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ORIGINAL PAPER

Attention as neurocognitive endophenotype of ADHD across the life span: a family study

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Abstract

Endophenotypes mediate pathways between genetic variations and the psychiatric phenotype, or share genetic risk with the psychiatric phenotype. Identifying endophenotypes is an important step to unravel disease pathways underlying complex psychiatric phenotypes such as ADHD. Potential viable endophenotypes for ADHD across the lifespan are neurocognitive measures of basic attention functions, such as *sustained attention*, and executive attention functions (EF), such as *inhibition*. The present study evaluated the endophenotype criteria of familiality and state-independency for measures of basic attention and EF in affected- and unaffected parents of children with ADHD ($N = 139$), and typically developing children ($N = 60$). In addition, the added value of neurocognitive measures relative to questionnaire data in genetically informed designs was explored by comparing the intergenerational transmission of neurocognitive measures to those of ADHD symptom scores. Results revealed small-to-medium-sized familial effects of ADHD for reaction time measures of EF components and state-independency given familial effects. Parent–child correlations as estimates of intergenerational transmission of those neurocognitive measures were not higher than those of behavioral ADHD symptom ratings. Taken together, our results argue against neurocognitive measures as pivotal endophenotypes for ADHD across the lifespan. If studied as neurocognitive endophenotypes of ADHD in adults, reaction time measures of *executive*—rather than *basic attention* function—seem to be more sensitive.

Keywords Endophenotype · TAP · ADHD · Attention · Cognition · Parent–child

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder that starts in early childhood and persists in a considerable amount of the affected individuals into adulthood [1–4]. Diagnostic criteria for ADHD comprise two core symptom domains: one symptom domain with inattention symptoms such as being easily distracted and disorganized, and one symptom domain with hyperactivity/impulsivity symptoms, such as talking excessively and interrupting conversations [5]. During the transition from childhood into adulthood, the overall amount of ADHD symptoms declines, yet hyperactivity/impulsivity symptoms decline more strongly than inattention symptoms [6–8].

ADHD shows high heritability across the lifespan, with shared and age-specific genetic variation underlying ADHD in child- and adulthood [9]. ADHD conforms to a multifactorial polygenic threshold model of heredity [10], which implies that from the gene level upwards, disease pathways connected to the ADHD disease phenotype involve many entities on different levels, such as protein cascades, cellular networks, neurophysiological processes, and (neuro)cognitive processes [10]. The endophenotype concept has been introduced to help unravel disease pathways of complex

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psychiatric phenotypes such as ADHD [11]. Endophenotypes mediate pathways between genetic variations and the psychiatric phenotype, or share genetic risk with the psychiatric phenotype [12]. Endophenotype candidates are evaluated by (#1) examining associations with the disease phenotype in the population, (#2) heritability, (#3) state-independency (i.e., the endophenotype is present in remitted- and affected patients), (#4) co-segregation with the disease phenotype within families, and (#5) the presence in non-affected family members and absence in the general population [11].

ADHD in child- and adulthood is associated with impaired performance on several neurocognitive measures of attention- and executive function (EF) [13–15]. Neurocognitive measures are hence promising endophenotype candidates for ADHD across the lifespan. Attention- and EF consist of several separately defined, but interdependent theoretical constructs. Separate attention- and EF constructs consequently cannot be measured entirely independently [16]. Neurocognitive tests may be more sensitive when the experimental design is based on a theoretical framework that considers this interdependency [17]. The Test Battery of Attention (TAP) is based on a theoretical model of attention by van Zomeren and Brouwer [18], and encompasses several attention- and EF components. Basic attention functioning is defined by the two dimensions of *attention intensity*- and *selectivity. Attention intensity* represents (in) voluntary increases in baseline arousal levels [19], and is composed of *tonic alertness* (general arousal), *phasic alertness* (heightened arousal after a warning cue), and *sustained attention* (maintaining increased arousal over a longer time period). Measures of *tonic*- and *phasic* alertness are typically assessed by short, simple reaction time tasks with- and without warning cues [20, 21]. *Sustained attention* is assessed by longer tasks, or as time-on-task effects [22]. *Attention selectivity* describes selective attention to certain stimuli [19], and comprises *focused attention* (focus on certain aspects only), and *divided attention* (focus on multiple aspects in parallel) [18]. The *intensity* and *selectivity* of attention are monitored by the Supervisory Attention System (SAS) [23], which comprises EF components (*attentional*) *flexibility* (adaptive control of the current focus of attention) and *inhibition* [18]. Inhibition measures assessed by TAP include *interference control* (suppressing responses in the presence of conflicting response sets- and environmental input) [24], and *impulsivity* (commission errors on tasks that present target and distractors sequentially) [15].

With regard to *intensity of attention* in children with ADHD, the previous findings reported impaired *tonic*- and intact *phasic* alertness [25, 26], but additionally no alertness impairments based on TAP task performance [27, 28]. More consistently replicated are large effects on impaired *sustained attention* performance of children with ADHD [29], and increased reaction time variability (RTV) across basic attention- and SAS tasks [30]. Both findings might reflect the same underlying impairment in attention regulation [31]. Concerning the *selectivity of attention* in children with ADHD, *focused attention* impairments have been observed when targets were difficult to distinguish from non-targets [27, 32]. Mixed results have been reported for *divided attention* [27, 33, 34]. For SAS component *inhibition*, previous findings reported small-to-large effects for impairments in *interference control* [25, 27, 35], and medium-sized effects for impairments in *impulsivity* [15, 32]. Finally, previous findings on SAS component *attentional flexibility* showed similar performance in children with ADHD relative to typically developing children (TD) [36, 37], and mixed results based on TAP tasks [27, 38].

Neurocognitive impairments in adult ADHD partly overlap with those in children, although the body of literature on neurocognitive impairments in adults with ADHD is considerably smaller. Similar to findings in childhood ADHD are impairments in *sustained attention* [39], increases in RTV across basic attention- and SAS tasks [14, 30], and impairments in *focused attention* when task conditions required a high level of perceptual sensitivity [22, 40, 41]. Evidence for impaired *alertness* in adult ADHD is inconsistent [28, 41]. Regarding the SAS component *inhibition*, adults like children with ADHD showed increased rates of *impulsivity* [28, 39], and slower [41] and more variable performance on *interference control* tasks [14, 41, 42], but see [43]. Finally, additional impairments for ADHD in adulthood have been reported for *divided attention* [13, 41], and *attentional flexibility* [41].

Taken together, in ADHD across the lifespan impairments in *sustained attention*, RTV, *focused attention, impulsivity*, and *interference control* have been observed most consistently (*endophenotype criterion* #1). Among these measures, RTV and *interference control* fulfill most endophenotype criteria in childhood ADHD [9], but endophenotype criteria have not been fully investigated across the lifespan. Significant heritability estimates of of underlying variance in neurocognitive performance (*endophenotype criterion #2*) have been reported for RTV in older adults [44], and for measures of *interference control* in young [45] and older adults [46]. Furthermore, affected and non-affected parents of children with ADHD showed increased RTV relative to healthy control parents [47, 48] (*endophenotype criterion #5*). Likewise, impairments in *interference control* were demonstrated in parents of children with ADHD, albeit without controlling for the effect of parental ADHD status [49]. Finally, previous studies reported evidence for impairments in *impulsivity* [50] and *interference control* [51] in participants with ADHD and remitted ADHD irrespective of diagnostic status (*endophenotype criterion #3*). In contrast, higher RTV during basic attention tasks was observed only in participants with current ADHD relative to

control- and participants with remitted ADHD [50, 51], suggesting RTV measures of basic attention tasks are not state-independent (for evidence for the opposite pattern see [52]).

To summarize, more research is clearly needed to evaluate whether measures associated with ADHD across the lifespan meet endophenotype criteria. Since a multifactorial polygenic threshold model of heredity underlies ADHD, measures etiologically or functionally closely related to the ADHD phenotype should explain more phenotypic variance relative to more distal measures [10]. Endophenotype criteria for ADHD across the lifespan are hence tested most efficiently when neuropsychological impairments in genetically-informed case–control samples inform future molecular genetic studies on ADHD. Furthermore, even though a family based design does not allow differentiating genetic from environmental effects, additional insights into the validity and sensitivity of ADHD endophenotypes across the lifespan can be obtained by comparing estimates of intergenerational transmission of endophenotype measures to those of the behavioural phenotype of ADHD. Estimating intergenerational transmission effects additionally allows to explore parent-of-origin effects, which play an important role in understanding the genetic architecture of complex traits [53].

Thus, the aims of the present study were: (1) to test for familial effects of ADHD on basic attention and SAS in affected and non-affected adult family members of childhood ADHD patients and TD controls (*endophenotype criterion #5*); (2) to test for the state-independency of basic attention and SAS impairments associated with ADHD across the lifespan (*endophenotype criterion #3*); (3) to explore the strength of intergenerational transmission effects of neurocognitive measures relative to behavioural phenotypic measures (i.e., ADHD symptom scores). We expected to find familial effects for the most frequently established and strongest neurocognitive impairments observed in adult ADHD. We hypothesized that, independent of current or past ADHD, parents of children with ADHD would show increased RTV across several attention and SAS tasks [14, 30] relative to parents of typically developing children (TD). Second, we hypothesized those impairments would exhibit state-independency. Finally, we expected to find stronger intergenerational transmission estimates for attention/SAS components associated with ADHD across the lifespan compared to those of the behavioural ADHD symptoms inattention and hyperactivity/impulsivity.

Methods

Participants

In total, 137 children (mean age: 9.1 years, SD: 2.03) and 199 parents (mean age: 39.5 years, SD: 5.62) participated in the study. The sample consisted of mothers and/or fathers with a child diagnosed with ADHD ($N = 98$ families), or a typically developing child (TD) ($N = 39$ families). Children across groups were matched for age. Sample characteristics are presented in Table 1.

All families were recruited from the University Hospital Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy in Frankfurt and Homburg, Germany. Only families with complete data were included, i.e., families who included one child and at least one parent. These families were assigned to either the ADHD or healthy control group based on the diagnostic status of the child. ADHD diagnosis of the child was obtained with the parent version of the structured Diagnostic Interview for Children and Adolescents (Kinder-DIPS) [54]. Children with ADHD received additional standard clinical assessment to exclude co-morbid Autism Spectrum Disorder (ASD). Exclusion criteria for all children were obsessive–compulsive disorder, depressive disorder, epilepsy, fragile X syndrome, dyslexia, dyscalculia, visual or hearing impairments, premature birth and birth weight less than 2000 g. TD children were excluded when they scored above clinical cut-off on any of the Child Behavior Checklist's (CBCL) narrow-band scales [55]. All participants who used stimulant medication were asked to withdraw medication either 24 h (immediate release) or 48 h (extended release).

Measures

Current ADHD—children

ADHD diagnosis in all children was obtained using a semi-structured interview (Kinder-DIPS) [54]. The Kinder-DIPS shows good interrater reliability [56].

Childhood- and current ADHD—parents

For all parents, ADHD symptoms during childhood were obtained using the short version of the Wender Utah Rating Scale (WURS-K) [57]. The WURS-K is a retrospective self-rating questionnaire for adults. Parents were considered to have fulfilled criteria for ADHD in childhood when the cut-off score was equal to, or exceeded 30. Both sensitivity and specificity for this cut-off score are excellent for females (i.e., respectively, 93% and 92%) [58], and, respectively, good (i.e., 85%) and moderate (i.e., 76%) for males [59]. Current ADHD in parents was calculated using information from the ADHD-self-report (SR; see below). ADHD symptoms were counted within each symptom domain (i.e., ADHD-SR items rated 2 or 3), parents were rated as having current ADHD if they met DSM-IV criteria and in addition scored above the cut-off on the WURS-K.

Table 1 Mean age, mean IQ, gender, ADHD symptom severity and ADHD diagnostic statuses of parents of a typically developing child (TD), parents of a child with ADHD (a) and their offspring (b)

(a) Sample characteristics parents	Parents of a TD child ($N=60$)	Parents of a child with ADHD ($N=139$)	Test statistic, p value	Group differences parents
Age, *M* (*SD*)	41.2 (*4.5*)	38.8 (*5.9*)	$t(145.99)=3.16$, $p=0.002$	ADHD < TD
IQ, *M* (*SD*)	111.6 (*15.8*)	102.1 (*14.7*)	$t(197)=4.12$, $p=0.006$	ADHD < TD
Sex (females), *N* (%)	37 (*61.7%*)	97 (*69.8%*)	$\chi(1)^2=0.91$, $p=0.339$	–
Inattentive symptoms, *M* (*SD*)	3.30 (*2.5*)	9.24 (*7.0*)	$t(192.93)=-9.82$, $p<0.001$	ADHD > TD
Hyperactive-impulsive symptoms, *M* (*SD*)	3.12 (*3.0*)	8.2 (*7.4*)	$t(196.03)=-6.88$, $p<0.001$	ADHD > TD
Diagnostic status, *N* (%)	Never ADHD: 54 (*90%*)	Never ADHD: 79 (*56.8%*)		
	Only childhood ADHD: 5 (*8.3%*)	Only childhood ADHD: 26 (*18.7%*)	$\chi(2)^2=22.17$, $p<0.001$	ADHD ≠ TD
	Current ADHD: 1 (*1.7%*)	Current ADHD: 34 (*24.5%*)		
(b) Sample characteristics children	Typically developing children (TD) ($N=39$)	Children with ADHD ($N=98$)	Test statistic, p value	Group differences children
Age, *M* (*SD*)	9.5 (*2.4*)	9.0 (*1.9*)	$t(56.95)=1.15$, $p=0.255$	–
IQ, *M* (*SD*)	110.3 (*12.6*)	102.7 (*12.0*)	$t(135)=3.29$, $p=0.001$	ADHD < TD
Sex (females), *N* (%)	16 (*41.0%*)	15 (*15.3%*)	$\chi(1)^2=9.12$, $p=0.003$	ADHD < TD
Inattentive symptoms, *M* (*SD*)	4.38 (*3.6*)	20.07 (*4.0*)	$t(135)=-21.21$, $p<0.001$	ADHD > TD
Hyperactive-impulsive symptoms, *M* (*SD*)	2.26 (*2.5*)	13.56 (*4.5*)	$t(122.29)=-18.67$, $p<0.001$	ADHD > TD

TD typically developing, *ADHD* attention deficit hyperactivity/disorder, *N* sample size, *M* mean, *SD* standard deviation, *IQ* intelligence quotient

Severity score ADHD: children

Severity of ADHD symptoms for all children was obtained using the Diagnostic Checklist for Attention Deficit Hyperactivity Disorder (DCL-ADHD) or the ADHD rating scale for parents (FBB-ADHD). The DCL-ADHD and the FBB-ADHD are disorder-specific questionnaires from the DISYPS-KJ based on DSM-IV and ICD-10 criteria with each item measuring ADHD symptom severity on a 3-point scale [60]. The Inattention- and Hyperactivity/Impulsivity scales that have been used in the present study show good factorial validity as well as internal consistency (Cronbach's α, respectively, 0.88 and 0.84) [61]. The DCL-ADHD is the expert version of the FBB-ADHD and was rated by a trained clinician based on information from the Kinder-DIPS. For 18 children in the control group (Frankfurt sample) DCL-ADHD data were missing; for these children FBB-ADHD data were used to obtain the same measures of ADHD symptom severity. In the remaining sample, ADHD symptom severity was obtained by DCL-ADHD.

Severity score ADHD: parents

Severity of ADHD symptoms in adulthood was measured with the ADHD-SR. The ADHD-SR is a 22-item long self-report questionnaire for adults, based on ICD-10 and DSM-IV criteria. Items are rated on a 4-point Likert scale, from 0 ('non-existent') to 3 ('severe'). The ADHD-SR shows that high test–retest reliability and internal consistency of the *Attention* and *Hyperactivity and Impulsivity* scales are good (Cronbach's α, respectively, 0.89 and 0.82) [57]. Sum-scores of these two scales were used as ADHD symptom severity measures.

IQ assessments

Parent IQ was assessed with the German Culture Fair Intelligence Test (CFT-20R [62]). Child IQ was measured using the CFT-20R [62], the Wechsler Intelligence Test for Children—IV (WISC-IV [63]), the Kaufman Assessment Battery for Children (K-ABC [64]), or Coloured and Standard Raven's Progressive Matrices (RPM [65]).

Neurocognitive attention: test battery for attention performance (TAP)

All participants completed six subtests of the computerized test battery TAP, version 2.1 [66].

Intensity of attention: alertness and sustained attention

The task used to measure *alertness* consists of two parts. In the 'tonic alertness' condition, the participant is required

to respond to a visual stimulus ('X' presented on the screen) by pressing a button. In the 'phasic alertness' condition, an acoustic stimulus (warning tone) appears prior to the presentation of the visual stimulus. The time span between the warning tone and the appearance of the stimulus was random (between 300 and 700 ms). The conditions are presented in an ABBA design (A = tonic alertness, B = phasic alertness). Measures of *tonic alertness* comprised the mean reaction time (MRT) and variability in reaction time (RTV) during the tonic alertness condition, measures of *phasic alertness* comprised MRT and RTV during the phasic- condition.

Sustained attention. Due to technical difficulties, we were not able to obtain sufficient measures of sustained attention for meaningful statistical analysis.

Selectivity of attention: focused- and divided attention

The *go/no-go task* requires the participant to select two patterns out of five by pressing the response button. During the task, one pattern at a time is presented in the center of the screen and the participant has to decide whether it refers to the two target stimuli. MRT, RTV, and omission errors were used as measures of *focused attention*.

In the *divided attention task* a 4 × 4 matrix, in which crosses continuously are changing their position, is displayed on the screen. The participant has to press a button whenever the crosses form a square. Simultaneously, an alternating sequence of low and high sounds is presented to the participant. In the case of inconsistency in this order, the participant has to press the button. Omission- and commission errors, MRT and RTV measures were used as measures of *divided attention*. Due to technical reasons, MRT and RTV were only available for the Homburg sample (N = 152).

Supervisory attentional system (SAS)

Commission errors of the *go/no-go task* (described above) were used to measure *impulsivity*.

In the *incompatibility* task, the participant is instructed to fixate on a central point on the screen. During the task, arrows pointing either to the left or right appear on either the left or right side of the screen. The participant is asked to only react to the direction the arrow is pointing. During compatible trials, pointing direction and location of appearance are the same; during incompatible trials these parameters differ. MRT, RTV, and false reactions during incompatible trials were used as measures of *interference control*.

In the *flexibility task*, two buttons are allocated in the front of the participant, corresponding to the, respectively, left and right sides of the computer screen. During the task, stimuli from two competing shape categories (angled and round) are presented simultaneously. The participant has to respond alternately to the location of the, respectively, angled or the round stimuli on the screen. MRT, RTV and false reactions were used as measures of *attentional flexibility*.

Procedure

Participants completed the TAP assessments in a quiet testing room, with tasks always administered in the same order (alertness, flexibility, divided attention, focused attention, and incompatibility). Each participant received a verbal instruction of each task as well as a short introduction of the test procedure on the monitor. Each session lasted 60–70 min. The study was approved by the local ethics committees and its later amendments or comparable ethical standards. Informed consent was obtained from all children and parents prior to inclusion of the study.

Statistics

Familiality and state-independency of basic attention functions and SAS

All statistical analyses were conducted using R statistics software 3.4.3 [67]. Familiality of basic attention and SAS impairments was first tested using four separate MANCOVA models for the ratio scaled measures MRT and RTV of the TAP subtests *intensity of attention* and *SAS*. The MANCOVA model included family status as fixed factor to differentiate between parent of a child with ADHD and parent of a TD child, with being a parent of a TD child as comparison level. To test for state-independency, ADHD diagnostic status was included in the model as ordered factor, and linear contrasts were specified to estimate the performance of adults who never met criteria for ADHD (0), who met criteria only in childhood (1), or who currently met criteria (2). Post-hoc tests for significant linear trends were carried out to test differences between current ADHD relative to only childhood- and never ADHD (2 vs. 1 and 0), and current ADHD and only childhood ADHD relative to never ADHD (2 and 1 vs. 0). In addition, the influence of age and sex on neurocognitive functioning was controlled for by including age and sex as covariates of no interest in the model. Following a significant overall family or diagnostic status effect in the MANCOVA model, ANCOVA models were specified including the same predictors to test for the family or diagnostic status effect on each MRT and RTV measure separately. In the case of selectivity of attention, data were not included in the MANCOVA, but ANCOVA models were directly specified, as MRT and RTV were only available for the Homburg sub-sample. Error rates of all TAP measures were binary coded (no mistakes vs. mistakes) and fitted with logistic regression models. For all models, Type III sums of squares were calculated to control for the influence of diagnostic status on familial effects and vice versa. False Discovery Rate (FDR)-adjusted p values corresponding to an overall significance level of 0.005 [68] were calculated to

correct for multiple testing, based on the number of MANOVAs and ANCOVAs that tested separate hypotheses.

In these models, IQ was not included as a covariate, as associations between ADHD and IQ seem at least partly independent from associations between ADHD and neurocognitive measures [69, 70]. Sensitivity analyses were done by re-running (M)ANCOVA models that included significant predictors with IQ as additional covariate.

The small sample of fathers ($N=65$) did not allow testing whether the familial effects with ADHD for neurocognitive functioning and state-dependency differed between fathers and mothers. To explore differential effects of ADHD family status and diagnostic status by sex, analysis was, therefore, repeated separately for fathers and mothers. Effect sizes (partial eta squared) were used to compare the female only with the male only sample.

Intergenerational transmission of neurocognitive performance and behavioral ADHD symptoms

To compare intergenerational transmission of basic attention and SAS measures to those of dimensional behavioral ADHD symptoms, separate exploratory regression models were specified for each TAP measure and ADHD symptom dimension. For each neurocognitive model, standardized regression coefficients (beta) with 95% confidence intervals were estimated by linear regression models with TAP performance of, respectively, mothers or fathers as dependent variable, child TAP performance as predictor, and parental age and location as covariates. Sensitivity analysis to obtain an estimate of the influence of IQ on neurocognitive performance was obtained by re-running models with significant ($p<0.05$) regression slopes with children's TAP performance standardized for IQ, and parental IQ. For each ADHD symptom dimension model, regression coefficients (beta) with 95% confidence intervals were estimated by linear regression models, with either parental inattention or hyperactivity/impulsivity score as dependent variable, and child inattention and hyperactivity/impulsivity score as predictor. Each model contained parental age and location as covariates, and the parental inattention or hyperactivity/impulsivity score to control for correlations between inattention- and hyperactivity/impulsivity symptoms in parents. Sensitivity analysis to obtain an estimate of the influence of IQ on ADHD symptoms was obtained by re-running models with significant ($p<0.05$) regression slopes with child inattention- and hyperactivity/impulsivity scores standardized for IQ, and parental IQ. All TAP measures and ADHD symptom variables were z-standardized to enable comparison between intergenerational transmission estimates of neurocognitive measures and those of behavioral ADHD symptoms.

Results

Sample description

In Table 1, descriptive data of the parents and the children are shown. Parent groups did not differ by sex, but parents of a child with ADHD were younger than parents of a TD child, had lower average IQ-, and higher inattentive- and hyperactive/impulsive symptom scores. The frequency of ADHD diagnostic status was not distributed equally across parents of a child with ADHD and parents of a TD child. Children with ADHD compared to TD showed a higher proportion of male participants, lower mean IQ, and higher inattentive- and hyperactive/impulsive symptom scores.

Familiality of basic attention and SAS

Basic attention: attention intensity and selectivity

Parents of children with ADHD and parents of TD children did not differ in MRT and RTV for measures of *attention intensity* (Table 2a) and *attention selectivity* (Table 2b). In addition, parental status was not significantly associated with a higher risk of making one or more false reactions on measures of *focused-* and *divided attention* (see Table 2c).

SAS: interference control and flexibility

Parents of children with ADHD showed higher MRT relative to parents of TD children across measures of SAS components *interference control* and *flexibility* (Table 2d; family effect with IQ: $F(2,191)=3.66$, $p=0.027$: Pillai's Trace $=0.037$, $\eta_p^2=0.037$), and for each SAS components separately (Table 2d; *interference control* family effect with IQ: $F(1,192)=6.36$, $p=0.013$, $\eta_p^2=0.032$; *flexibility* family effect including IQ: $F(1,192)=3.957$, $p=0.048$, $\eta_p^2=0.0158$).

Parents of children with ADHD in addition showed higher RTV than parents of TD children across measures of SAS components *interference control* and *flexibility* (Table 2d; family effect with IQ: $F(2,191)=3.93$, $p=0.021$: Pillai's Trace $=0.040$, $\eta_p^2=0.040$), and for each SAS component separately (Table 2d; *interference control* family effect with IQ: $F(1,192)=5.14$, $p=0.024$, $\eta_p^2=0.026$, *flexibility* family effect with IQ: $F(1,192)=4.7085$, $p=0.031$, $\eta_p^2=0.020$). Parental status was not significantly associated with a higher risk of making one or more false reactions on measures of SAS components *impulsivity, interference control* and *flexibility* (Table 2e).

Post-hoc analysis on sex specific multivariate effects of SAS measures showed a similar pattern of results in mothers

Table 2 Familial effects of ADHD on mean reaction time (MRT), reaction time variability (RTV) and false reactions as measures of basic attention and SAS

(a) Attention intensity—estimated marginal means

		Family status						
MANOVA **Attention component** (*TAP subtask*)	Dependent variable	Parents of a TD child ($N = 60$)	Parents of a child with ADHD ($N = 139$)	Pillai-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
attention intensity—overall performance (*tonic- and phasic alertness*)	MRT, *M* (*SE*)	233.75 (*6.47*)	243.84 (*4.49*)	0.012 (*2, 192*)	0.305	0.495	0.0123	–
	RTV, *M* (*SE*)	35.11 (*2.8*)	40.64 (*1.93*)	0.023 (*2, 192*)	0.112	0.348	0.0226	–

(b) Attention selectivity—estimated marginal means

		Family status						
ANOVA **Attention component** (*TAP subtask*)	Dependent variable	Parents of a TD child ($N = 60$)	Parents of a child with ADHD ($N = 139$)	*F*-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
focused attention (*Go/NoGo*)	MRT, *M* (*SE*)	523.42 (*11.82*)	542.78 (*8.21*)	2.57 (*1, 193*)	0.111	0.348	0.0131	–
	RTV, *M* (*SE*)	71.64 (*5.24*)	83.57 (*3.64*)	4.97 (*1, 193*)	0.027	0.151	0.0251	–
divided attention[a] (*divided attention*)	MRT, *M* (*SE*)	668.02 (*16.15*)	684.88 (*8.66*)	1.06 (*1, 147*)	0.306	0.495	0.0071	–
	RTV, *M* (*SE*)	193.62 (*11.28*)	201.80 (*6.05*)	0.51 (*1, 147*)	0.476	0.597	0.0035	–

(c) Attention selectivity—log odds

		Family status				
Logistic regression **Attention component** (*TAP subtask*)	Dependent variable	Parents of a child with ADHD ($N = 139$) vs. Parents of a TD child ($N = 60$)	*z*-value	*p*-value	FDR-corrected *p*-value	Group differences
focused attention (*Go/NoGo*)	Omission errors ≥ 1 vs. no omission errors log odds, (*SE*)	1.35 (*0.66*)	2.032	0.042	0.197	–
divided attention[a] (*divided attention*)	Omission errors ≥ 1 vs. no omission errors log odds, (*SE*)	0.66 (*0.35*)	1.885	0.060	0.238	–
	Commission errors ≥ 1 vs. no commission errors log odds, (*SE*)	0.33 (*0.34*)	0.963	0.336	0.495	–

Table 2 (continued)

(d) SAS—estimated marginal means

		Family status						
MANOVA **SAS component** (*TAP subtask*)	Dependent variable	Parents of a TD child ($N = 60$)	Parents of a child with ADHD ($N = 139$)	Pillai-value* (*df*)/*F*-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
SAS—overall performance (*incompatibility- and flexibility*)	MRT, *M* (*SE*)	600.65 (*26.80*)	700.22 (*18.61*)	0.070* (*2, 192*)	0.001	0.013	0.0700	ADHD parents > TD parents
	RTV, *M* (*SE*)	121.81 (*14.45*)	177.80 (*10.03*)	0.076* (*2, 192*)	0.001	0.013	0.0757	ADHD parents > TD parents
ANOVA **interference control** (*incompatibility*)	MRT, *M* (*SE*)	452.26 (*15.64*)	505.59 (*10.86*)	11.14 (*1, 193*)	0.001	–	0.0545	ADHD parents > TD parents
	RTV, *M* (*SE*)	84.33 (*8.49*)	111.75 (*5.89*)	10.00 (*1, 193*)	0.002	–	0.0492	ADHD parents > TD parents
ANOVA **flexibility** (*flexibility*)	MRT, *M* (*SE*)	749.04 (*44.27*)	894.85 (*30.74*)	10.39 (*1, 193*)	0.001	–	0.0511	ADHD parents > TD parents
	RTV, *M* (*SE*)	159.30 (*24.99*)	243.84 (*17.35*)	10.96 (*1, 193*)	0.0001	–	0.0531	ADHD parents > TD parents

(e) SAS—log odds

		Family status			
Logistic regression **SAS component** (*TAP subtask*)	Dependent variable	Parents of a child with ADHD ($N = 139$) vs. Parents of a TD child ($N = 60$)	*z*-value	*p*-value	FDR-corrected *p*-value	Group differences
impulsivity (*Go/NoGo*)	Commission errors ≥ 1 vs. no commission errors log odds, (*SE*)	0.35 (*0.66*)	0.528	0.598	0.668	–
interference control (*incompatibility*)	Incompatible false reactions ≥ 1 vs. no false reactions log odds, (*SE*)	0.38 (*0.37*)	1.050	0.294	0.495	–
flexibility (*flexibility*)	False reactions ≥ 1 vs. no false reactions log odds, (*SE*)	0.53 (*0.36*)	1.467	0.142	0.399	–

SAS supervisory attention system, *TAP* test of attentional performance, *TD* typically developing, *ADHD* attention deficit hyperactivity, *N* sample size, *FDR* false discovery rate, η_p^2 partial eta squared, *MRT* mean reaction time, *SE* standard error, *RTV* reaction time variability

[a]For divided attention MRT and RTV, measures were only available for the Homburg sample: parents of a TD child ($N = 38$); parents of a child with ADHD ($N = 114$)

and fathers (*mothers*: table S1a; *fathers*: table S1b). Post-hoc univariate analyses of differential family status effects for mothers and fathers showed medium-sized effects for MRT as measure of *interference control* in mothers, but not in fathers with a child with ADHD relative to parents with a TD child (MRT $_{\text{mothers}}$: $\eta_p^2 = 0.0973$; MRT $_{\text{fathers}}$ $\eta_p^2 = 0.0071$). In addition, in the fathers sample medium-sized effects for MRT and RTV as measures of *flexibility* were found (MRT: $\eta_p^2 = 0.0811$, RTV: $\eta_p^2 = 0.0900$), whereas in the sample of mothers only small effects for both measures were observed (MRT: $\eta_p^2 = 0.0352$, RTV: $\eta_p^2 = 0.0324$).

State-independency for measures of basic attention and SAS

Basic attention: attention intensity and attention selectivity

Adjusted for familial effects, no effect of parental ADHD diagnostic status was found on MRT across measures of *attention intensity* (Table 3a), and for *attention selectivity* components *focused*- and *divided attention* (Table 3b). Similarly, no effect of parental ADHD diagnostic status was found on RTV across measures of *attention intensity* (Table 3a), and for *attention selectivity* components *focused*- and *divided attention* (Table 3b), and errors in the *focused*- and *divided attention* tasks (see Table 3c).

SAS: impulsivity, interference control and flexibility

Adjusted for familial effects, no effects of parental ADHD status were found on MRT or RTV across measures of SAS (Table 3d), and errors related to *impulsivity, interference control* - and *flexibility* (see Table 3e).

Intergenerational transmission of basic attention and SAS

Intergenerational transmission estimates of basic attention and SAS are reported in Table 4.

Basic attention: attention intensity and selectivity

For the attention intensity component *tonic alertness*, significant intergenerational transmission estimates were found for paternal MRT (Table 4a; with IQ: $\beta = 0.32$, 95% CI: 0.05–0.60, $t(60) = 2.369$, $p = 0.021$), and for paternal and maternal RTV (Table 4a; with IQ *fathers:* $\beta = 0.29$, 95% CI:0.03–0.56, $t(60) = 2.207$, $p = 0.031$; with IQ *mothers:* $\beta = 0.14$, 95% CI: 0.00–0.10, $t(129) = 1.691$, $p = 0.093$). For the attention intensity component, *phasic alertness*, significant intergenerational transmission estimates were found for paternal MRT and RTV (Table 4a; with IQ MRT: $\beta = 0.18$, 95% CI: − 0.02–0.39, $t(60) = 1.783$, $p = 0.080$; with IQ RTV: $\beta = 0.45$, 95% CI: 0.20–0.71, $t(60) = 3.55$, $p = 0.001$), but not for maternal MRT and RTV.

For the attention selectivity component *focused attention* intergenerational transmission estimates were not significant for maternal or paternal MRT. Significant intergenerational transmission estimates were found for maternal RTV (Table 4b; with IQ: $\beta = 0.19$, 95% CI: 0.20–0.36, $t(129) = 2.22$, $p = 0.028$), but not for paternal RTV and risk of making one or more omission errors. For the attention selectivity component *divided attention*, no significant intergenerational transmission estimates were found for measures of MRT, RTV (Table 4b) and number of omission or commission errors (Table 4c).

To summarize, within the area of *attention intensity*, MRT and RTV as measures of *tonic*-and *phasic alertness* were familial in fathers. In mothers, only RTV as measure of *tonic alertness* was familial. Effect sizes were comparable when controlling for IQ. Within the area of attention selectivity, only RTV as a measure of *focused attention* was familial in mothers, with comparable effect sizes when controlling for IQ.

SAS

For SAS component *interference control*, no intergenerational transmission effects were found for measures of maternal or paternal MRT, but effects sfor maternal and paternal RTV were significant (Table 4d; with IQ *mothers:* $\beta = 0.25$, 95% CI: 0.03–0.18, $t(129) = 2.825$, $p = 0.005$; with IQ *fathers:* $\beta = 0.28$, 95% CI: 0.029–0.54, $t(60) = 2.228$, $p = 0.030$). No intergenerational transmission effects were found for commission errors as a measure of *impulsivity*, or false reactions as a measure of *interference control* (Table 4e).

For the SAS component *flexibility* intergenerational transmission effects were found for maternal and paternal measures of MRT (Table 4d; with IQ *mothers:* $\beta = 0.17$, 95% CI: 0.01–0.33, t (129) = 2.138, $p = 0.034$; with IQ *fathers:* $\beta = 0.16$, 95% CI: −0.05–0.37, $t(60) = 1.548$, $p = 0.127$). No intergenerational transmission effects were found for measures of maternal or parental RTV, or number of false reactions (Table 4e).

To summarize, intergenerational transmission effects were found for maternal and paternal RTV as a measure of *interference control*, and maternal and paternal MRT as a measure of *attentional flexibility*, with comparable effect sizes when controlling for IQ.

Intergenerational transmission of ADHD symptom severity ratings

Intergenerational transmission estimates of ADHD dimensional symptom ratings are reported in Table 5.

Table 3 State-independency of mean reaction time (MRT), reaction time variability (RTV) and false reactions as measures of basic attention and SAS

(a) Attention intensity—estimated marginal means

		ADHD diagnostic status							
MANOVA **Attention component** (*TAP subtask*)	Dependent variable	Never ADHD ($N=133$)	Only childhood ADHD ($N=31$)	Current ADHD ($N=35$)	Pillai-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
attention intensity—overall performance (*tonic- and phasic alertness*)	MRT, *M* (*SE*)	233.90 (*3.80*)	238.80 (*4.48*)	243.69 (*7.52*)	0.013 (*2, 192*)	0.290	0.495	0.0130	–
	RTV, *M* (*SE*)	33.61 (*1.63*)	37.88 (*1.92*)	42.15 (*3.23*)	0.038 (*2, 192*)	0.025	0.151	0.0376	–

(b) Attention selectivity—estimated marginal means

		ADHD diagnostic status							
ANOVA **Attention component** (*TAP subtask*)	Dependent variable	Never ADHD ($N=133$)	Only childhood ADHD ($N=31$)	Current ADHD ($N=35$)	*F*-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
focused attention (*Go/NoGo*)	MRT, *M* (*SE*)	523.42 (*6.95*)	533.10 (*8.19*)	542.77 (*13.75*)	1.81 (*1, 193*)	0.180	0.430	0.0093	–
	RTV, *M* (*SE*)	76.74 (*3.08*)	77.61 (*3.63*)	78.47 (*6.09*)	0.07 (*1, 193*)	0.786	0.786	0.0038	–
divided attention[a] (*divided attention*)	MRT, *M* (*SE*)	651.37 (*8.39*)	676.45 (*10.03*)	701.53 (*17.13*)	7.73 (*1, 147*)	0.006	0.057	0.0500	–
	RTV, *M* (*SE*)	191.29 (*5.86*)	197.71 (*7.01*)	204.14 (*11.97*)	1.04 (*1, 147*)	0.309	0.495	0.0070	–

(c) Attention selectivity—log odds

		ADHD diagnostic status				
Logistic regression **Attention component** (*TAP subtask*)	Dependent variable	Never ADHD (0) ($N = 133$) vs. Only childhood ADHD (1) ($N = 31$) vs. Current ADHD (2) ($N = 35$)	*z*-value	*p*-value	FDR-corrected *p*-value	Group differences
focused attention (*Go/NoGo*)	Omission errors ≥ 1 vs. no omission errors log odds, (*SE*)	0.21 (*0.36*)	0.565	0.572	0.667	–
divided attention[a] (*divided attention*)	Omission errors ≥ 1 vs. no omission errors log odds, (*SE*)	0.22 (*0.32*)	0.690	0.491	0.597	–
	Commission errors ≥ 1 vs. no commission errors log odds, (*SE*)	− 0.25 (*0.28*)	0.879	0.379	0.531	–

Table 3 (continued)

(d) SAS—estimated marginal means

		ADHD diagnostic status							
MANOVA **SAS component** (*TAP subtask*)	Dependent variable	Never ADHD ($N = 133$)	Only childhood ADHD ($N = 31$)	Current ADHD ($N = 35$)	Pillai-value (*df*)*/*F*-value (*df*)	*p*-value	FDR-corrected *p*-value	η_p^2	Group differences
SAS—overall performance (*incompatibility- and flexibility*)	MRT, *M* (*SE*)	638.74 (*15.75*)	650.4363 (*18.56*)	662.1280 (*31.18*)	0.003 (*2, 192*)*	0.765	0.786	0.0028	–
	RTV, *M* (*SE*)	146.89 (*8.489*)	149.80 (*10.01*)	152.72 (*16.81*)	0.012 (*2, 192*)*	0.322	0.495	0.0117	---

(e) SAS—log odds

		ADHD diagnostic status				
Logistic regression **SAS component** (*TAP subtask*)	Dependent variable	Never ADHD (0) ($N = 133$) vs. Only childhood ADHD (1) ($N = 31$) vs. Current ADHD (2) ($N = 35$)	*z*-value	*p*-value	FDR-corrected *p*-value	Group differences
impulsivity (*GolNoGo*)	Omission errors ≥ 1 vs. no omission errors log odds, (*SE*)	0.14 (*0.47*)	0.307	0.759	0.786	–
interference control (*incompatibility*)	Incompatible false reactions ≥ 1 vs. no false reactions log odds, (*SE*)	-0.24 (*0.31*)	-0.778	0.437	0.583	–
flexibility (*flexibility*)	False reactions ≥ 1 vs. no false reactions log odds, (*SE*)	0.39 (*0.29*)	1.328	0.184	0.430	–

SAS supervisory attention system, *TAP* test of attentional performance, *ADHD* attention deficit hyperactivity, *N* sample size, *FDR* false discovery rate, η_p^2 partial eta squared, *MRT* mean reaction time, *SE* standard error, RTV reaction time variability

[a]For divided attention MRT and RTV, measures were only available for the Homburg sample: never ADHD ($N = 100$), only childhood ADHD ($N = 19$), current ADHD ($N = 33$)

Intergenerational transmission effects were found in mothers and fathers for inattention symptom severity ratings (with IQ *mothers:* $\beta = 0.28$, 95% CI: 0.12–0.43, $t(127) = 3.495$, $p < 0.001$; with IQ *fathers:* $\beta = 0.46$, 95% CI: 0.14–79, $t(58) = 2.856$, $p = 0.006$), but transmission effects for hyperactivity-impulsivity symptom severity ratings were only found in mothers (with IQ: $\beta = 0.28$, 95% CI: 0.12–0.43, $t(127) = 3.504$, $p < 0.001$). Higher inattention symptom severity in children additionally predicted lower hyperactive-impulsive symptom severity in mothers (with IQ: $\beta = -0.17$, 95% CI: − 0.33–0.09, $t(127) = -2.098$, $p = 0.038$), but did not predict hyperactive-impulsive symptom severity in fathers. Similarly, higher hyperactive/impulsive symptom severity in children predicted lower inattention symptom severity in mothers (with IQ: $\beta = -0.17$, 95% CI: − 0.32– − 0.01, $t(127) = -2.096$, $p = 0.038$), but did not predict inattention symptom severity in fathers.

Intergenerational transmission of basic attention and SAS compared to those of ADHD symptom severity ratings

In mothers, intergenerational transmission estimates of ADHD inattention and hyperactive-impulsive symptoms were descriptively higher than those of basic attention and SAS measures, but 95% confidence intervals overlapped (Tables 4a–c, 5). In fathers, intergenerational transmission estimates of *tonic alertness* MRT and *phasic alertness* RTV were descriptively higher than those of ADHD inattention symptom severity ratings, but 95% confidence intervals overlapped (Tables 4a–c, 5). Intergenerational transmission estimates of hyperactivity/impulsivity symptom ratings were not significant in fathers (Table 5).

Discussion

ADHD across the lifespan is characterized by pervasive impairments in behavior ratings of attention function [6] as well as neurocognitive measures of attention function and EF [13, 15, 71]. The present study evaluated whether neurocognitive measures of basic and executive attention functions (*SAS*) [18] are eligible endophenotype candidates for ADHD across the lifespan. Endophenotype criteria [11] were tested in a sample of affected and unaffected parents of children with ADHD- and typically developing children. First, we tested for familial effects of ADHD on basic attention and *SAS*, independent of current- or ADHD diagnosis in childhood (*endophenotype criterion #5*). Second, we tested for state-independency effects of ADHD diagnostic status on basic attention and *SAS* (*endophenotype criterion #3*). Finally, the added value of neurocognitive measures in genetically informed designs was evaluated by comparing intergenerational transmission estimates of neurocognitive measures of basic attention- and *SAS* functions to those of ADHD symptom severity ratings of inattention- and hyperactivity/impulsivity. In line with our predictions, our results demonstrated familial effects of ADHD on measures of response variability (RTV), and in addition on measures of response speed (MRT), independent of current- or childhood ADHD (*endophenotype criterion #5*). Familial effects of ADHD on MRT and RTV were found on *SAS*- but not on *basic attention* functions. In addition, adjusted for familial effects no effects of current- or childhood ADHD were found, and the reported familial effects were hence independent of ADHD diagnostic status (*endophenotype criterion #3*). Explorative intergenerational transmission analysis indicated several measures associated with ADHD across the lifespan (i.e., RTV, *focused attention, interference control*), and adult ADHD (i.e. *attentional flexibility*) were familial. However, intergenerational transmission estimates of inattention symptom scores in mothers and fathers were overall descriptively higher (with overlapping confidence intervals) than those of neurocognitive measures associated with ADHD across the lifespan, and adult ADHD.

Endophenotype effects were most evident for RTV as a measure of *interference control* and MRT as a measure of *attentional flexibility*; i.e. results demonstrated familial effects of ADHD in adulthood (*endophenotype criterion #5*), complemented by significant intergenerational transmission estimates. Familial effects of ADHD on MRT/RTV in adulthood, complemented by significant intergenerational transmission effects have been reported previously by studies with comparable statistical designs [47, 48]. Multivariate genetic model fitting results, furthermore, suggested a common familial pathway to MRT and RTV impairments in children [72], adolescents and young adults with ADHD [73]. Here, we replicated the familial effects of ADHD on MRT and RTV in an adult sample. Longer- and more variable reaction times during neurocognitive tasks may hence reflect an etiological pathway underlying the ADHD phenotype that not only extends from childhood [72], to adolescence and young adulthood [73] but also to (middle) adulthood.

Endophenotype effects for neurocognitive functions associated with ADHD across the lifespan were exclusively found for RTV measures of executive attention function (*SAS*) *interference control*. Correspondingly, strongest endophenotype effects for ADHD across the lifespan have been reported for Attention Network Theory (ANT) [74, 75] reaction time indices of *executive attention*- relative to indices of basic attention components *orienting* and *alerting* [49]. Interestingly, studies on the persistence of ADHD in the transition from childhood to (young) adulthood provided evidence for the state-independency of executive-,

Table 4 Intergenerational transmission estimates of basic attention (a–c) and SAS (d–e)—mean reaction time (MRT), reaction time variability (RTV) and false reactions

(a) Attention intensity—*MRT* and *RTV*			
		Mothers (*N* = 134)	**Fathers (*N* = 65)**
Attention component (*TAP subtask*)	Dependent variable [parent measure]	(standardized) Beta TAP offspring, [95% CI], *t*(df), *p*-value	
tonic alertness (*alertness*)	*MRT*	0.16 [− 0.01, 0.34], *t*(130) = 1.85, *p* = 0.066	0.49 [0.20, 0.77], *t*(61) = 3.40, *p* = 0.001
	RTV	0.20 [0.03, 0.37], *t*(130) = 2.361, *p* = 0.020	0.34 [0.07, 0.62], *t*(61) = 2.491, *p* = 0.020
phasic alertness (*alertness*)	*MRT*	0.17 [− 0.01, 0.35], *t*(130) = 1.89, *p* = 0.061	0.23 [0.02, 0.44], *t*(61) = 2.236, *p* = 0.029
	RTV	0.04 [− 0.14, 0.22], *t*(130) = 0.43, *p* = 0.665	0.50 [0.24, 0.77], *t*(61) = 3.79, *p* < 0.001
(b) Attention selectivity—*MRT* and *RTV*			
		Mothers (*N* = 134)	**Fathers (*N* = 65)**
Attention component (*TAP subtask*)	Dependent variable [parent measure]	(standardized) Beta TAP offspring, [95% CI], *t*(*df*), *p*-value	
focused attention (*Go/NoGo*)	*MRT*	0.04 [− 0.22, 0.30], *t*(130) = 0.32, *p* = 0.754	0.13 [− 0.16, 0.42], *t*(61) = 0.891, *p* = 0.376
	RTV	0.20 [0.03, 0.38], *t*(130) = 2.31, *p* = 0.023	0.15 [− 0.20, 0.20], *t*(61) = 0.852, *p* = 0.398
divided attention (*divided attention*)	*MRT*	0.01 [− 0.21, 0.20], *t*(99) = − 0.07, *p* = 0.944	0.00 [− 0.26, 0.26], *t*(47) = 0.015, *p* = 0.988
	RTV	− 0.09 [− 0.16, 0.06], *t*(99) = − 0.88, *p* = 0.381	0.13 [− 0.09, 0.34], *t*(47) = 1.156, *p* = 0.253
(c) Attention selectivity- false reactions			
		Mothers (*N* = 134)	**Fathers (*N* = 65)**
Attention component (*TAP subtask*)	Dependent variable [parent measure]	Odds Ratio TAP offspring, [95% CI], *z* value, *p*-value	
focused attention (*Go/NoGo*)	*Omission errors ≥ 1 vs. no omission errors*	1.65 [0.64, 1.14], *z* = 1.056, *p* = 0.291	*n.a.* (*no mistakes in fathers*)
divided attention (*divided attention*)	*Omission errors ≥ 1 vs. no omission errors*	1.47 [0.66, 3.44], *z* = 0.927, *p* = 0.354	− 0.86 [0.29, 2.66], *z* = − 0.260, *p* = 0.795
	Commission errors ≥ 1 vs. no commission errors	1.92 [0.76, 5.06], *z* = 1.360, *p* = 0.174	0.75 [0.17, 2.97], *z* = − 0.400, *p* = 0.689
(d) SAS–*MRT* and *RTV*			
		Mothers (*N* = 134)	**Fathers (*N* = 65)**
SAS component (*TAP subtask*)	Dependent variable [parent measure]	(standardized) Beta TAP offspring [95% CI], t(df), *p*-value	
interference control (*incompatibility*)	*MRT*	0.06 [− 0.11, 0.24], *t*(130) = 0.717, *p* = 0.475	− 0.01 [− 0.25, 0.22], *t*(61) = − 0.124, *p* = 0.902
	RTV	0.21 [0.03, 0.39], *t*(130) = 2.252, *p* = 0.026	0.40 [0.12, 0.68], *t*(61) = 2.817, *p* = 0.007
flexibility (*flexibility*)	*MRT*	0.19 [0.02, 0.37], *t*(130) = 2.237, *p* = 0.027	0.27 [0.04, 0.49], *t*(61) = 2.376, *p* = 0.021
	RTV	0.08 [− 0.01, 0.26], *t*(130) = 0.931, *p* = 0.353	0.12 [− 0.11,0.35], *t*(61) = 1.040, *p* = 0.302

Table 4 (continued)

(e) *SAS- false reactions*

		Mothers (*N* = 134)	**Fathers (*N* = 65)**
SAS component (*TAP subtask*)	Dependent variable [parent measure]	Odds Ratio TAP offspring [95% CI], *z* value, *p*-value	
impulsivity (*Go/NoGo*)	*Commission errors ≥ 1 vs. no commission errors*	1.77 [0.73, 4.63], $z = 1.228$, $p = 0.220$	− 0.46 [0.12, 1.80], $z = -1.151$, $p = 0.250$
interference control (*incompatibility*)	*Incompatible false reactions ≥ 1 vs. no commission errors*	− 0.40 [0.05, 2.07], $z = -1.016$, $p = 0.309$	2.94 [0.59, 14.90], $z = 1.346$, $p = 0.178$
flexibility (*flexibility*)	*False reactions ≥ 1 vs. no commission errors*	0.88 [0.27, 2.95], $z = -0.222$, $p = 0.824$	1.92 [0.36, 11.38], $z = 0.768$, $p = 0.442$

but state-dependency of basic attention impairments [50, 51, 76]. Executive rather than basic attention impairments thus not only seem to capture familial variation of ADHD across the lifespan, but may in contrast to basic attention impairments remain detectable irrespective of changes in the diagnostic status.

The lack of diagnostic status effects above familial effects of ADHD in the present study may imply that familial traits of ADHD are better predictors of neurocognitive impairments than the diagnostic status. A limitation of the present study, however, is that diagnostic statuses were assigned to the parents in retrospect (i.e. never ADHD, only childhood ADHD, current ADHD), and only based on self-report ratings. The presence of other psychiatric disorders may thus have confounded the ADHD symptom ratings [77] and diagnostic status assignment in our parent sample. Furthermore, our results on the intergenerational transmission estimates of ADHD symptom scores suggest a rater contrast effect: higher inattention symptom ratings in children predicted lower hyperactive/impulsive symptom self-ratings in mothers, and higher hyperactive/impulsive symptom ratings in children predicted lower inattention symptom self-ratings in mothers (see Table 5). Mothers of a child with ADHD were more familiar with the ADHD symptoms presented by their children, and may have contrasted their own ratings of ADHD symptoms to those of their children's, influencing mother–child transmission estimates. Mothers of a child with ADHD were additionally aware of the familial risk of having ADHD themselves and resultantly may have over-reported their symptoms [78]. The prevalence estimates of current ADHD may have been inflated as a consequence, which could have attenuated the state-independency effects. Taken together, results especially on the intergenerational transmission estimates of ADHD symptoms need to be viewed with caution, and a replication of our findings is necessary.

Another limitation was the fixed order of assessment; weaknesses in sustained attention capacities may have disproportionally affected attentional performance at the end of test sessions. Furthermore, information on the psychometric properties of the TAP was limited, to which end we were not able to evaluate the familial estimates of neurocognitive measures in relation to the reliability of the trait [12]. Our results further showed minor differences between mothers and fathers in the familial effects of ADHD on measures of basic attention and SAS. The number of fathers in our sample was nevertheless low. To exclude the possibility of chance findings, replications of these findings with better balanced study designs are warranted. Analyses also did not distinguish between relatives of girls- and boys with ADHD, which should additionally be addressed by future studies, as females diagnosed with a neurodevelopmental disorder (ND) as well as mothers of children with a ND carry a higher mutational burden [79], and may present more severe cognitive familial impairments relative to affected males and fathers [47].

In summary, our results demonstrated familial effects of ADHD on MRT and RTV measures of executive attention (*SAS*), independent of diagnostic status and complemented by intergenerational transmission effects. Effects were only small- to medium-sized, and intergenerational transmission estimates were not higher for neurocognitive measures compared to those of behavioural ratings of ADHD symptom severity. Overall, our results thus argue against neurocognitive impairments in attention and executive attention functions (*SAS*) as pivotal endophenotypes of ADHD across the lifespan. Results rather align with a recent finding in adolescents and (young) adults that reaction time measures of neurocognitive tasks capture one of multiple etiological pathways in ADHD [73]. In the search for genetic markers of ADHD across the lifespan, neurocognitive measures seem, therefore, viable only when combined with physiological markers [9, 73, 80, 81]. Nevertheless, regarding the liability to ADHD that neurocognitive measures do capture, our results suggest that reaction time measures of executive- relative to basic attention functions are more sensitive in detecting familial effects of ADHD in adulthood, and

Table 5 Intergenerational transmission estimates of ADHD symptom measures

	Mothers ($N = 134$)		**Fathers** ($N = 65$)	
	Attention symptom severity [child measure]	**Hyperactivity/impulsivity symptom severity** [child measure]	**Attention symptom severity** [child measure]	**Hyperactivity/impulsivity symptom severity** [child measure]
Dependent variable	(standardized) Beta offspring [95% CI], $t(df)$, p-value		(standardized) Beta offspring [95% CI], $t(df)$, p-value	
attention symptom severity [parent measure]	0.29 [0.14, 0.44], $t(128) = 3.878$, $p < 0.001$	− 0.16 [− 0.32, − 0.01], $t(128) = 2.106$, $p = 0.037$	0.45 [0.14, 0.75], $t(59) = 2.891$, $p = 0.005$	− 0.29 [− 0.60, 0.02], $t(59) = -1.861$, $p = 0.068$
hyperactivity/impulsivity symptom severity [parent measure]	− 0.20 [− 0.36, − 0.04], $t(128) = -2.512$, $p = 0.013$	0.29 [0.13, 0.44], $t(128) = 3.715$, $p < 0.001$	− 0.21 [− 0.56, 0.14], $t(59) = -1.210$, $p = 0.231$	0.09 [− 0.25, 0.43], $t(59) = 0.522$, $p = 0.604$

across the lifespan. Future research should further examine differential familial effects of ADHD on basic- and executive attention performance in child- and adulthood using longitudinal study designs. If differential effects exist, quantitative genetic study designs may benefit more from including executive- instead of basic measures of attention as neurcognitive endophenotype of ADHD. Other promising future approaches to further unravel neurocognitive impairments underlying ADHD comprise of testing other neurocognitive measures of EF, such as working memory [82–84], using neurocognitive measures with well-established test–retest reliability to evaluate familiality in relation to the reliability of the trait [12]. Finally, future studies should aim for adequate sample sizes to further examine sex differences in underlying genetic- and neurocognitive liabilities to ADHD [47, 79]; a critical step to further unravel the complexity of disease pathways underlying the ADHD phenotype [85].

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