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Ignore the glitch but mind the switch: Positive effects of methylphenidate on cognition in attention deficit hyperactivity disorder are related to prediction gain

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ABSTRACT

Neuropsychological symptoms such as inattention and distractibility constitute a core characteristic of attention deficit hyperactivity disorder (ADHD). Here, we tested the hypothesis that attentional dysfunctions result from a deficit in neural gain modulation, which translates into difficulty in predictively weighting relevant sensory input while ignoring distraction.

We compared thirty-seven hitherto untreated adults diagnosed with ADHD and thirty-eight healthy participants with a serial switch-drift task that requires internal models of predictable digit sequences to be either updated or stabilized. Switches between sequences that had to be indicated by key presses and digit omissions within a sequence (drifts) that should be ignored varied by stimulus-bound surprise quantified as Shannon information. To investigate whether catecholaminergic modulation by increasing extracellular norepinephrine and dopamine levels leads to an amelioration in prediction gain, participants were tested twice, with patients receiving a single dose of methylphenidate, a norepinephrine/dopamine reuptake inhibitor, in the second session.

Patients and controls differed in both updating and stabilizing, depending on the respective event surprise. Specifically, patients showed difficulty in detecting expectable switches, while having greater difficulty to ignore surprising distractions.

Thus, underconfident prior beliefs in ADHD may fail to appropriately weight expected relevant input, whereas the gain of neural responses to unexpected irrelevant distractors is increased. Methylphenidate improved both flexibility and stability of prediction and had a positive effect on selective responding over time. Our results suggest that ADHD is associated with an impairment in the use of prior expectations to optimally weight sensory inputs, which is improved by increasing catecholaminergic neurotransmission.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood persisting into adulthood in approximately 50% of the patients (Sibley et al., 2022). With a prevalence of ~2.5% in adults (Fayyad et al., 2017), the severity of the disorder is characterized by impairments in multiple contexts (Barbaresi et al., 2013; Sobanski et al., 2007), including a greater risk for substance abuse (Wilens and Morrison, 2011), lower career ability, and unstable relationships (Biederman et al., 1993). Neuropsychological symptoms of adult ADHD mainly include impulsive and disorganized behavior, difficulty in maintaining attention, distractibility, and psychomotor agitation (Wilens et al., 2004). Although there is still no unifying theory on the pathophysiology of the disease, dysfunctions in frontal-executive processes involving the balance between the need to adapt to relevant environmental changes ("flexibility") and the need to ignore potential distractors ("stability") can be considered a hallmark of ADHD (Bush et al., 2005; Sebastian et al., 2012).

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In this context, the neurotransmitter dopamine is thought to play a crucial role (Wu et al., 2012). Dopamine encodes the weight afforded to sensory input by modulating a neurons' signal-to-noise ratio (Ott and Nieder, 2019). This idea has been put forward by *predictive coding theory*, according to which cognitive systems continuously predict the most likely sensory stimulation based on implicit prior beliefs about the state of the world, i.e., internal models (Clark, 2013). During perceptions and behaviors, prior beliefs and incoming signals are compared, which can reveal *prediction errors* used to inform us of what is surprising to update current predictions. Prediction errors are weighted with respect to their *precision*, i.e., the confidence with which they may revise the internal model (Friston, 2005). Crucially, dopamine is associated with encoding the precision of prediction errors by controlling the *neural gain*, i.e., the sensitivity of postsynaptic neurons to inputs such as sensory stimuli. The higher the precision, the higher the gain of neurons that encode prediction errors and thus determine whether those lead to updating or stabilizing current predictions (Fiorillo et al., 2003). Several neuropsychiatric disorders associated with dopaminergic dysfunction are thought to be accompanied by impaired precision weighting of sensory input relative to predictions (Friston, 2017). As for ADHD, positron emission tomography and functional neuroimaging studies show a dopaminergic hypofunction (Plichta and Scheres, 2014) as well as atypical connectivity (Liston et al., 2011) of striatal and prefrontal areas, which are suggested to complement each other to enable situation-dependent flexible or stable behavior (Cools and D'Esposito, 2011). A recent computational model suggests that symptoms of ADHD result from impaired neuronal gain modulation due to disturbances in the development of the corticostriatal catecholamine system (Hauser et al., 2016). Indeed, experimental studies provide evidence for disruptions in the development of top-down predictions whilst excessive precision weighting of bottom-up input in patients with ADHD (Gonzalez-Gadea et al., 2015; Hasler et al., 2016). However, there is mixed evidence for difficulties in implicit learning, crucial for the development of prior expectations, with some studies reporting impairment in ADHD (Barnes et al., 2010; Huang-Pollock et al., 2017), while others do not (Pedersen and Ohrmann, 2018; Takács et al., 2017). Moreover, no in-vivo study has yet demonstrated the effects of dopaminergic modulation on predictive gain in ADHD.

Studies investigating drugs acting on the catecholamine system, especially methylphenidate (MPH), have supported an involvement of dopamine in the etiopathology of ADHD. MPH blocks dopamine and noradrenaline transporters, which leads to an increase in extracellular levels of the two neurotransmitters. It effectively reduces impairment of working memory, vigilance or response inhibition of both children and adults (Cortese et al., 2018); (Pievsky and McGrath, 2018). Crucially, prior experience and learning has been shown to modulate the positive effect of MPH on response inhibition, post-error behavioral adaptation, and action-perception integration in healthy participants (Bensmann et al., 2019; Eggert et al., 2021; Mückschel et al., 2020). MPH could thus trigger a selective increase in the gain for those stimuli that prove to be relevant while learning, whereas irrelevant stimuli can be filtered out.

Thus, previous studies have indicated that in ADHD, both stability and flexibility and the weighting of predictions against sensory input are impaired. However, a possible link between the two impairments inferring dopaminergic dysfunction has not yet been investigated.

We therefore examined ADHD patients in flexible updating and stabilization of predictions and additionally tested, if MPH improved either stability or flexibility or both. Patients and healthy controls performed the so-called *serial switch-drift task* (Trempler et al., 2017), which requires tracking predictable digit sequences serving as internal models. Tracking should enable participants to indicate the occurrence of sequential model "switches" while ignoring model-uncritical omissions of digits within a sequence ("drifts"). Participants completed two sessions, with patients tested once with and once without a single dose of MPH. In order to assess effects of probability of expectation violations, the relative proportion of switch vs. drift occurrences varied over time. Information theory was used to describe effects of uncertainty due to varying probabilities (Shannon, 1948). The information content of a particular event (i.e., switch or drift) was quantified by the level of *surprise* derived from the event's improbability. *Entropy* measures the average surprise of all possible events and was calculated to quantify predictability.

We tested the following hypotheses: Due to impaired gain modulation, patients with ADHD would show insufficient predictive flexibility and stability compared to a group of healthy controls reflected by a lower rate of switch detection and a higher rate of false-positive responses to interfering drifts. Due to the impaired build-up of predictions for relevant and excessive weighting of irrelevant input, we also assumed that the impairment of flexible updating manifests itself mainly when switches could be expected, whereas difficulties in stabilization should show up mainly when highly unexpected drifts are to be ignored. Differences between controls and patients should be reduced by the administration of MPH because of its positive effect on gain modulation, reflected in an improved selective responding over the course of the experiment.

2. Methods

2.1. Participants

Forty-one right-handed participants suspected of having ADHD (15 females, 26 males; 29.63 ± 8.80 years old; range, 20–48 years) were acquired from the psychiatric outpatient clinic of the Department of Psychiatry and Psychotherapy at the University Hospital of Muenster, Germany. Forty healthy participants (18 females, 22 males; 28.00 ± 7.38 years old; range 18–47 years) served as control subjects. No participant had a history of other neurological or psychiatric diseases. One patient and two healthy participants were excluded due to difficulties in completing the main experiment (see 2.3 Data analysis).

Patients received their first diagnosis in the course of study participation, based on the diagnostic criteria of the structured Diagnostic Interview for Adult ADHD (Kooij and Francken, 2010) and the structured clinical interview for DSM-IV diagnosis (Wittchen et al., 1997). Three participants of the potential patient sample did not meet the criteria and were excluded from further testing. Standardized psychometrical scales were conducted by all participants to further assess ADHD symptoms. These included the German versions of the ADHD Self Rating Scale (Rösler et al., 2008), the Wender Utah Rating Scale (Retz-Junginger et al., 2002), and the Adult Self-Report Scale for ADHD (Kessler et al., 2005). The final sample comprised of 37 patients with ADHD (18 females, 22 males; 29.59 ± 8.97 years; range 20–48 years) and 38 healthy controls (14 females, 23 males; 27.05 ± 6.24 years; range 18–47 years).

The study consisted of two test sessions, with the second session taking place approximately two weeks after the first session. As part of the diagnostic procedure, patients received a single oral dose of 10 mg MPH (Ritalin®) approximately 1 h before neuropsychological testing for the second session. Since the patients were first diagnosed with ADHD, they had not been treated with medication before and thus received their first (non-individualized) MPH dose to test its effect on a series of psychological tests (for similar procedures see Duval et al., 2021; Ertlé et al., 2013; Kurscheidt et al., 2008). Control participants were also tested twice (without receiving medication) to control for training effects across the two sessions. In both sessions, participants completed a standard neuropsychological test battery assessing core cognitive functions. German versions of all tests were used. Table 1 depicts demographic data and mean values along with standard deviations of all applied tests for the final samples.

The study was performed in accordance with the latest version of the Declaration of Helsinki and had been approved by the ethics committee of the Psychological Institute of the University of Muenster, Germany. Each participant submitted a signed informed consent notification after

Table 1
Demographic and clinical data.

Characteristic	Mean (±SD)				*p*-value[a]
	Controls		Patients		
	(*n* = 38)		(*n* = 37)		
Age (years)	27.05 (6.24)		29.59 (8.97)		0.157
female	25.88 (7.48)		26.50 (6.60)		0.811
male	28.00 (5.01)		31.48 (9.80)		0.143
ADHS-SB	7.5 (4.23)		32.38 (8.40)		<0.001
WURS-k	12.55 (9.96)		36.84 (11.16)		<0.001
ASRS	1.45 (1.81)		13.49 (2.64)		<0.001
BDI-II	4.29 (4.09)		12.11 (9.21)		<0.001
BIS 11	57.95 (7.74)		78.49 (8.21)		<0.001
	S1	**S2**	**S1**	**S2**	
TAP					
Divided Attention RT (ms)	599.21 (54.26)	596.81 (55.06)	669.55 (85.13)	615.18 (61.06)	<0.001
Go/NoGo RT (ms)	373.99 (67.62)	362.61 (54.94)	403.35 (83.63)	360.70 (42.31)	0.529
Cued Alertness RT (ms)	227.54 (31.89)	221.50 (27.92)	257.08 (70.26)	227.84 (38.38)	0.036
Uncued Alertness RT (ms)	229.42 (34.76)	277.97 (281.26)	278.03 (85.83)	240.11 (55.59)	0.079
Working Memory RT (ms)	556.28 (144.55)	579.91 (135.93)	661.55 (197.59)	574.88 (134.00)	0.001
CKV					
Perseveration Score (%)	9.49 (12.25)	6.29 (8.88)	13.22 (14.24)	7.03 (10.11)	0.363
Concept Perseveration	5.87 (0.67)	5.97 (0.16)	5.73 (0.90)	5.86 (0.67)	0.847
VLMT					
Learning	56.55 (8.02)	61.24 (7.55)	49.95 (11.72)	55.65 (10.02)	0.377
Delayed Recall	13.00 (2.22)	12.86 (2.43)	11.05 (3.18)	12.27 (2.43)	<0.001
Recognition	14.55 (1.27)	14.62 (0.76)	13.92 (1.40)	14.30 (1.13)	0.090
FAIR					
Achievement Score	397.47 (88.24)	473.16 (93.09)	367.24 (108.27)	458.57 (96.60)	0.207
Quality Score	0.95 (0.04)	0.96 (0.04)	0.92 (0.07)	0.96 (0.03)	0.005
Continuity Value	377.53 (85.94)	454.37 (93.08)	357.02 (146.05)	441.19 (96.01)	0.730

ADHD-SB, ADHD Self Rating Scale; WURS-k, Wender Utah Rating Scale; ASRS, Adult Self-Report Scale for ADHD; BDI-II, Beck Depression Inventory-II; BIS-11, Barratt Impulsiveness Scale; FAIR, Frankfurt Attention Inventory; TAP, Test of Attentional Performance; CKV, computerized card sorting test; VLMT, Visual Learning and Memory Test.

[a] *p*-value of mixed ANOVA with session (S1 vs. S2) as within-, and group (controls vs. patients) as between-subject factor.

the procedures had been fully explained and received reimbursement for participation afterwards.

2.2. Serial switch-drift paradigm

Participants performed the *serial switch-drift paradigm* consisting of two constantly repeating digit sequences, one ascending (1–2–3–4) and one descending (4–3–2–1) (Fig. 1A) (Standke et al., 2021). Digits, each representing a trial, were presented for 1000 ms, separated by a 100 ms intertrial interval. Occasionally, either *switches* from the ascending to the descending sequence or vice versa, or *drifts*, i.e., single digit omissions, occurred at pseudorandom ordinal positions within the sequence. The participant's task was to signal the switches as quickly and accurately as possible by key press, but to ignore the sequential omissions. In addition, motor control trials (n = 25) were randomly interspersed throughout the experiment, in which individual digits were repeated up to eight times until the participant responded by button press.

The experiment was divided into 12 blocks with an average number of 125 digits, in which high and low probabilities for switches and drifts were combined in a two-by-two full factorial design with the factors PROBABILITY (high vs. low) and EVENT TYPE (switch vs. drift), resulting in four different block types (Fig. 1B). Unmixed blocks consisted of equally high (8% each) and low (4% each) drift and switch probability, respectively, while mixed blocks consisted of either high switch or drift (12%) and correspondingly low drift or switch (4%) probability. Transitions between blocks were balanced throughout the experiment and blocks were separated by the presentation of a 6s fixation cross. Randomization was programmed using MATLAB R2012b (The MathWorks Inc., Natick, USA) and stimuli were presented using Presentation (Neurobehavioral Systems, San Francisco, USA).

To ensure task comprehension, participants completed an instructed training with five blocks of 60 trials each directly prior to the main experiment. At the beginning of this training, the duration of a trial was 1500 ms and was reduced by 100 ms in the following block if the participants responded correctly to 75% or more of switches or drifts.

2.3. Data analysis

We assessed task performance according to the rate of correct switch detection (i.e., hits) vs. misses and the rate of correct rejection of drifts vs. false alarms. Motor control trials were used to determine the 90% quantile of each participant's reaction time (RT), which then served as an individual time window in which button presses were counted as hits and false alarms, respectively. Outliers within each sample were determined by computing the 1.5 interquartile ranges (IQR) for the discrimination index *Pr*, which quantifies the participants' ability to specifically select the correct response to either switches or drifts (P_r=*H*–*FA*, Snodgrass and Corwin, 1988). Values that fell below the IQR were considered as outliers leading to the exclusion of one patient (P_r = 0.14) and two healthy participants (P_r = 0.09 and 0.19).

We tested whether information theoretic quantities, i.e., Shannon's surprise $I(x_i)$ and entropy $H(X)$ (Shannon, 1948) reflecting the inverse probability and predictability of a single stimulus, respectively, could predict RTs and correct responses on a trial-by-trial level. We first calculated each stimulus' probability based on the frequency of a trial type x_i, normalized by the sum of all past trials in the block:

$$p(x_i) = \frac{n(x_i) + 1}{\sum x_t + 1}$$

The counts before observing the first trial in the block were set to 1/3 for each event type (hence reflecting a discrete uniform distribution) to give a weak influence of the prior. The surprise $I(x_i)$ of each stimulus that is unique to a particular event and given by the negative logarithm of its probability quantifies the amount of information provided by the current stimulus:

$$I(x_i) = -\ln p(x_i)$$

Finally, entropy $H(X)$ measures the average surprise of all possible events (i.e., switch, drift, standard digits) and quantifies the expected information of a stimulus regarding its predictability:

$$H(X) = \sum_i -p(x_i)\ln p_k(x_i)$$

We used generalized linear and logistic mixed-effects models in R, version 3.6.2 (R Core Team, 2018) via the package *lme4*, version 1.1.21 (Bates et al., 2015). We assessed whether RTs and dichotomous correct responses were predicted by fixed effects of GROUP (controls vs. patients), EVENT TYPE (drift vs. switch), and SESSION (first vs. second), as well as the interaction between the three factors. We used dummy coding with controls, drifts, and first session as reference groups, respectively. In addition to including SURPRISE and ENTROPY at each trial as continuous predictors, we included TRIAL NUMBER to assess learning over the course of each session. Main and interaction effects of these factors were included as follows, with TRIAL NUMBER, EVENT TYPE and SESSION additionally also

considered as random slopes:

reaction_time/correct_responses~(group*session*trial_number)+(group*-session*event_type*surprise)+(group*session*entropy)+(session+event_type+trial_number | participant).

Statistical significance for each fixed effect was calculated via *lmerTest*, version 3.1.1 (Kuznetsova et al., 2017), using the Satterthwaite's approximation to denominator degrees of freedom. The significance level was set to $\alpha = 0.05$. We report fixed effect estimates along with *t*- and *p*-values, and back-transformed estimated marginal means (EMMs) and standard errors (SEs) for significant effects (note that we factorized low (0) and high (4) levels for the continuous surprise variable to also report EMMs and SEs for the four-way interaction of GROUP, EVENT TYPE, SESSION and SURPRISE).

In addition, we calculated Bayesian linear and logistic multilevel models in R (R Core Team, 2018) via the *brms* package and Stan using default priors (Bürkner, 2017; Carpenter et al., 2017), and here report regression coefficients and 95% credible intervals (CIs; i.e., Bayesian confidence intervals).

3. Results

Results of the generalized linear mixed-effects model used to predict RTs revealed significant main effects of SESSION, $b = -0.23$, $t = -6.47$, $p < 0.001$, with lower RTs in the second ($EMM = 807$ ms,$SE = 24.1$) than in the first session ($EMM = 904$ ms,$SE = 26.0$), and of ENTROPY, $b = 0.02$, $t = 2.18$, $p = 0.03$, with increasing RTs as a function of increasing entropy. The Bayesian model supported the effects of SESSION, $b = -0.23$, 90%-CI = [−0.30,-0.16], and ENTROPY, $b = 0.02$, 90%-CI = [0.00,0.04]

Consistent with our hypothesis, the factor GROUP significantly interacted with SESSION, $b = 0.16$, $t = 3.04$, $p = 0.002$, as also revealed by the Bayesian model, $b = 0.16$, 90%-CI = [0.06,0.26]. Compared to controls, patients showed higher RTs at switch hits and drift false alarms in the first ($EMM_{S1\_C} = 857$ ms,$SE = 34.7$ vs. $EMM_{S1\_P} = 950$ ms,$SE = 38.8$) but not in the second session ($EMM_{S2\_C} = 818$ ms,$SE = 34.6$ vs. $EMM_{S2\_P} = 796$ ms,$SE = 33.5$). An interaction effect with EVENT TYPE could not be observed ($p > 0.20$) (Fig. 2a). Main or interaction effects including TRIAL NUMBER also had no significant influence on RTs (all $p > 0.49$, Fig. 2b).

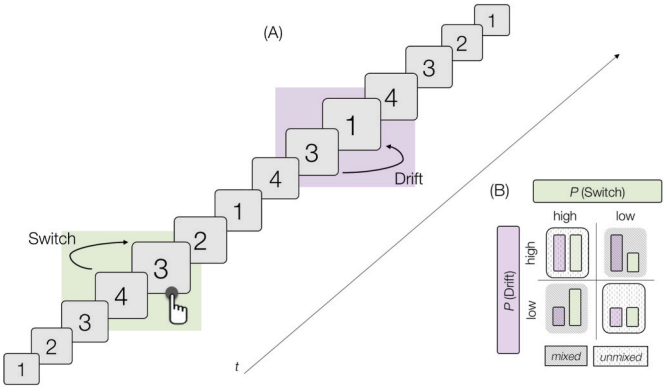

Fig. 1. Schematic diagram of the task. (A) Participants were asked to indicate a directional change (*switch*) within a simple 4-digit sequence via button press but to ignore the omission of a single digit (*drift*). (B) The probabilities of switches and drifts varied block-wise across the experiment in a 2x2 design, resulting in mixed and unmixed blocks with unequal and equal probabilities of the two event types, respectively. In unmixed blocks, the maximum probability was 16% (i.e., 8% switches, 8% drifts) and the minimum probability was 8% (i.e., 4% switches, 4% drifts). For mixed blocks, the maximum probability was 12%, while the minimum probability remained the same with 4%. In this way, the level of difficulty relative to the overall 16% probability of unexpected events was kept constant throughout the experiment (except for the low-probability unmixed blocks).

Likewise, we did not find differences between the groups in the RT modulation by ENTROPY and SURPRISE (all $p > 0.33$).

The logistic mixed-effects model predicting correct responses revealed significant main effects for SESSION, $b = 0.42$, $t = 3.83$, $p < 0.001$, with more correct responses in the second ($EMM = 0.90$,$SE = 0.01$) than in the first session ($EMM = 0.84$,$SE = 0.01$), and for EVENT TYPE, $b = -1.27$, $t = -6.44$, $p < 0.001$, with a lower rate of switch hits ($EMM = 0.81$,$SE = 0.02$) than of drift rejections ($EMM = 0.93$,$SE = 0.00$). Moreover, we found a significant main effect for TRIAL NUMBER, $b = -0.11$, $t = -2.65$, $p = 0.008$, with correct response rate decreasing as a function of increasing trial number, and for SURPRISE, $b = -0.28$, $t = -4.50$, $p < 0.001$, showing that fewer correct responses are given with increasing surprise. No main effect of ENTROPY was observed ($p = 0.276$). Consistent with our hypothesis, there was a significant three-way interaction of SESSION, EVENT TYPE, and GROUP, $b = -0.64$, $t = -4.04$, $p < 0.001$, as also supported by the Bayesian logistic multilevel model, $b = -0.65$, 90%-CI = [−0.97,-0.33]. While the increase in switch hits from the first to the second session was significantly greater in patients ($EMM_{S1} = 0.72$,$SE = 0.03$ vs. $EMM_{S2} = 0.85$,$SE = 0.02$) than in controls ($EMM_{S1} = 0.81$,$SE = 0.03$ vs. $EMM_{S2} = 0.85$,$SE = 0.02$), no difference was found between patients ($EMM_{S1} = 0.90$,$SE = 0.01$ vs. $EMM_{S2} = 0.93$,$SE = 0.01$) and controls ($EMM_{S1} = 0.92$,$SE = 0.01$ vs. $EMM_{S2} = 0.95$,$SE = 0.01$) in terms of improvement in correct drift rejections (Fig. 3a). Regarding the learning effect within each session, both the frequentist model, $b = -0.30$, $t = -4.09$, $p < 0.001$, and the Bayesian model, $b = -0.31$, 90%-CI = [−0.45,-0.16], supported a significant interaction between TRIAL NUMBER, SESSION, and GROUP. The patients' performance decreased over time in the first session without MPH, but increased in the second session when receiving medication. In contrast, no (or, if at all, the reverse) modulation of correct responses by trial number was observed in either session in healthy controls (Fig. 3b).

As expected, a significant four-way interaction of SESSION, EVENT TYPE, GROUP, and SURPRISE was observed, $b = -0.38$, $t = -2.45$, $p = 0.014$, that was also supported by the Bayesian model, $b = -0.38$, 90%-CI = [0.07,0.67] (Fig. 4). Patients ($EMM_{S1} = 0.98$,$SE = 0.01$ vs. $EMM_{S2} = 0.97$,$SE = 0.01$) and controls ($EMM_{S1} = 0.98$,$SE = 0.01$ vs. $EMM_{S2} = 1.00$,$SE = 0.00$) did not differ in their responses to expected drifts in both sessions. However, compared to controls ($EMM_{S1} = 0.76$,$SE = 0.07$ vs. $EMM_{S2} = 0.63$,$SE = 0.09$), patients had difficulty rejecting highly surprising drifts in the first session ($EMM_{S1} = 0.62$,$SE = 0.09$), but performed better than controls in the second session, i.e., showed a higher rate of correct rejections of surprising drifts ($EMM_{S2} = 0.82$,$SE = 0.06$). In contrast, patients ($EMM_{S1} = 0.61$,$SE = 0.08$) and controls ($EMM_{S1} = 0.60$,$SE = 0.09$) had the same difficulties in detecting surprising switches in the first session. However, the more the switches could be expected (i.e., the lower the surprise), the more likely the hit rate increased for controls ($EMM_{S1} = 0.92$,$SE = 0.02$) compared with patients ($EMM_{S1} = 0.81$,$SE = 0.05$). Notably, this significant difference leveled off completely with medication in the second session, in which patients ($EMM_{S2} = 0.80$,$SE = 0.06$) and controls ($EMM_{S2} = 0.79$,$SE = 0.07$) both responded equally better to surprising switches, and patients - like controls ($EMM_{S2} = 0.89$,$SE = 0.04$) - were now also more likely to respond correctly to expectable switches ($EMM_{S2} = 0.90$,$SE = 0.04$). Finally, there was no differential modulation of error rate by entropy across the groups or sessions (all $p > 0.094$).

4. Discussion

In the present study, we investigated gain modulation in ADHD patients with a switch-drift paradigm using stimuli to be attended and stimuli to be ignored. As hypothesized, patients showed difficulty with both flexible updating and stabilizing current predictions as a function of stimulus-bound surprise. Patients were especially impaired at detecting expectable relevant changes, while at the same time having difficulty ignoring surprising distractions. A standard dose of MPH given to the previously untreated patients improved flexibility and stability of

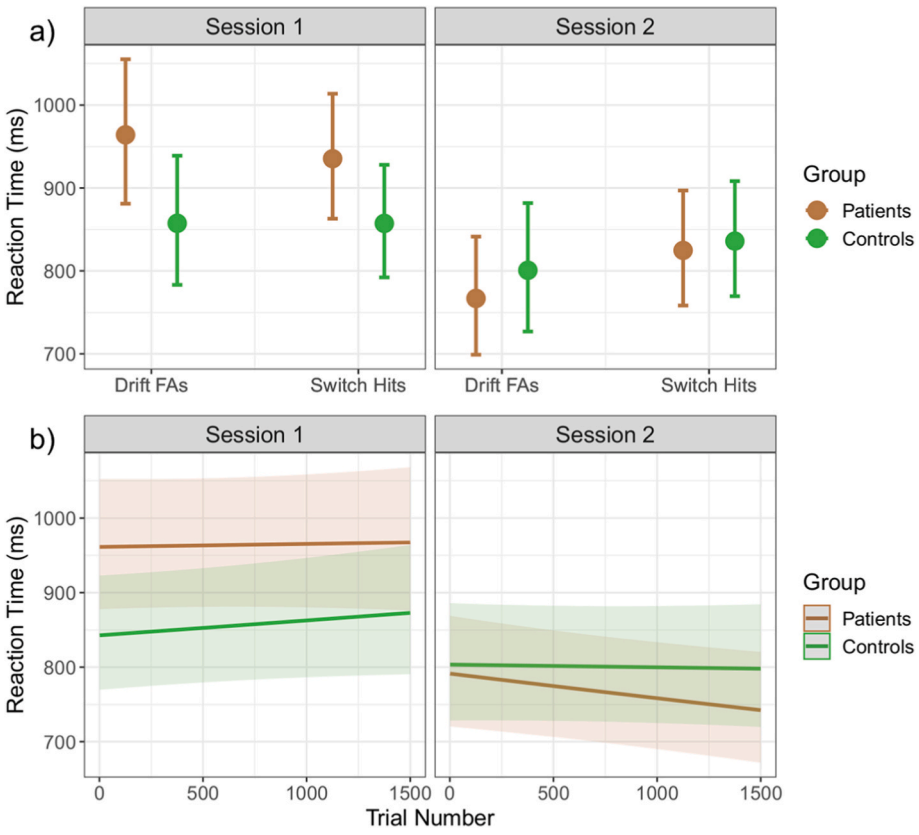

Fig. 2. The top panels **a)** depicts reaction time (in ms) for drift false alarms (FAs) and switch hits for the first session (left) and second session (right), stratified by group (i.e., patients with ADHD and healthy controls). In the second session, ADHD patients received a single dose of methylphenidate. The bottom panel **b)** shows time-on-task effects for each session and group, represented by the reaction time (in ms) as a function of trial number, independent of event type. Error bars and shaded areas represent 95% confidence intervals.

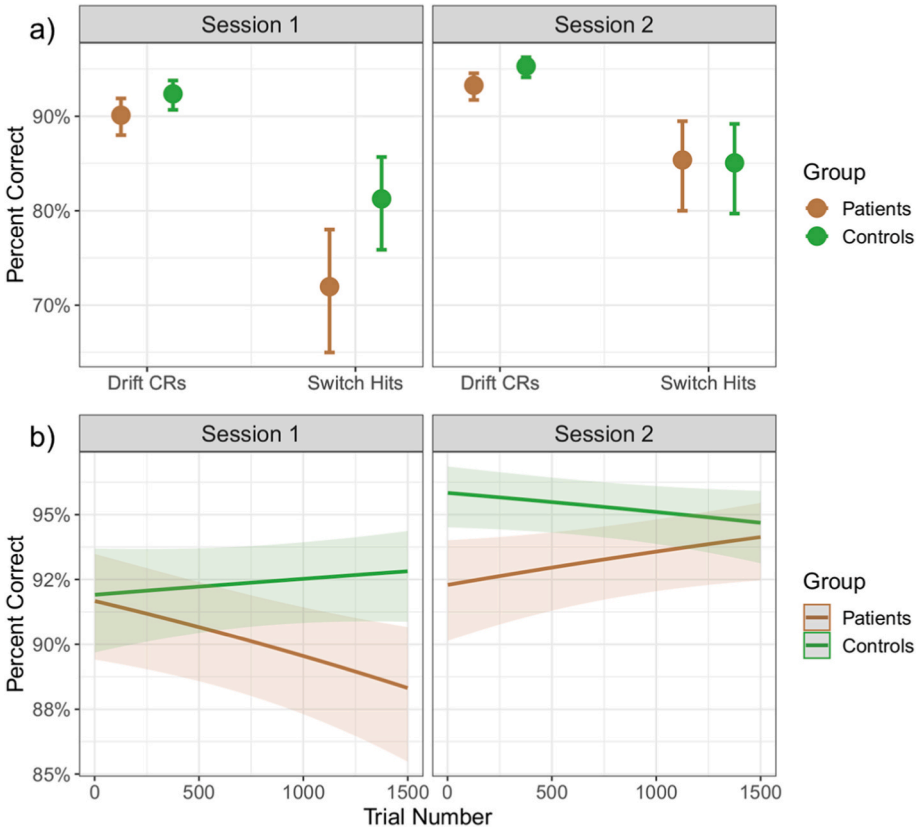

Fig. 3. The top panels **a)** depicts rate of correct responses at drifts (i.e., rate of correct rejections, CRs) and switches (i.e., rate of hits) for the first session (left) and second session (right), stratified by group (i.e., patients with ADHD and healthy controls). In the second session, ADHD patients received a single dose of methylphenidate. The bottom panel **b)** shows time-on-task effects for each session and group, represented by rate of correct responses as a function of trial number, independent of event type. Error bars and shaded areas represent 95% confidence intervals.

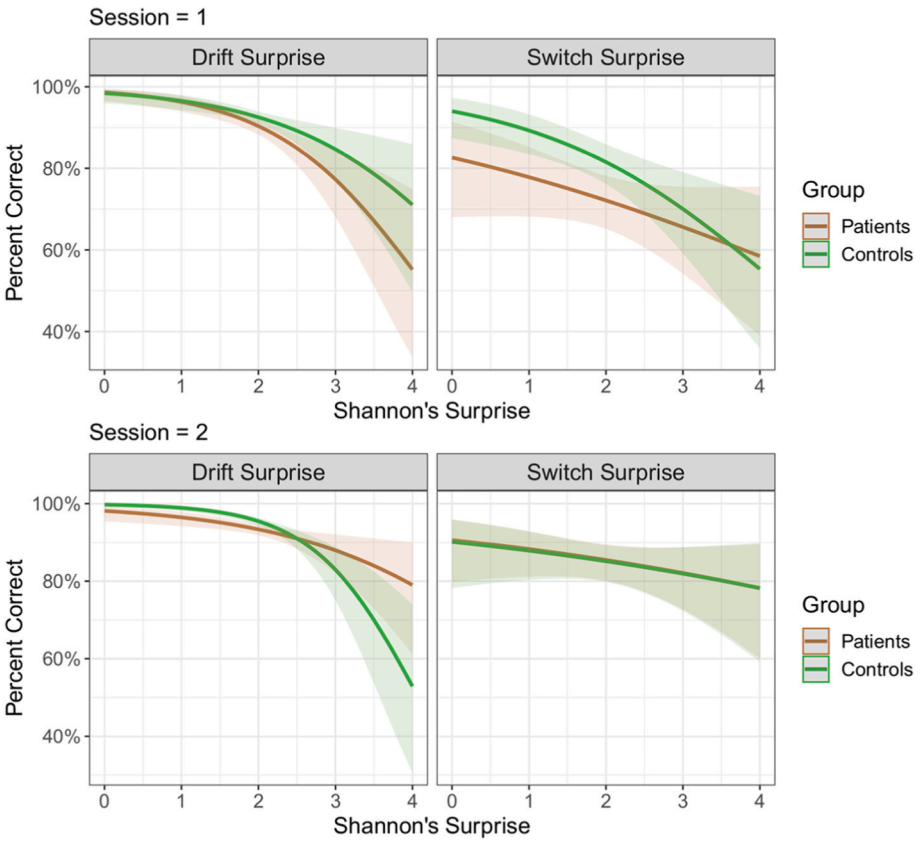

Fig. 4. Marginal effects of Shannon's surprise at drifts (left) and switches (right) on the rate of correct responses of patients with ADHD and healthy controls in the first session (top panel) and second session, where patients received a single dose of methylphenidate (bottom panel). Error bars and shaded areas represent 95% confidence intervals.

prediction. This positive effect increased over the course of the MPH session, suggesting that MPH also had a beneficial effect on learning to respond selectively to relevant and irrelevant stimuli.

4.1. *Impaired predictive flexibility and stability and time-on-task effects*

An impairment in both flexibility and stability of prediction in ADHD was reflected in lower switch hit and drift rejection rates in patients compared with controls. It is important to note that switch detection and drift rejection are independent measures of flexibility and stability, as we have shown previously (Trempler et al., 2017). Impairments in cognitive flexibility have been revealed in ADHD previously, as measured by task- and/or set-shifting (Halleland et al., 2012; Roshani et al., 2020) as well as in inhibitory control, which is an important component of cognitive stability (Roberts et al., 2011; Woltering et al., 2013). However, while previous studies were not designed to distinguish sharply between these two functions (i.e., the operationalization of flexibility also includes processes important for stability and vice versa), our design allows the same premises when flexibility and stability are studied independently in the same paradigm.

According to the hypo-arousal theory of ADHD, a lower baseline tonic physiological arousal can cause boosted phasic responses to sensory input, manifested by hyperactivity, distractibility and highly variable performance (Huang-Pollock et al., 2006; Sikström and Söderlund, 2007). Consistent with this, we observed longer RTs in patients versus controls, i.e., lower responsiveness to unexpected events during the first session, which may indicate lower tonic arousal levels. At the same time, we found time-on-task effects on responses, i.e., fewer hits and correct rejections as a function of time in the first session in patients, which could additionally represent compensatory hyperactivity. Previous studies reported deficits in sustained attention in several tasks in children (Dekkers et al., 2017; Huang-Pollock et al., 2012) and adults with ADHD (Christakou et al., 2013; Tucha et al., 2017). Our findings support the assumption that low arousal level and compensatory hyperactivity in ADHD lead to difficulties in recognizing relevant and ignoring irrelevant events especially over an extended period of time.

4.2. *Differential response modulation by stimulus-bound surprise*

We found that the modulation of correct response rates by surprise differed between patients with ADHD and healthy controls. Regarding switches, we found a comparably low rate of hits at highly surprising switches in the first session in both groups. However, as the probability of switches increased, patients could no longer keep up with controls, who were more likely to detect expectable switches. Thus, at high probability (i.e., low surprise) patients showed a lower switch hit rate than controls. For drifts, on the other hand, performance was comparable when drift probability was high, but when drift surprise increased, patients were more likely to respond to drifts than controls and thus showed a lower rate of correct rejections.

In keeping with the predictive coding theory, our results provide evidence that patients with ADHD are especially impaired in the selective modulation of the precision of certain prediction errors, i.e., so-called *second-order* predictions (Barron et al., 2020; Kanai et al., 2015). Previous studies have shown that ADHD patients exhibit altered behavior while anticipating visual stimuli (Dankner et al., 2017; Fried et al., 2014), and altered neural signals to unexpected sensory stimuli (Pertermann et al., 2019). We elaborate on these findings by showing that ADHD patients have difficulty in weighting relevant targets as they become more likely, while failing to attenuate sensory salience caused by surprising irrelevant distractors. This pattern, which has also been observed in children with ADHD (Gonzalez-Gadea et al., 2015), suggests

that underconfident prior expectations fail to amplify prediction errors, impeding learning to increase the precision of *expected* relevant stimuli, whereas the precision of prediction errors generated by *unexpected* salient distractors is increased.

Our findings seem at odds with studies reporting evidence of intact statistical learning in ADHD (Parks and Stevenson, 2018; Pedersen and Ohrmann, 2018). However, tasks used to investigate statistical learning differ in terms of whether perceptual or motor learning is being investigated, the implementation of the respective statistic, or the timeframes over which the statistic is learned. Moreover, subtle impairments in statistical learning were only found in certain time intervals of experiments, suggesting a role of time-on-task effects (Barnes et al., 2010; Richards et al., 2020). Here, we were particularly interested in rapid adaptation to environments requiring either flexible states with high precision of incoming signals or stable states in favor of current predictions, or even both simultaneously. The observed behavior in patients could be due to an impairment in selective responsiveness rather than a deficit in capturing the statistical structure. This interpretation is supported by the finding that entropy, i.e., the predictability of events, modulated the behavior of both groups equally.

4.3. Effects of methylphenidate (MPH) on predictive flexibility and stability

A key finding of our study concerns the effect of catecholaminergic medication on prediction in ADHD patients. In the second session, where patients but not controls received MPH, all participants increased their performance, indicative of training effects across the two sessions. Notably, the switch hit rate increased to a greater extent in patients than in healthy participants, which points to a specific positive effect of MPH on prediction updating, while the impairment in distractor inhibition remained unchanged. However, with regard to the modulation of correct responses by surprise, the differences between the groups observed in the first session could no longer be detected for either switches or drifts. If at all, the patients here even revealed a higher rate of correct rejections of surprising drifts than the controls. Our results suggest that MPH compensates for the deficit in gain modulation, which had been reflected in a weak weighting of top-down expectations of relevant input along with an overweighting of irrelevant bottom-up input.

Our findings might partially explain the observation of improved clinical symptoms in ADHD patients when treated with agents that increase extracellular dopamine (Gold et al., 2014; Mehta et al., 2019; Sonuga-Barke, 2005). Low levels of dopamine lead to comparable activity in the direct and indirect pathway of the basal ganglia and thus to competing signals and interferences, resulting in poor differentiation among stimuli that would actually have sharpened predictions in the cortex (Hauser et al., 2016; Kok et al., 2012). Our findings may therefore indicate that an increase in dopamine levels after MPH administration can restore signal differentiation by amplification of predicted and suppression of unpredicted features in the two pathways.

In contrast to the first session, during which the patients showed a drop in performance compared to controls, their performance with regard to correct responses increased over the course of the experiment with MPH. This supports previous findings according to which learning modulates the positive effect of MPH on various cognitive functions (Bensmann et al., 2019; Eggert et al., 2021; Mückschel et al., 2020). The observation that there was no corresponding time-on-task effect on RTs in the second session contradicts the assumption that increased catecholamine levels exclusively affect physiological arousal and vigilant attention (Ranjbar-Slamloo and Fazlali, 2020). Rather, they enable participants to selectively increase the gain for those stimuli and responses that prove significant over time.

Because all patients received the same dose of MPH, it is likely that the strength of the effect of MPH differed among participants. Individual differences in pharmacokinetics are also due to body weight as it can influence the volume of distribution of a drug. Future studies should include this measure as a covariate in data analysis to account for these differences. Moreover, due to study constraints we could not balance the order of drug administration in the two sessions, which is why we also tested controls twice to control for a training effect. As the factors group and session were not kept constant, training and medication effects could not be clearly differentiated. Due to general adaptation deficits in the first session and possible motivational deficits (Dovis et al., 2013), we expected training effects to be lower in patients than controls making it all the more likely that session differences are due to MPH. For example, it has recently been shown that ADHD patients benefit from working memory training with adaptive difficulty, but show smaller training effects compared to controls when the difficulty level is held constant (Dotare et al., 2020). Still, future studies should balance the medication intake across sessions.

5. Conclusion

In summary, the present study demonstrates that updating and stabilization in response to expectation violations in ADHD patients is impaired compared to healthy controls. This impairment is ameliorated by an increase in extracellular catecholamine levels as induced by MPH. Our results support the importance of gain modulation in cognitive performance and learning, and deepen our understanding of the pathophysiology of ADHD correlated to the catecholaminergic system.

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CRediT authorship contribution statement

Ima Trempler: Conceptualization, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Alexander Heimsath:** Investigation. **Julia Nieborg:** Investigation. **Benedikt Bradke:** Resources, Data curation, Project administration. **Ricarda I. Schubotz:** Conceptualization, Resources, Writing – review & editing, Supervision. **Patricia Ohrmann:** Conceptualization, Resources, Project administration, Writing – review & editing, Supervision.

Declarations of competing interest

All authors declare that they have no conflicts of interest.

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