Participants were instructed to press the space key 1, 2 s after the appearance of the white square. Participants received a smiley and written feedback depending on the time of their key press. If no answer was recorded 3000 ms after the appearance of the white square, the feedback "Did not react!" was presented.

t-tests (paired and unpaired, respectively) were used to further analyse any main effects or interactions. We used Pearson's correlations for correlational analyses. Bonferroni- and Greenhouse-Geisser-corrections were applied when necessary. All dependent variables were normally distributed within the groups according to Kolmogorov-Smirnov tests ($p \geq .145$).

RESULTS

The descriptive statistics of the behavioural data, that is the percentage of trials, reaction times (RTs), and standard deviations of the reaction times (RT-SDs) for the correct (in-time) responses, as well as for the early and late responses are displayed in Figure 3. The percentage of missed trials did not differ between the groups (HC: 0 ± 1%, NF1:2 ± 4%, ADHD: 2 ± 4%; $F(2,72) = 1.60$, $p = .210$, $\eta_p^2 = .044$). For the analyses, age was included as a covariate because of significant correlations with some of the dependent variables (Table 1) and previous findings of age influencing time estimation in childhood (Meyers, 2019).

Percentage of Trials

A repeated-measures ANCOVA of the percentage of trials revealed a main effect of *Response* ($F(2,136) = 7.37$; $p = .001$; $\eta_p^2 = .098$) with significantly more correct (49 ± 16%) than early (30 ± 14%) or late (19 ± 10%) responses as well as significantly more early than late responses ($t \geq 4.66$; all $p < .001$) across all three groups. The main effect of *Group* was not significant ($F(2,68) = 1.26$, $p = .290$, $\eta_p^2 = .036$). There was a significant interaction of *Response* * *Group* ($F(4,136) = 2.82$; $p = .028$; $\eta_p^2 = .077$). Further post-hoc analyses revealed an effect of *Group* for the correct responses only (HC: 57 ± 12%, NF1:45 ± 16%, ADHD: 46 ± 18%; $F(2, 68) = 4.71$; $p = .012$; $\eta_p^2 = .122$). Specifically, we found significantly more correct responses in the HC than in either of the patient groups ($t \geq 2.66$; $p \leq .011$). The main effect of *Response* was significant in all three groups ($F \geq 8.31$; $p \leq .001$). In the HC group, analyses revealed significantly more correct (57 ± 12%) than early (25 ± 10%) or late (17 ± 8%) responses as well as significantly more early than late responses ($t \geq 3.19$; $p \leq .004$). For the ADHD group, analyses revealed significantly more correct (46 ± 18%) than error (early: 32 ± 16%, late: 21 ± 14%) responses ($t \geq 2.12$; $p \leq .047$), but only marginally significant differences between the frequencies of early and late responses ($t(19) = 1.98$; $p = .063$). Within the NF1 group, the difference between the number of correct (45 ± 16%) and early (34 ± 16%) responses was only marginally significant ($t(25) = 1.85$; $p = .077$), but both occurred significantly more frequently than late responses (20 ± 9%; $t \geq 3.21$; $p \leq .004$). Bonferroni-adjusted correlational analyses revealed a significant association of the percentage of early responses with reported hyperactivity ($r(19) = .701$, $p < .001$) and impulsivity ($r(19) = .699$, $p < .001$) only in the NF1 group.

Reaction Time (RT) and RT Variability (RT-SD)

A repeated-measures ANCOVA of the RTs revealed a main effect of *Response* (correct: 1183 ± 19 ms, early: 817 ± 61 ms, late: 1574 ± 53 ms; $F(1.1,73.6) = 358.45$; $p < .001$; $\eta_p^2 = .846$) with significant differences between all three response types ($t \geq 49.05$; all $p < .001$). The main effect of *Group* was not significant ($F(2,65) = .04$, $p = .959$, $\eta_p^2 = .001$). We further found a significant *Response* * *Group* interaction ($F(2.3,73.6) = 3.76$; $p = .023$; $\eta_p^2 = .104$). The HC group showed slower RTs within the early trials (842 ± 42 ms) and faster RTs within the late trials (1552 ± 43 ms) than it was the case for the patient groups (NF1: early: 803 ± 66 ms, late: 1582 ± 48 ms; ADHD: early: 800 ± 66 ms, late: 1594 ± 63 ms; $t \geq 2.37$; $p \leq .022$). For the correct responses, there was no significant group difference (HC: 1183 ± 21 ms, NF1:1186 ± 16 ms, ADHD: 1177 ± 19 ms; $F(2,65) = 1.08$, $p = .346$, $\eta_p^2 = .032$).

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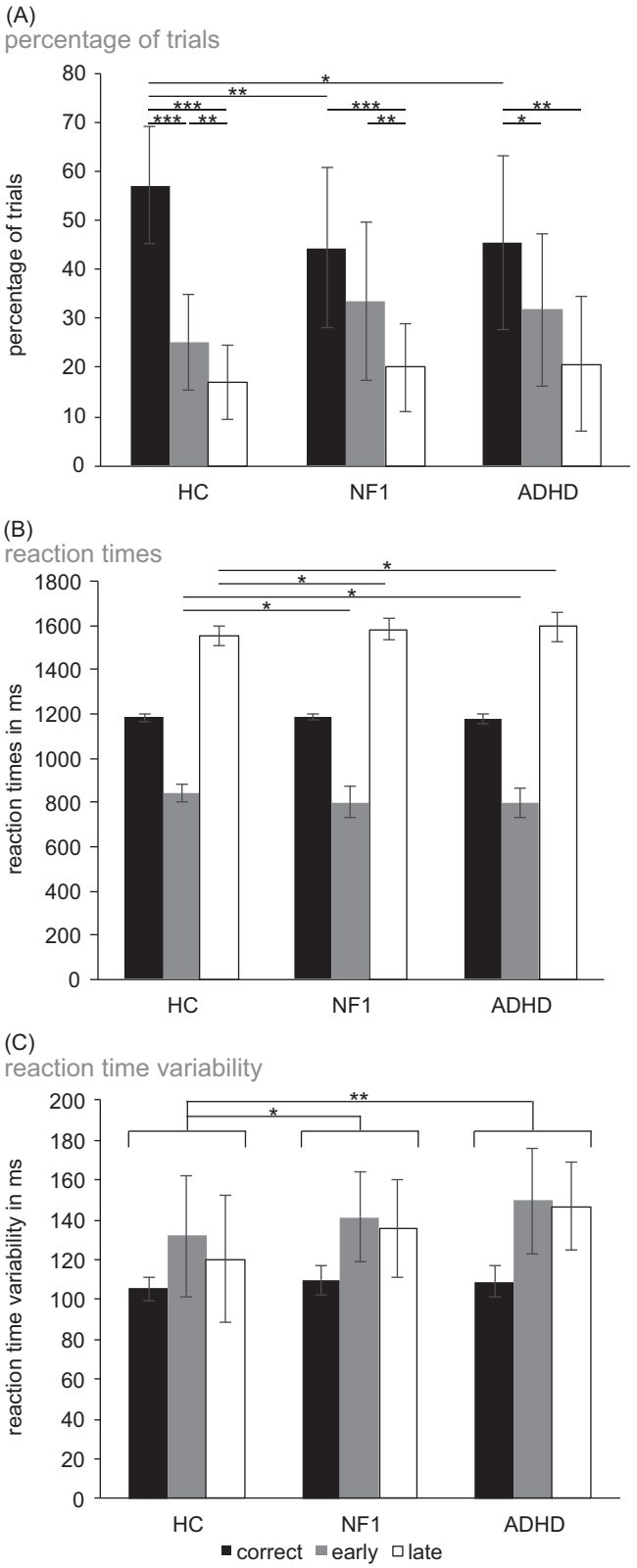

Fig. 3. (A) Percentage of trials of each response type for the three groups. (B) Reaction times of each response type for the three groups. (C) Reaction time variability of each response type for the three groups. Significant results are denoted with asterisks (* $p < .05$, ** $p < .01$, *** $p < .001$). Error bars show standard deviations of the mean.

A repeated-measures ANCOVA of the RT-SDs showed a significant main effect of Response ($F(2,130) = 13.18$; $p < .001$; $\eta_p^2 = .169$). RT-SD was significantly larger for early (140 ± 27 ms) than for late (133 ± 29 ms) and correct (108 ± 7 ms) responses. Also, RT-SD was significantly larger for the late than for the correct responses ($t \geq 2.25$; all $p \leq .027$). Further, we found a significant main effect of the factor Group ($F(2,65) = 4.72$; $p = .012$; $\eta_p^2 = .127$). In the HC group, RT-SDs were significantly smaller than in the other two groups (HC: 119 ± 19 ms, NF1:129 ± 13 ms, ADHD: 135 ± 15 ms; $t \geq 2.14$; $p \leq .038$). The Group*Response interaction was not significant ($F(4,130) = 1.43$; $p = .228$; $\eta_p^2 = .042$).

Bonferroni-adjusted correlational analyses revealed no significant associations with symptom severity in any of the groups.

Analysis of Learning Effects

To examine the learning process throughout the task, we analysed the three blocks of the task separately. To examine whether a successful learning process could be observed, we conducted these analyses only for the in-time responses. Therefore, we included the factors *Block* and *Group* in the analyses. The percentage of trials, reaction times (RTs), and standard deviations of the reaction times (RT-SDs) separated for blocks and groups as well as the changes in RTs are displayed in Figure 4.

In regards to the percentage of trials, a repeated-measures ANCOVA revealed a main effect of *Group* ($F(2,68) = 4.71$; $p = .012$; $\eta_p^2 = .122$). HC responded correctly significantly more often than the patients (HC: 57 ± 12%, NF1:45 ± 16%, ADHD: 46 ± 18%; $t \geq 2.66$; $p \leq .011$). There was no significant main effect of *Block* ($F(1.8,124.0) = .064$, $p = .925$, $\eta_p^2 = .001$) and no significant *Block*Group* interaction ($F(3.6,124.0) = 1.04$, $p = .384$, $\eta_p^2 = .030$).

In regards to RTs, a repeated-measures ANCOVA revealed no significant main effect of *Block* ($F(2,130) = .85$, $p = .431$, $\eta_p^2 = .013$) or *Group* ($F(2,65) = 1.08$, $p = .346$, $\eta_p^2 = .032$). We found a significant *Block*Group* interaction ($F(4,130) = 4.31$; $p = .003$; $\eta_p^2 = .117$). In the second block, there was a significant difference between the ADHD and the NF1 groups (NF1:1190 ± 29 ms, ADHD: 1163 ± 28 ms; $t(41) = 3.07$; $p = .004$), with the HC group (1177 ± 25 ms) differing only marginally from the NF1 group ($t(49) = 1.73$; $p = .090$) and the ADHD ($t(42) = 1.73$; $p = .092$) group. Within the other two blocks, the main effect of *Group* was not significant ($F \leq 1.98$; $p \geq .146$). In the HC group, there was a significant effect of the factor *Block* ($F(2, 48) = 5.04$; $p = .010$; $\eta_p^2 = .173$). The RTs in the third block (1199 ± 33 ms) differed significantly from the RTs in the first (1173 ± 29 ms) and the second (1177 ± 25 ms) block ($t \geq 3.34$; $p \leq .003$), with the reaction times in the third block being closer to the target time of 1200 ms. The first and the second block did not differ from each other ($t(25) = .71$; $p = .485$).

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Table 1. Pearson's correlations (uncorrected) of dependent variables with covariate age

Variable	HC	NF1	ADD
% correct responses	.231 (.255)	**.555** (.003)	**.685** (.001)
% early responses	−.367 (.065)	**−.577** (.002)	−.335 (.149)
%. late responses	.107 (.603)	.028 (.892)	−.371 (.108)
RT correct responses	.157 (445)	.019 (.930)	−.124 (.623)
RT early responses	**.541** (.004)	**.460** (.021)	**.576** (.012)
RT late responses	−.199 (.329)	−.163 (.436)	**−.723** (.001)
RT-SD correct responses	.101 (.624)	−.319 (.120)	.004 (.988)
RT-SD early responses	**−.554** (.003)	−.032 (.881)	−.456 (.057)
RT-SD late responses	−.168 (.413)	−.194 (.353)	**−.689** (.002)
% correct responses 1st block	.384 (.053)	**.584** (.002)	**.484** (.030)
% correct responses 2nd block	.156 (.448)	**.436** (.026)	**.694** (.001)
% correct responses 3rd block	.063 (.760)	**.522** (.006)	**.684** (.001)
RT correct responses 1st block	**.416** (.035)	.067 (.749)	−.309 (.213)
RT correct responses 2nd block	.062 (.764)	−.133 (.527)	.168 (.505)
RT correct responses 3rd block	−.105 (.608)	.125 (.551)	−.073 (.773)
RT-SD correct responses 1st block	.027 (.894)	−.156 (.458)	.101 (.691)
RT-SD correct responses 2nd block	.213 (.295)	**−.406** (.044)	.042 (.870)
RT-SD correct responses 3rd block	−.040 (.845)	.012 (956)	−.136 (.591)

Note. HC = healthy controls; NF1 = patients with Neurofibromatosis Type 1; ADD = patients with ADHD diagnosis with predominantly inattentive symptoms. *p*-values of the correlations are given in brackets. Significant correlations are in bold print.

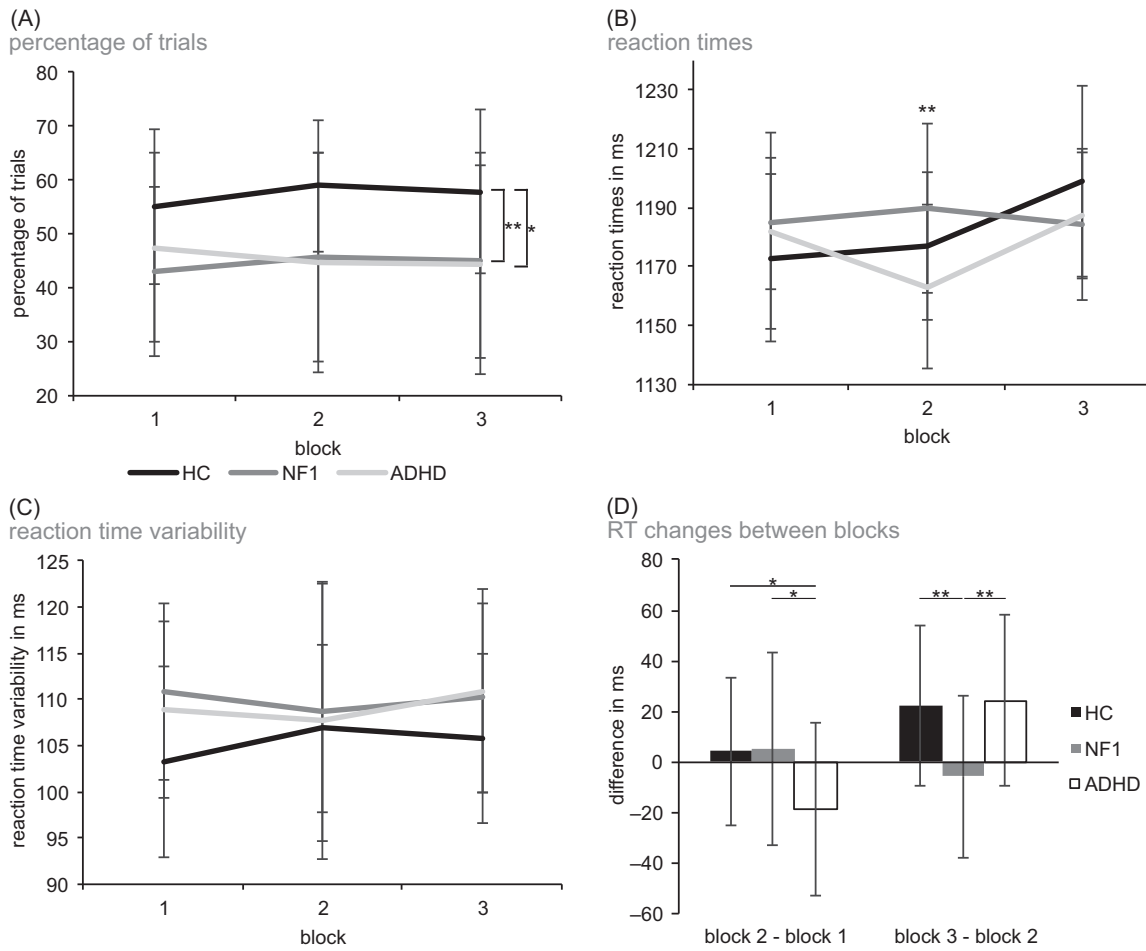

Figure 4. (A) Percentage of trials of each block for the three groups. (B) Reaction times of each block for the three groups. (C) Reaction time variability of each block for the three groups. (D) RT changes, calculated as differences between the blocks for the three groups. Significant results are denoted with asterisks (* $p < .05$, ** $p < .01$, *** $p < .001$). Error bars show standard deviations of the mean.

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For further post-hoc analyses, we calculated the change as the difference between successive blocks. The change from the first to the second block differed significantly between the ADHD group and the other two groups (HC: 4 ± 29 ms, NF1:5 ± 38 ms, ADD: −19 ± 34 ms; $t \geq 2.14$; $p \leq .038$) due to a decrease of RTs within the ADD group. The change from the second to the third block differed significantly between the NF1 group and the other two groups (HC: 22 ± 32 ms, NF1: −6 ± 32 ms, ADD: 24 ± 34 ms; $t \geq 2.94$; $p \leq .005$) due to an increase in RTs towards the target time in the HC and the ADD groups but not in the NF1 group.

In regards to the RT-SDs, there was a marginally significant main effect of *Group* ($F(2, 65) = 2.7$; $p = .073$; $\eta_p^2 = .078$) indicating a lower variability in the HC group (105 ± 6 ms) than in the patient groups (NF1:110 ± 7 ms, ADHD: 109 ± 8 ms). We found no significant main effect of *Block* ($F(2,130) = 0.2$; $p = .844$; $\eta_p^2 = .003$) and no significant *Block*Group* interaction ($F(4,130) = 0.7$; $p = .584$; $\eta_p^2 = .021$).

DISCUSSION

In this study, we undertook a transdiagnostic approach and compared time estimation performance in children with NF1, ADHD of inattentive subtype, and healthy controls. Data revealed better time estimation performance in healthy controls than in ADHD patients, which is in line with previous research (Bluschke et al., 2018; Hwang et al., 2010). Symptom severity and performance only correlated in the NF1 group, indicating for higher hyperactivity/impulsivity to be related to the number of early, that is impulsive, responses. However, for the ADHD group, no correlations were found, which contradicts previous findings (Bluschke et al., 2018), but might be due to the limited statistical power in this group. In the cases of early and late responses (i.e. erroneous time estimations), healthy controls consistently responded closer to the correct time window than both patient groups and were less variable in their reaction times (RTs). The patient groups did not differ from each other regarding the number of in-time responses, corroborating the assumption of similarities in cognitive processes between ADHD and NF1 (Coudé et al., 2007; Koth et al., 2000). However, the patient groups differed somewhat in regards to the types of committed errors. In patients with ADHD, the number of early and late errors did not differ, while patients with NF1 were slightly more prone to respond too early. In addition, performance in the in-time trials was compared between the three blocks of the task to analyse the processes of learning-based adjustments of timing. In healthy controls, a learning curve is present, with RTs continuously approaching the target time across the three blocks. In both patient groups, however, such learning-based adjustments were not observed. Crucially, in ADHD patients, performance was rather unstable since RTs first decreased between Block 1 and 2 before then returning to "baseline" levels in Block 3. In contrast, no performance changes could be observed in patients with NF1 across the entire task, suggesting a significant lack of behavioural adjustments after feedback in this group. In other words, in NF1, we see a generally high RT variability with stable RT means across the blocks, while in ADHD besides a high general RT variability RT means additionally fluctuate across blocks (refer to Figure 4).

The distribution of errors as well as the performance fluctuations across the three blocks indicate a strong variation of responses around the correct time window in ADHD, matching previous findings of high intra-individual performance fluctuations in ADHD (Bluschke, Mückschel, Roessner, & Beste, 2020; Bluschke, Zink, et al., 2020; Kofler et al., 2013; Vahid, Bluschke, Roessner, Stober, & Beste, 2019; Yordanova et al., 2011). Further, no learning curve as in the healthy control group was evident, but drawing conclusions about the learning process in ADHD is somewhat difficult in the current study because of the high-performance fluctuations. However, previous studies could show that feedback processing is intact in the inattentive subtype of ADHD, but preparatory processes for the response are deficient (Bluschke et al., 2018). Higher intra-individual variability in ADHD has been attributed to dopamine system dysfunctions (Klein et al., 2017). In ADHD, there are multiple alterations in the dopaminergic system such as decreased receptor density and increased dopamine transporter (DAT) density, resulting in a less efficient dopaminergic system (Klein et al., 2017). Moreover, the norepinephrine system also plays a significant role in ADHD (Sharma & Couture, 2014), but appears to be more important for processes of self-timing and durations lasting several seconds (Rammsayer, Hennig, Haag, & Lange, 2001; Suzuki & Tanaka, 2017), which both are not required in the current study. Dopaminergic dysfunctions cause a lower signal-to-noise ratio (SNR; Li, Lindenberger, & Sikström, 2001; MacDonald, Nyberg, & Bäckman, 2006) and result in imprecise and unstable cognitive performance (Li et al., 2001), an aspect also reported in ADHD (Pertermann, Bluschke, Roessner, & Beste, 2019). According to the pacemaker-accumulator model, the pulses emitted from the pacemaker are counted during the clock stage (Buhusi & Meck, 2005; Gibbon, 1977; van Rijn et al., 2014). Considering that the dopaminergic system is particularly important for clock stage-based mechanisms in time estimation/interval timing (Matell, King, & Meck, 2004; Meck, 1983), dysfunctions at the clock stage may underlie the observed deficits in ADHD. This is in line with other interpretations concerning ADHD-related time estimation deficits (Buhusi & Meck, 2005; Gibbon, 1977; van Rijn et al., 2014). The higher level of noise in ADHD might cause pacemaker pulses to be missed and for the elapsed time to be underestimated (Coull et al., 2011). However, at times, noise may also be misinterpreted as a pulse (i.e. false-positive pulse), leading to occasional overestimations of the elapsed time. Therefore, increased noise can explain the over- and under-estimations of time intervals and hence a stronger fluctuation of estimated times around the desired time interval in the ADHD group.

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NF1 is associated with deficient dopamine synthesis in mouse models (Brown et al., 2010; Diggs-Andrews et al., 2013), likely also leading to insufficient dopaminergic neurotransmission and hence a lower SNR (Li et al., 2001; MacDonald et al., 2006). Interestingly, however, the pattern of deficits on the behavioural level in patients with NF1 differed somewhat from ADHD patients, indicating that different mechanisms may be altered compared to ADHD. Generally, results indicated an overestimation of the elapsed time in NF1 rather than an underestimation. Further, behavioural fluctuations concerning mean RTs were less strongly pronounced in NF1 than in ADHD. Importantly, no significant improvement of performance took place across the task, indicating deficient behavioural adjustments after feedback in this group. However, since the current study was limited to the behavioural level it remains elusive if these alterations are due to deficient feedback processing or deficient preparatory processes, because this only can be resolved by neurophysiological data. Comparing performance fluctuations between the patient groups, the neural mechanisms underlying timing deficits in NF1 are likely to be different from those playing a role in ADHD. Although NF1 patients are thought to also show dopaminergic alterations, these deficits are somewhat different from the ones in ADHD. In animal models of NF1, dopamine synthesis has been shown to be reduced (Brown et al., 2010, 2011), resulting in a tonic lack of dopamine. In ADHD, phasic availability of dopamine is also impaired, leading to the observed behavioural fluctuations (Bluschke, Zink, et al., 2020). These problems in dopamine synthesis probably lead to deficits at the clock stage of the evidence accumulation of the internal pacemaker just like it is the case in ADHD, resulting in similar general reductions of behavioural accuracy, but it seems likely that the deficits shown in NF1 cannot be explained by pure deficits at the clock stage.

However, dopamine is not the only deficient neurotransmitter system in NF1 (Brown, Diggs-Andrews, Gianino, & Gutmann, 2012; Gutmann, Cole, & Collins, 1994). In addition, processes related to memory formation impairments have also been clearly defined and described in NF1. Here, alterations in nitric oxide, cGMP, and glutamate functioning have been proposed to underlie learning deficits in NF1 by ultimately affecting long-term potentiation (Costa et al., 2002). Interestingly, acetylcholine has been suggested to play a mediating role in this cascade and has also been implicated in the functioning of the memory stage of the pacemaker accumulator model (Buhusi & Meck, 2005). The deficit in NF1 might thus additionally be present at the memory stage, resulting in less efficient updating of the reference memory in response to feedback (Buhusi & Meck, 2005; Gibbon, 1977; van Rijn et al., 2014).

There are some limitations of the current study. The IQ was not assessed in NF1 and that it was thus not possible to control for any potential IQ differences between the patient groups. However, taking the number of NF1 patients attending regular school into account, we assume that the sample is representative for this patient group and therefore the results are somewhat generalizable. Moreover, the sample size is somewhat small, because the NF1 sample consisted of children with a rare disease. However, regarding the conducted sensitivity analysis it is possible to detect small to medium effects with the current sample size. Another limitation might be the binning of the 300 trials of the task into three blocks for the analysis of learning effects. However, based on previous studies by our group on time estimation in ADHD (Bluschke et al., 2018), we expected error rates of about 50%. To still have sufficient trials for the analyses and in order to derive reliable mean values and SDs, we divided the 300 trials into three bins. Further, the conclusions regarding the neurotransmitter systems are on a quite theoretical level. For future studies, it might be interesting to manipulate neurotransmitter systems directly, for example by administering a single dose of methylphenidate before performing the task.

To summarize, deficits in timing and learning of timing are evident in ADHD as well as in NF1 compared to healthy controls. Importantly, ADHD and NF1 differ in feedback learning-based adjustments of time estimation processes. Patients with ADHD are characterised by behavioural fluctuations during the learning process, while no feedback learning could be observed in those with NF1. Thus, the mechanisms leading to the timing problems differ between these two groups. In ADHD, these deficits likely occur primarily at the clock stage of evidence accumulation of the internal timing pacemaker. On a neurobiological level, this is likely to be associated with inefficiencies in the dopaminergic system. In NF1, the deficit is presumably additionally related to the memory stage, corroborating deficient learning processes in general in NF1. On a neurobiological level, these deficits could be due to the deficient synthesis of dopamine on the one hand as well as due to other affected neurotransmitter systems relevant for learning on the other. Tying up with other data (Bluschke, von der Hagen, Papenhagen, Roessner, & Beste, 2017a, 2017b), the results show that despite the strong overlap in clinical phenotype and neuropsychological deficits in NF1 and ADHD, the underlying cognitive mechanisms are different. This is important to consider regarding pharmacological interventions in these diseases.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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REFERENCES

American Psychiatric Association, & American Psychiatric Association (Eds.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). Washington, DC: American Psychiatric Association. Retrieved from http://swbplus.bsz-bw.de/bsz381494357inh.htm

Bauermeister, J.J., Barkley, R.A., Martinez, J.V., Cumba, E., Ramirez, R.R., Reina, G., … Salas, C.C. (2005). Time estimation and performance on reproduction tasks in subtypes of children with attention deficit hyperactivity disorder. *Journal of Clinical Child & Adolescent Psychology*, *34*(1), 151–162.

Beste, C., Saft, C., Andrich, J., Müller, T., Gold, R., & Falkenstein, M. (2007). Time processing in Huntington's disease: a group-control study. *PloS One*, *2*(12), e1263.

Bluschke, A., Chmielewski, W.X., Mückschel, M., Roessner, V., & Beste, C. (2017). Neuronal intra-individual variability masks response selection differences between ADHD subtypes – a need to change perspectives. *Frontiers in Human Neuroscience*, *11*, 329.

Bluschke, A., Mückschel, M., Roessner, V., & Beste, C. (2020). Intact stimulus-response conflict processing in ADHD-multilevel evidence and theoretical implications. *Journal of Clinical Medicine*, *9*(1), 234.

Bluschke, A., Schreiter, M.L., Friedrich, J., Adelhöfer, N., Roessner, V., & Beste, C. (2020). Neurofeedback trains a superordinate system relevant for seemingly opposing behavioral control deficits depending on ADHD subtype. *Developmental Science*, *23*(6), e12956.

Bluschke, A., Schuster, J., Roessner, V., & Beste, C. (2018). Neurophysiological mechanisms of interval timing dissociate inattentive and combined ADHD subtypes. *Scientific Reports*, *8*(1), 2033.

Bluschke, A., von der Hagen, M., Papenhagen, K., Roessner, V., & Beste, C. (2017a). Conflict processing in juvenile patients with neurofibromatosis type 1 (NF1) and healthy controls – two pathways to success. *NeuroImage : Clinical*, *14*, 499–505.

Bluschke, A., von der Hagen, M., Papenhagen, K., Roessner, V., & Beste, C. (2017b). Response inhibition in Attention deficit disorder and neurofibromatosis type 1 – clinically similar, neurophysiologically different. *Scientific Reports*, *7*, 43929.

Bluschke, A., Zink, N., Mückschel, M., Roessner, V., & Beste, C. (2020). A novel approach to intra-individual performance variability in ADHD. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-020-01555-y

Brown, J.A., Diggs-Andrews, K.A., Gianino, S.M., & Gutmann, D.H. (2012). Neurofibromatosis-1 heterozygosity impairs CNS neuronal morphology in a cAMP/PKA/ROCK-dependent manner. *Molecular and Cellular Neurosciences*, *49*(1), 13–22.

Brown, J.A., Emnett, R.J., White, C.R., Yuede, C.M., Conyers, S.B., O'Malley, K.L., … Gutmann, D.H. (2010). Reduced striatal dopamine underlies the attention system dysfunction in neurofibromatosis-1 mutant mice. *Human Molecular Genetics*, *19*(22), 4515–4528.

Brown, J.A., Xu, J., Diggs-Andrews, K.A., Wozniak, D.F., Mach, R.H., & Gutmann, D.H. (2011). PET imaging for attention deficit preclinical drug testing in neurofibromatosis-1 mice. *Experimental Neurology*, *232*(2), 333–338.

Buhusi, C.V., & Meck, W.H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nature Reviews. Neuroscience*, *6*(10), 755–765.

Buhusi, C.V., & Meck, W.H. (2009). Relative time sharing: new findings and an extension of the resource allocation model of temporal processing. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *364*(1525), 1875–1885.

Costa, R.M., Federov, N.B., Kogan, J.H., Murphy, G.G., Stern, J., Ohno, M., … Silva, A.J. (2002). Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. *Nature*, *415*(6871), 526–530.

Coudé, F.X., Mignot, C., Lyonnet, S., & Munnich, A. (2007). Early grade repetition and inattention associated with neurofibromatosis type 1. *Journal of Attention Disorders*, *11*(2), 101–105.

Coull, J.T., Cheng, R.-K., & Meck, W.H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 3–25.

Descheemaeker, M.-J., Ghesquière, P., Symons, H., Fryns, J.P., & Legius, E. (2005). Behavioural, academic and neuropsychological profile of normally gifted Neurofibromatosis type 1 children. *Journal of Intellectual Disability Research*, *49*(1), 33–46.

Diggs-Andrews, K.A., & Gutmann, D.H. (2013). Modeling cognitive dysfunction in neurofibromatosis-1. *Trends in Neurosciences*, *36*(4), 237–247.

Diggs-Andrews, K.A., Tokuda, K., Izumi, Y., Zorumski, C.F., Wozniak, D.F., & Gutmann, D.H. (2013). Dopamine deficiency underlies learning deficits in neurofibromatosis-1 mice. *Annals of Neurology*, *73*(2), 309–315.

Doehnert, M., Brandeis, D., Schneider, G., Drechsler, R., & Steinhausen, H.-C. (2013). A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, *54*(3), 260–270.

Döpfner, M., Görtz-Dorten, A., & Lehmkuhl, G. (2009). *Diagnostik-System für psychische Störungen nach ICD-10 und DSM-IV für Kinder und Jugendliche - II/DISYPS-II*. Bern: Huber, Hogrefe AG. Retrieved from http://primoproxy.slub-dresden.de/cgi-bin/permalink.pl?libero_mab216128740

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191.

Gibbon, J. (1977). Scalar expectancy theory and Weber's law in animal timing. *Psychological Review*, *84*(3), 279–325.

Gibbon, J., Church, R.M., & Meck, W.H. (1984). Timing and time perception. *The New York Academy of Sciences*, (423), 52–77.

Gutmann, D.H., Cole, J.L., & Collins, F.S. (1994). Modulation of neurofibromatosis type 1 gene expression during in vitro myoblast differentiation. *Journal of Neuroscience Research*, *37*(3), 398–405.

Heimgärtner, M., Granström, S., Haas-Lude, K., Leark, R.A., Mautner, V.-F., & Lidzba, K. (2019). Attention deficit predicts intellectual functioning in children with neurofibromatosis type 1. *International Journal of Pediatrics*, *2019*, 9493837.

Hwang, S.-L., Gau, S.S.-F., Hsu, W.-Y., & Wu, Y.-Y. (2010). Deficits in interval timing measured by the dual-task paradigm among children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *51*(3), 223–232.

Hyman, S.L., Shores, A., & North, K.N. (2005). The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology*, *65*(7), 1037–1044.

Kayl, A.E., & Moore, B.D. (2000). Behavioral phenotype of neurofibromatosis, type 1. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*(2), 117–124.

Kerns, K.A., McInerney, R.J., & Wilde, N.J. (2001). Time reproduction, working memory, and behavioral inhibition in children with ADHD. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *7*(1), 21–31.

Klein, M., Onnink, M., van Donkelaar, M., Wolfers, T., Harich, B., Shi, Y., … Franke, B. (2017). Brain imaging genetics in ADHD and beyond - mapping pathways from gene to disorder at different levels of complexity. *Neuroscience and Biobehavioral Reviews*, *80*, 115–155.

Kofler, M.J., Rapport, M.D., Sarver, D.E., Raiker, J.S., Orban, S.A., Friedman, L.M., & Kolomeyer, E.G. (2013). Reaction time variability in ADHD: a meta-analytic review of 319 studies. *Clinical Psychology Review*, *33*(6), 795–811.

Koth, C.W., Cutting, L.E., & Denckla, M.B. (2000). The association of neurofibromatosis type 1 and attention deficit hyperactivity disorder. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *6*(3), 185–194.

Li, S.C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: from neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479–486.

MacDonald, S.W. S., Nyberg, L., & Bäckman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences*, *29*(8), 474–480.

Mahone, E.M., & Denckla, M.B. (2017). Attention-deficit/hyperactivity disorder: a historical neuropsychological perspective. *Journal of the International Neuropsychological Society : JINS*, *23*(9–10), 916–929.

Matell, M.S., King, G.R., & Meck, W.H. (2004). Differential modulation of clock speed by the administration of intermittent versus continuous cocaine. *Behavioral Neuroscience*, *118*(1), 150–156.

Mautner, V.-F., Kluwe, L., Thakker, S.D., & Leark, R.A. (2002). Treatment of ADHD in neurofibromatosis type 1. *Developmental Medicine and Child Neurology*, *44*(3), 164–170.

Meck, W.H. (1983). Selective adjustment of the speed of internal clock and memory processes. *Journal of Experimental Psychology. Animal Behavior Processes*, *9*(2), 171–201.

Merchant, H., & de Lafuente, V. (2014). Introduction to the neurobiology of interval timing. *Advances in Experimental Medicine and Biology*, *829*, 1–13.

Meyers, J.E. (2019). Time estimation: Close your eyes and tell me when a minute goes by. *Applied Neuropsychology: Adult (World)*, *27*(3), 279–283. Retrieved from https://www.tandfonline.com/doi/pdf/10.1080/23279095.2018.1535435

Mullins, C., Bellgrove, M.A., Gill, M., & Robertson, I.H. (2005). Variability in time reproduction: difference in ADHD combined and inattentive subtypes. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(2), 169–176.

Pertermann, M., Bluschke, A., Roessner, V., & Beste, C. (2019). The modulation of neural noise underlies the effectiveness of methylphenidate treatment in attention-deficit/hyperactivity disorder. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2019.03.011

Ptacek, R., Weissenberger, S., Braaten, E., Klicperova-Baker, M., Goetz, M., Raboch, J., … Stefano, G.B. (2019). Clinical implications of the perception of time in Attention Deficit Hyperactivity Disorder (ADHD): A review. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *25*, 3918–3924.

Rammsayer, T.H., Hennig, J., Haag, A., & Lange, N. (2001). Effects of noradrenergic activity on temporal information processing in humans. *The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology*, *54*(3), 247–258.

Sharma, A., & Couture, J. (2014). A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). *The Annals of Pharmacotherapy*, *48*(2), 209–225.

Smith, A., Taylor, E., Rogers, J.W., Newman, S., & Rubia, K. (2002). Evidence for a pure time perception deficit in children with ADHD. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *43*(4), 529–542.

Sohn, H., & Lee, S.-H. (2012). Dichotomy in perceptual learning of interval timing: calibration of mean accuracy and precision differ in specificity and time course. *Journal of Neurophysiology*, *109*, 344–362.

Soucy, E.A., Gao, F., Gutmann, D.H., & Dunn, C.M. (2012). Developmental delays in children with neurofibromatosis type 1. *Journal of Child Neurology*, *27*(5), 641–644.

Suzuki, T.W., & Tanaka, M. (2017). Causal role of noradrenaline in the timing of internally generated saccades in monkeys. *Neuroscience*, *366*, 15–22.

Swanson, J.M., Flodman, P., Kennedy, J., Spence, M.A., Moyzis, R., Schuck, S., … Posner, M. (2000). Dopamine genes and ADHD. *Neuroscience and Biobehavioral Reviews*, *24*(1), 21–25.

Toplak, M.E., & Tannock, R. (2005). Time perception: modality and duration effects in attention-deficit/hyperactivity disorder (ADHD). *Journal of Abnormal Child Psychology*, *33*(5), 639–654.

Vahid, A., Bluschke, A., Roessner, V., Stober, S., & Beste, C. (2019). Deep learning based on event-related EEG differentiates children with ADHD from healthy controls. *Journal of Clinical Medicine*, *8*(7), 1055.

van Rijn, H., Gu, B.-M., & Meck, W.H. (2014). Dedicated clock/timing-circuit theories of time perception and timed performance. *Advances in Experimental Medicine and Biology*, *829*, 75–99.

Waldmann, H.-C. (2008). Kurzformen des HAWIK-IV: Statistische Bewertung in verschiedenen Anwendungsszenarien. *Diagnostica*, *54*(4), 202–210.

Walg, M., Oepen, J., & Prior, H. (2015). Adjustment of time perception in the range of seconds and milliseconds: the nature of time-processing alterations in children with ADHD. *Journal of Attention Disorders*, *19*(9), 755–763.

Wild-Wall, N., Willemssen, R., Falkenstein, M., & Beste, C. (2008). Time estimation in healthy ageing and neurodegenerative basal ganglia disorders. *Neuroscience Letters*, *442*(1), 34–38.

Yordanova, J., Albrecht, B., Uebel, H., Kirov, R., Banaschewski, T., Rothenberger, A., & Kolev, V. (2011). Independent oscillatory patterns determine performance fluctuations in children with attention deficit/hyperactivity disorder. *Brain: A Journal of Neurology*, *134*(Pt 6), 1740–1750.

Zimerman, M., Wessel, M.J., Timmermann, J.E., Granström, S., Gerloff, C., Mautner, V.F., & Hummel, F.C. (2015). Impairment of procedural learning and motor intracortical inhibition in Neurofibromatosis Type 1 patients. *EBioMedicine*, *2*(10), 1430–1437.