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Neurocognitive markers of late-onset ADHD: a 6-year longitudinal study

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Background: There is an increased interest in 'late-onset' attention-deficit/hyperactivity disorder (ADHD), referring to the onset of clinically significant ADHD symptoms after the age of 12 years. This study aimed to examine whether unaffected siblings with late-onset ADHD could be differentiated from stable unaffected siblings by their neurocognitive functioning in childhood. **Methods:** We report findings from a 6-year prospective, longitudinal study of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study, including individuals with childhood-onset (persistent) ADHD (n = 193), their siblings with late-onset ADHD (n = 34), their stable unaffected siblings (n = 111) and healthy controls (n = 186). At study entry (mean age: 11.3) and follow-up (mean age: 17.01), participants were assessed for ADHD by structured psychiatric interviews and multi-informant questionnaires. Several neurocognitive functions were assessed at baseline and after 6 years, including time reproduction, timing variability (reaction time variability and time production variability), reaction time speed, motor control and working memory; intelligence was taken as a measure of overall neurocognitive functioning. **Results:** Siblings with late-onset ADHD were similar to individuals with childhood-onset ADHD in showing longer reaction times and/or higher error rates on all neurocognitive measures at baseline and follow-up, when compared to healthy controls. They differed from stable unaffected siblings (who were similar to healthy controls) by greater reaction time variability and timing production variability at baseline. No significant group by time interaction was found for any of the tasks. **Conclusions:** For unaffected siblings of individuals with ADHD, reaction time variability and timing production variability may serve as neurocognitive marker for late-onset ADHD. **Keywords:** Late-onset ADHD; unaffected siblings; neurocognitive markers.

Introduction

Recently, there has been an increased interest in 'late-onset' attention-deficit/hyperactivity disorder (ADHD), referring to the onset of clinically significant ADHD symptoms after the age of 12 (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2016; Riglin et al., 2016). Whereas some studies reported similar psychiatric comorbidity, functional impairment, familial transmission and intelligence in childhood versus late-onset ADHD (Agnew-Blais et al., 2018; Chandra, Biederman, & Faraone, 2016), other studies observed potentially important differences between individuals with childhood and late-onset ADHD (Cooper et al., 2018; Moffitt et al., 2016; Murray, Eisner, Obsuth, & Ribeaud, 2017). Questions remain as to the nature and aetiology of late-onset ADHD, and no study, so far, has investigated, longitudinally, neurocognitive markers of late-onset ADHD.

Several explanations for late-onset ADHD have been put forward. First, late-onset ADHD might be a distinct disorder with a different aetiology than childhood-onset ADHD. This was supported by findings that individuals with late-onset ADHD differ from those with childhood-onset ADHD in characteristics that are typical for childhood-onset ADHD, such as male preponderance, neuropsychological deficits or childhood ADHD genetic liability (Moffitt et al., 2016). Second, individuals with late-onset ADHD might have the same underlying liability as individuals with childhood-onset ADHD, but with symptoms not manifesting until later in life because difficulties at first were compensated for, or masked by, protective factors, such as high cognitive ability or supportive family environments (Agnew-Blais et al., 2016). Some reports on late-onset ADHD were more sceptical and reported that late-onset ADHD (in most cases) could be explained by methodological

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shortcomings of previous studies, most importantly by including subthreshold ADHD cases in childhood, being susceptible to false-positive diagnoses (Faraone & Biederman, 2016) and not considering comorbid disorders as the source of the symptoms in young adulthood (Sibley et al., 2018). Other important methodological shortcomings of previous studies include change in information source (parent in childhood to self-report in adulthood; Caye et al., 2016; Moffitt et al., 2016), undetected childhood ADHD symptoms (Castellanos, 2015; Faraone et al., 2005; Solanto, 2017) and relying the diagnosis in (young) adulthood solely on screening instruments (Caye et al., 2016; Riglin et al., 2016)).

Investigating late-onset ADHD in a family study including unaffected siblings of children with ADHD might further our understanding of the aetiology of late-onset ADHD. Biological siblings share on average one-half of their genome variance and they also share environmental risk factors, making them at increased risk of developing a full diagnosis after childhood. Indeed, our previous investigation of late-onset ADHD found that a large proportion (26%) of unaffected biological siblings of children with ADHD had clinical levels of ADHD in young adulthood, with age of onset after 12 but prior to 18 years (Ilbegi et al., 2018). These findings supported the idea that biological siblings are at increased risk of developing late-onset ADHD. For early detection and intervention of late-onset ADHD, it is important to elucidate potential neurocognitive markers that could possibly identify siblings at increased risk.

Neurocognitive functioning may act as a neurocognitive marker for identifying late-onset ADHD in unaffected siblings, as neurocognitive dysfunction is a key aspect of the disorder (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008) and is at the heart of several models of ADHD (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, Bitsakou & Thompson, 2010). Although longitudinal cognitive data are limited (van Lieshout et al., 2019; Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), and ADHD is characterized by large heterogeneity at the neuropsychological level (Nigg et al., 2005), cross-sectional data on cognitive impairments and their aetiology in ADHD point to an etiological separation of two familial cognitive impairments in ADHD. The first comprises measures of reaction time variability (Kuntsi et al., 2010) and intra-individual variability of responses (Frazier-Wood et al., 2012). The second comprises executive function impairments, including response inhibition (Kuntsi et al., 2010) and working memory (Frazier-Wood et al., 2012). Longitudinal data on neurocognitive functioning in relation to the aetiology of unaffected siblings developing late-onset ADHD, however, are still lacking.

The current study aimed to investigate whether siblings with late-onset ADHD could be differentiated from stable unaffected siblings by their neurocognitive functioning at two time points. We would expect that, as hypothesized by Faraone and Biederman (2016), if late-onset ADHD is a delayed manifestation of the same liability that underlies childhood-onset symptoms, siblings with late-onset ADHD would have a similar neurocognitive profile in childhood as individuals with typical childhood-onset ADHD (Thapar, Cooper, & Rutter, 2017). Several neurocognitive functions including timing, reaction time (variability), motor control, working memory and intelligence were assessed at baseline and after 6 years in participants of a 6-year prospective, longitudinal study of a subsample of the Dutch International Multicenter ADHD Genetics (IMAGE) cohort.

Methods

Participants

A sample of 524 participants with ADHD combined type (ADHD/C), their unaffected siblings and healthy controls participated in this study. The sample was part of a follow-up study of the Dutch part of the IMAGE study (von Rhein et al., 2015). The original sample ($N = 1092$) was contacted and invited for follow-up on average of 5.9 years ($SD = 0.8$) after enrolment. Of these 1,092 participants, 76.7% was retained successfully ($N = 838$). For this study, only participants who had complete diagnostic and neurocognitive data at baseline and follow-up ($N = 595$) were included. Participants with remittent ADHD ($n = 11$) and subthreshold ADHD ($n = 60$) were excluded from the analyses. Selection and diagnostic procedures at baseline (Müller, Asherson, Banaschewski, Buitelaar, Ebstein, & Eisenberg, 2011; Müller, Asherson, Banaschewski, Buitelaar, Ebstein, Eisenberg, et al., 2011) and at follow-up (von Rhein et al., 2015) have been detailed previously. Briefly, inclusion criteria for entry at baseline were Caucasian descent, IQ ≥ 70, no diagnosis of autism, epilepsy, general learning difficulties, brain disorders and known genetic disorders. *Childhood-onset (persistent) ADHD* ($n = 193$) was ADHD probands, meeting full DSM-IV criteria of ADHD/C at baseline, and meeting full DSM-5 criteria of ADHD regardless of type, at follow-up. *Siblings with late-onset ADHD* ($n = 34$) were siblings of ADHD probands who were unaffected in childhood and did not meet criteria of ADHD, any type, at baseline but did meet full DSM-5 criteria for ADHD at follow-up. *Stable unaffected siblings* ($n = 111$) were siblings of ADHD probands who did not meet criteria of ADHD, any type, both at baseline and follow-up. *Healthy controls* ($n = 186$) were required to not have a clinical score on any of the measures used for diagnostic criteria at baseline and follow-up. Subthreshold cases were defined as meeting criteria of subthreshold ADHD at baseline and/or follow-up: <6 symptoms of inattention and hyperactivity/impulsivity, but ≥4 symptoms of inattention and/or hyperactivity/impulsivity at follow-up for children <18 years. For participants ≥18 years, thresholds were five and three symptoms, respectively. See Appendix S1 for a more detailed description on selection and diagnostic procedures and procedure.

Neurocognitive variables

Neurocognitive variables were identically measured at baseline and at follow-up. Measures were chosen at the time of baseline assessment based on their potential to discriminate between ADHD, unaffected siblings and healthy controls. Included were time reproduction (Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007), timing variability (reaction time variability and time production variability) (Rommelse, Altink, Oosterlaan, Beem et al., 2008; Rommelse, Altink, Oosterlaan,

Buschgens, et al., 2008), reaction time speed (Rommelse, Altink, Oosterlaan, Beem et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008; Willcutt et al., 2012), motor control (Carte, Nigg, & Hinshaw, 1996; Pitcher, Piek, & Barrett, 2002; Rommelse et al., 2007), verbal working memory (Rommelse, Altink, Oosterlaan, Beem et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008) and intelligence (Rommelse, Altink, Oosterlaan, Beem et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008; Willcutt et al., 2012). The order of neurocognitive tasks was fixed. See for further details on neurocognitive measures that were used in Appendix S1 and Table S1.

Data analysis

Statistical computations were performed using Statistical Package for the Social Sciences (SPSS) version 20.0. Demographic and clinical variables at baseline were compared between groups (four groups: childhood-onset ADHD, siblings with late-onset ADHD, stable unaffected sibling and healthy controls) with univariate ANOVAs for continuous variables and chi-square tests for categorical variables, with significance set at $p < .05$. Not all dependent variables were normally distributed. These variables were successfully normalized by applying a Van der Waerden transformation. Linear mixed models with group as fixed factor, time (baseline and follow-up) as repeated measure and family as a random effect to account for within-family correlation were used to analyse differences in cognitive functioning among these groups at baseline and follow-up as well as in change in cognitive functioning between baseline and follow-up (group by time interaction). IQ, gender and follow-up time were used as covariates. For the cognitive outcome measures that showed group differences, we estimated the effect sizes using Cohen's d (see Table S2 for details). To explore potential moderating effects of age on neurocognitive functioning and ADHD outcome, interactions of age and significant neurocognitive predictors of late-onset ADHD were examined. When an interaction effect with age was significant, the finding was further explored by subdividing the sample based on age at baseline (<12 years and ≥12 years). Additionally, receiver operating curve was analysed (see Appendix S1).

Sensitivity analyses

As the results may have been impacted by including subjects with anxiety and/or emotional lability scores above the clinical range ($T \geq 63$) and/or with substance use disorder (alcohol and/or drug use disorder) and/or nicotine dependence (ND), we checked whether results of our main analyses were robust when excluding these subjects.

Results

Demographic and clinical characteristics

Table 1 describes demographic and clinical characteristics of the four groups. Attrition analyses are described in Appendix S1. Siblings with late-onset ADHD did not differ significantly in their IQ compared with stable unaffected siblings and healthy controls and had a higher IQ compared to individuals with childhood-onset ADHD at baseline and follow-up (see Table 1 for details). Furthermore, there were small, but statistically significant, group differences in follow-up interval and gender. All subsequent analyses were statistically corrected for follow-up interval, gender and IQ.

Moderating effects of age

The age x neurocognitive functioning × group interaction was significant for motor timing variability (childhood-onset ADHD vs. stable unaffected siblings: $b = -.03$, $p = .004$). Further analyses in two equal-sized age groups (<12 years and ≥12 years) revealed that the motor timing variability (the group x time interaction effect) was significant only in the youngest age group ($p < .006$).

Baseline symptoms and neurocognitive functioning

At baseline, parents reported significantly higher total symptom severity in siblings with late-onset ADHD compared with stable unaffected siblings. Siblings with late-onset ADHD, but not stable unaffected siblings, scored significantly higher compared with healthy controls. None of the siblings with late-onset ADHD scored in the clinical range (total ADHD $T \geq 63$), and they had significantly lower total ADHD symptom severity compared to individuals with childhood-onset ADHD at baseline. Teachers did not report higher total ADHD symptom severity scores in siblings with late-onset ADHD compared with stable unaffected siblings at baseline. Both groups had significantly lower total ADHD symptom severity scores compared to individuals with childhood-onset ADHD and higher compared to healthy controls at baseline. At baseline, parents did report similar levels of anxiety and emotional lability in siblings with late-onset ADHD compared to stable unaffected siblings. Both groups had significantly lower levels of anxiety and emotional lability compared to individuals with childhood-onset ADHD at baseline. None of the siblings with late-onset ADHD scored in the clinical range ($T \geq 63$). See Table 1 for details.

Regarding neurocognitive functioning, no significant group differences were found for *reaction time speed* (F (3, 431.49) = 1.76, $p = .15$) or *motor control precision* (pursuit task; F (3, 437.68) = .89, $p = .44$) at baseline (Table S2 and Figure 1). The four groups differed significantly on measures of *time reproduction precision* (F (3, 474.7) = 12.19, $p < .001$, $d = 0.45$), *reaction time variability* (F (3, 479.88) = 5.24, $p = .001$), *time production variability* (F (3, 406.73) = 6.76, $p < .001$), *motor control precision* (tracking task; F (3, 464.93) = 12.3, $p \leq .001$) and *verbal working memory* (F (3, 484.02) = 7.25, $p < .001$) at baseline. Pairwise comparisons showed that siblings with late-onset and childhood-onset ADHD did not differ significantly from each other on any of the measures, and both performed worse compared with healthy controls on all neurocognitive measures studied at baseline (see Table S2 for details and Table S3 for effect sizes of all group comparisons). Conversely, stable unaffected siblings performed comparable to healthy controls and both groups performed better than the late-onset and

Table 1 Sample characteristics at baseline and follow-up (N = 524)

	Childhood-onset ADHD (1)		Siblings with late-onset ADHD (2)		Stable unaffected siblings (3)		Healthy controls (4)			
	n = 193		n = 34		n = 111		n = 186			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	Test statistic	Post hoc
Baseline										
Age in years	11.5	2.7	11.0	3.5	11.2	3.7	11.6	3.3	p = .611	1 = 2 = 3 = 4
Sex, *N* male (%)	168	81.6	16	47.1	44	39.6	71	38.2	χ^2 = 93.59, p < .001	1 > 2 = 3 = 4
Estimated full-scale IQ	99	12	104	11	105	11	107	11	p < .001	1 < 2 = 3 = 4
CPRS-R:L inattentive symptom severity	71.3	9.1	54.4	12.2	47.0	6.1	46.3	4.7	p < .001	1 > 2 > 3 = 4
CPRS-R:L hyperactive/impulsive symptom severity	78.3	10.4	57.1	15.6	47.8	5.7	47.0	4.7	p < .001	1 > 2 > 3 = 4
CPRS anxiety/shy *T*-score	57.5	14.1	52.9	12.5	49.9	9.8	48.7	8.2	p < .001	1 > 3 = 4; 2 = 1&3&4
CPRS emotional liability *T*-score	63.2	12.9	51.7	10.1	48.3	8.3	45.6	7.0	p < .001	1 > 2 = 3; 3 = 4; 1 > 2 > 4
CTRS-R:L inattentive symptom severity	65.3	8.8	49.8	6.9	48.7	7.1	46.1	4.4	p < .001	1 > 2 = 3 > 4
CTRS-R:L hyperactive/impulsive symptom severity	69.2	11.5	50.6	9.5	48.8	7.6	46.8	4.3	p < .001	1 > 2 = 3 = 4
Follow-up										
Age in years	17.3	2.7	16.8	3.5	17.0	3.7	16.8	3.2	p = .904	1 = 2 = 3 = 4
Estimated full-scale IQ	94	17	100	13	101	15	107	14	p < .001	1 < 2 = 3 = 4
Mean follow-up period	5.9	.6	5.8	.5	5.9	.6	5.2	1.2	p < .001	1 = 2 = 3 > 4
CPRS-R:L inattentive symptom severity	66.0	10.8	62.6	12.8	46.9	6.5	46.7	6.0	p < .001	1 = 2 > 3 = 4
CPRS-R:L hyperactive/impulsive symptom severity	70.4	13.8	63.9	16.5	47.4	6.4	46.6	5.0	p < .001	1 = 2 > 3 = 4
CPRS-R:L anxiety/shy *T*-score	54.6	12.2	51.3	9.6	49	8.0	49.0	8.3	p < .001	1 = 2&3&4; 1 > 3 = 4
CPRS-R:L emotional liability *T*-score	57.1	14.0	52.9	9.1	45.7	5.5	44.6	4.5	p < .001	2 = 1 > 3 = 4
CTRS-R:L inattentive symptom severity	66.8	11.9	62.3	14.8	49.0	8.9	47.3	9.3	p < .001	2 = 1 > 3 = 4
CTRS-R:L hyperactive/impulsive symptom severity	58.3	13.0	63.0	14.2	47.1	11.0	44.7	9.1	p < .001	2 = 1 > 3 = 4

Estimated IQ based on Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale-III Vocabulary and Block design. Multiple comparisons adjusted with the Benjamini–Hochberg procedure.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CPRS-R:L, Conners' Parent Rating Scale-Revised: Long version; CTRS-R:L, Conners' Teacher Rating Scale-Revised: Long version; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders (4th edition); *M*, mean; *SD*, standard deviation.

childhood-onset ADHD groups on measures of *reaction time variability* and *time production variability*. This indicates that siblings who developed late-onset ADHD could be differentiated from stable unaffected siblings in reaction time variability and time production variability in childhood. For *motor control precision* (tracking task), the same pattern was observed; however, no significant difference was found between stable unaffected siblings and siblings with late-onset ADHD. Pairwise comparisons for *time reproduction precision* and *verbal working memory* showed no significant differences between siblings with late-onset ADHD, childhood-onset ADHD and stable unaffected siblings, and all performed worse compared with healthy controls. This indicates that in childhood, measures of time reproduction and verbal working memory are related to the familial predisposition to ADHD.

Follow-up symptoms and neurocognitive functioning

At follow-up, both parents and teachers reported no significant difference in total symptom severity in siblings with late-onset ADHD and childhood-onset ADHD and both had significantly higher total symptom severity compared with stable unaffected siblings and healthy controls. Parents reported significantly higher levels of emotional lability, but not anxiety, in siblings with late-onset ADHD compared with stable unaffected siblings at follow-up. Levels of emotional lability were similar between siblings with late-onset ADHD and childhood-onset ADHD group at follow-up, but were not in the clinical range ($T \geq 63$; see Table 1 for details). At follow-up, significant group differences were found for all neurocognitive tasks studied including *time*

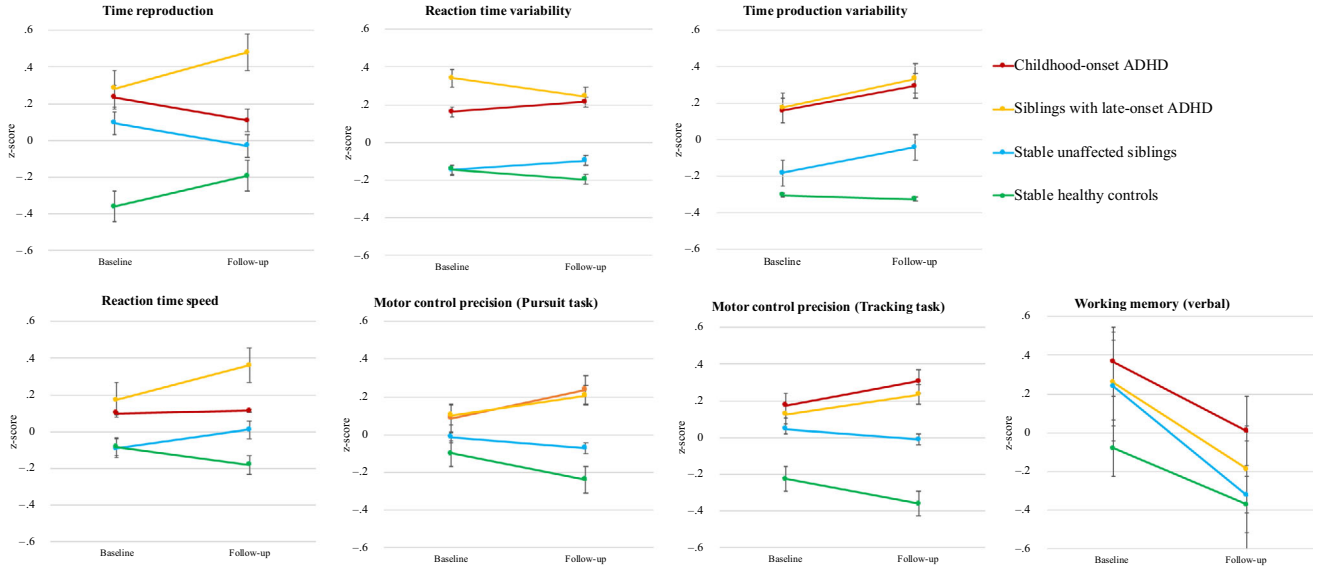

Figure 1 Baseline and follow-up neurocognitive functioning in individuals with childhood-onset ADHD (n = 193), siblings with late-onset ADHD (n = 34), stable unaffected siblings (n = 111) and healthy controls (n = 186). Higher z-scores indicate worse performance [Colour figure can be viewed at wileyonlinelibrary.com]

reproduction precision (F (3, 415.0) = 5.3, p = .001), *reaction time variability* (F (3, 392.0) = 5.2, p = .002), *time production variability* (F (3, 430.8) = 12.2, p < .001), *reaction time speed* (F (3, 381.9) = 3.8, p = .01), *motor control precision* (pursuit task: F (3, 429.9) = 6.1, p < .001; tracking task; F (3, 418.3) = 5.4, p = .001) and *verbal working memory* (F (3, 415.3) = 7.0, p < .001). Pairwise comparisons showed that siblings with late-onset and childhood-onset ADHD did not differ significantly from each other and both performed worse compared with healthy controls on all neurocognitive measures studied at follow-up (see Tables S2 and S3 for details and effect sizes). Conversely, stable unaffected siblings performed similar as healthy controls on all neurocognitive tasks, except for *motor control precision* (tracking task). Pairwise comparisons for *motor control precision* (tracking task) showed no significant differences between siblings with late-onset ADHD, childhood-ADHD and stable unaffected siblings, and all performed worse compared with healthy controls. Siblings with late-onset ADHD performed worse than stable unaffected siblings on measures of *time production variability* and *time reproduction precision*. This indicates that siblings who developed late-onset ADHD could be differentiated from stable unaffected siblings in time production variability and time reproduction precision in adolescence. No significant differences were found between siblings with late-onset ADHD and stable unaffected siblings on the other tasks.

Neurocognitive change over time

No significant *group by time interaction* was present for *time reproduction precision* (F (3, 707.2) = 2.2, p = .08), *reaction time variability* (F (3, 669.2) = 0.2, p = .88), *time production variability* (F (3, 686.1) = 0.7, p = .56), *reaction time speed* (F (3, 661.5) = 1.0, p = .38), *motor control precision* (pursuit task: F (3, 685.8) = 1.8, p = .15; tracking task: F (3, 685.8) = 1.8, p = .15) or *verbal working memory* (F (3, 472.5) = 2.1, p = .10). These findings indicate that all groups had a similar course of neurocognitive change over the 6-year follow-up period.

Sensitivity analyses

Findings were replicated when excluding subjects with anxiety and/or emotional lability scores above the clinical range ($T \geq 63$, n = 4 and n = 5, respectively) and/or with SUD (n = 8) and/or ND (n = 7), total n = 15. Similar or comparable (non)significance levels and effect sizes were obtained.

Discussion

This 6-year prospective longitudinal study found that siblings with late-onset ADHD were similar to individuals with childhood-onset ADHD in showing longer reaction times and higher error rates on all neurocognitive measures at baseline and follow-up and differed from stable unaffected siblings by greater reaction time variability and timing production variability at baseline. No significant differences in neurocognitive change over time were observed. Overall, our findings indicate that measures of reaction time variability and timing production variability could serve as a neurocognitive marker to identify children with an increased familial susceptibility for ADHD who are at increased risk of developing late-onset ADHD.

The ongoing debate about late-onset ADHD is mainly based on whether late-onset ADHD is a continuation of childhood-onset ADHD or is a distinct disorder with a different aetiology (Agnew-Blais

et al., 2016; Moffitt et al., 2016). The current prospective longitudinal study adds important knowledge to this topic by investigating potential neurocognitive markers of late-onset ADHD in unaffected biological siblings of children with ADHD, characterized by increased genetic and environmental risk of ADHD. Our findings are mostly in line with the hypothesis that late-onset ADHD has the same underlying neurocognitive aetiology as childhood-onset ADHD, but with a delayed phenotypical manifestation. Indeed, siblings who developed late-onset ADHD had similar patterns of neurocognitive dysfunction as individuals with childhood-onset (persistent) ADHD with respect to all studied neurocognitive measures, except for IQ, at baseline and follow-up. This indicates that although clinical levels of ADHD were not observed in these siblings in childhood, they subsequently developed late-onset ADHD and showed neurocognitive vulnerabilities similar to individuals with childhood-onset ADHD in childhood.

Consistent with previous findings (Agnew-Blais et al., 2016; Cooper et al., 2018; Moffitt et al., 2016), siblings with late-onset ADHD had a higher IQ in childhood and adolescence compared to individuals with childhood-onset ADHD. As such, it may be that higher IQ represents an important compensatory mechanism for ADHD in childhood (Michelini et al., 2016) and acts as a protective factor to delay the onset of ADHD (Faraone & Biederman, 2016). Clinical levels of ADHD might manifest later in adolescence or young adulthood, when the demands of the environment (e.g. school/relationships/work) increase and compensatory mechanisms fail. It is unlikely that our late-onset ADHD cases are individuals with undetected childhood symptoms or that the symptoms could be explained by other disorders, since all participants were comprehensively assessed on ADHD and comorbid disorders by multi-informant questionnaires and a semi-structured diagnostic interview by a clinically trained professional at baseline and follow-up.

Reaction time variability and time production variability (both measures of timing variability) distinguished siblings with late-onset ADHD from stable unaffected siblings in childhood. Conversely, measures of higher-order cognitive functioning (working memory) did not distinguish siblings with late-onset ADHD from siblings that remained unaffected, and thus were not sensitive to late-onset ADHD. Our findings are consistent with previous reports that reaction time variability, but not executive dysfunction, is a stable and etiologically important characteristic of the disorder (Cheung et al., 2016; Kuntsi et al., 2010). Reaction time variability refers to inconsistency in an individuals' speed of responding, measured in milliseconds, and has been argued to reflect a subset of abnormally slow responses during laboratory tasks (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Leth-Steensen, King Elbaz, & Douglas, 2000; Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007; Zeeuw et al., 2008). A large body of research indicates that individuals with ADHD have increased reaction time variability across a wide range of tasks, including tasks measuring reaction time on motor speed, choice decision, vigilance, behavioural inhibition, cognitive interference, working memory, visual saccades and visual discrimination (Alderson, Rapport, & Kofler, 2007; Klein et al., 2006; Willcutt, Sonuga-Barke, Nigg & Sergeant, 2008). Moreover, reaction time variability has been proposed as an underlying trait (Hicks, Mayo, & Clayton, 1989) or potential endophenotype of ADHD (Rommelse, Altink, Oosterlaan, Beem et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008; Sonuga-Barke & Castellanos, 2007). Our findings emphasize that measures of (reaction) time variability reflect an etiologically important characteristic of (late-onset) ADHD.

Important strengths of the current study are that ADHD symptoms and comorbid disorders were prospectively and comprehensively assessed by multiple informants at all time points. In addition, subthreshold cases in childhood were excluded and comorbid disorders were taken into account. Furthermore, neurocognitive functioning was assessed at two time points, making it possible to investigate the longitudinal course of neurocognitive functioning and the course of ADHD. There were, however, also some limitations. The sample size of the siblings with late-onset ADHD group was relatively small and might lack the statistical power to detect small group differences, especially between siblings with late-onset ADHD and stable unaffected siblings. Nevertheless, it is unlikely that group differences in the siblings with late-onset ADHD and childhood-onset ADHD group were missed due to lack of statistical power, since their group means were clearly overlapping (Table S2). Although we did include a broad array of neurocognitive functions, we were not able to include all neurocognitive domains currently regarded important in ADHD, such as reward-related neurocognitive functions. Furthermore, the last assessment was in young adulthood. New late-onset cases might appear later in development.

In conclusion, the present prospective longitudinal study showed that siblings with late-onset ADHD had comparable neurocognitive deficits, including time reproduction, timing variability (reaction time variability and time production variability), reaction time speed, motor control and working memory as individuals with childhood-onset (persistent) ADHD. Measures of reaction time variability and time production variability distinguished siblings developing late-onset ADHD from stable unaffected siblings and may serve among unaffected siblings as neurocognitive marker for late-onset ADHD. Our data suggest that ADHD symptoms and impairments might be masked or compensated by protective factors in

childhood, such as higher intelligence. Our work also suggests that late-onset ADHD shares a neurodevelopmental aetiology with childhood-onset ADHD. This study might have clinical implications for diagnosis and clinical care of biological siblings of children with ADHD. The finding that siblings with late-onset ADHD had a milder clinical picture and less ADHD and broader externalizing symptoms, but similar pattern of neurocognitive dysfunction, puts them at risk of being overseen and under recognized. For this reason, clinicians should know that these siblings may have a less typical course of ADHD with onset after age 12 years. Future research is needed to understand the causes, course and optimal treatment of late-onset ADHD.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Statistical analyses, diagnostic assessment and neurocognitive variables.
Table S1. Description of neurocognitive measurement at baseline and follow-up.
Table S2. Means and standard deviations of the untransformed baseline and follow-up neurocognitive measures.
Table S3. Effect sizes of significant group differences on neurocognitive tasks.

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Key points

- Recently there has been an increased interest in 'late-onset' ADHD.
- Questions remain as to the nature and aetiology of late-onset ADHD and no study, so far, has investigated, longitudinally, neurocognitive markers of late-onset ADHD.
- Measures of reaction time variability and time production variability may serve as neurocognitive marker for late-onset ADHD.
- This study might have clinical implications for diagnosis and clinical care of biological siblings of children with ADHD. Siblings with late-onset ADHD had a milder clinical picture and less ADHD and broader externalizing symptoms, but similar pattern of neurocognitive dysfunction, which puts them at risk of being overseen and under recognized. Clinicians should know that these siblings may have a less typical course of ADHD with onset after age 12 year.

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