The role of executive and general cognitive functioning in the attention problems of very and extremely preterm adults

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ABSTRACT

Objective—To determine whether the attention problems in adults born very preterm/very low birthweight (VP/VLBW; <32 weeks' gestation/ <1500g) or extremely preterm (EP; <26 weeks' gestation) are associated with specific executive or general cognitive deficits.

Method— Cohorts of VP/VLBW (the Bavarian longitudinal study (BLS)) and EP (the EPICure Study) participants were followed from birth to early adulthood, each also following a respective control group. Adult ADHD symptoms were assessed via self-report in both cohorts and additionally by parent-report in the BLS. Participants in both cohorts also had their attention span rated by trained observers. Performed separately in each cohort, hierarchical regression analyses were used to assess whether the association between preterm birth status and attention problems remained after accounting for executive functioning (inhibitory control and working memory) in adulthood, childhood IQ or sex.

Results— In the discovery cohort of the BLS, significant differences were found between VP/VLBW adults and controls for parent-rated inattention (p<0.001). However, for self-reported measures of ADHD, no significant differences were found in the BLS or in the EPICure replication cohort. In both cohorts, observer-rated attention spans were lower for VP/VLBW and EP participants in comparison to their respective control groups (p <0.001). In final models for the BLS, inhibitory control and childhood IQ were significantly associated with parent-rated inattention symptoms (p<0.006). Whereas working memory and childhood IQ were significantly associated with observer-rated attention span (p<0.001). The effect of childhood IQ on observer-rated attention span was replicated in EPICure.

Conclusions—VP/VLBW and EP adults are at increased risk of observer-rated attention problems. These problems were predominantly associated with poorer general cognitive ability in early childhood and somewhat with adult executive functioning.

Key Terms

Attention-deficit/Hyperactivity Disorder; Preterm; attention; executive functioning; intelligence

INTRODUCTION

In comparison to term born controls, those born very preterm or at very low birthweight (<32 weeks' gestation or <1500g, VP/VLBW) have been found to have greater attention problems[1]. In childhood, this has been found when assessed via parent report,[2] teacher rating[3] and observer rating of attention span.[4] VP/VLBW individuals are also at increased risk of Attention Deficit Hyperactivity Disorder (ADHD) diagnosis in childhood[1] and adulthood.[4] In particular, a preterm specific phenotype of ADHD, consisting of increased number of inattention symptoms (ADHD-I) with relatively few problems of hyperactivity/impulsivity (ADHD-H)[2] has been proposed. While males are more likely to have ADHD symptoms or diagnosis in the general population, this sex difference has not been consistently found within VP/VLBW groups.[1]

Attention problems have been primarily associated with deficits in executive functioning, a set of higher-order neurocognitive processes required for decision making and goal orienting.[5] While there is discussion over which behaviours and tasks best measure executive functioning, Diamond's (2013) framework states that two main components are the ability to hold and manipulate information in mind - working memory - and the ability to selectively attend and suppress attention to stimuli - inhibitory control.[6] In comparison to controls, VP/VLBW children and adolescents show deficits on a range of executive functioning tasks,[7] which may explain the attention problems seen in VP/VLBW children. For example, working memory has been found to mediate the relationship between VP/VLBW birth and teacher-rated inattention.[3] Similarly, impulse control, a component of inhibitory control, has been associated with attention scores in VP/VLBW children and controls.[8] Thus, the greater childhood attention problems seen in VP/VLBW when compared to term born may be partly explained by executive functioning. However, whether these specific executive functions explain differences in adulthood has not yet been explored.

Alternatively, it has been suggested that the differences in attention between VP/VLBW individuals and term born controls may be explained by VP/VLBW individuals having, on average, lower intelligence scores (IQ).[2] However, scores on tests of IQ and executive function are correlated with poor executive functioning being partially responsible for poor IQ scores.[9] This is especially true for adult IQ tests that have working memory as a subtest for the calculation of full-scale IQ, meaning the two constructs are not independent. To reduce this issue, childhood IQ can be used to control for general cognitive ability while being less correlated with current abilities in executive function. Overall, if adult inattention is primarily a result of specifically poor executive function, then concurrent measures of executive function should provide the best ability to explain differences in attention between groups, over and above the effect of childhood IQ scores.

The aim of this study was to investigate whether the greater attention problems seen in VP/VLBW as compared to term born adults are best explained by specific executive functioning deficits, general cognitive abilities or sex. The discovery sample is the Bavarian Longitudinal Study (BLS) and replication was conducted in the EPICure study of extremely preterm participants (EP, <26 weeks' gestation). It was hypothesised that the poorer attention seen in VP/VLBW and EP adults would be significantly associated with poor executive functioning, as measured by inhibitory control and working memory, and that these effects would remain after controlling for other potential risk factors of low childhood IQ and male sex.

METHOD

Participants

Bavarian Longitudinal Study (BLS)**.** Details of the design of the BLS have been previously reported,[10] as have the details of the assessments at 26 years of age.[11] Briefly, of

682 VP/VLBW infants born alive between January 1985 and March 1986 in Southern Bavaria, Germany, and who required admission to a children's hospital within the first 10 days after birth, 411 were alive and eligible for the 26-year follow-up assessment. 260 participated (63%) with 194 (47%) completing measures of self-reported ADHD and experimental measures of executive functioning. Three hundred and fifty eligible healthy term-born controls born in the same hospitals, matched for sex and socioeconomic status, served as controls and were also followed from birth. In adulthood, 308 controls were eligible for inclusion, 229 (74%) participated with 197 (64%) completing self-reported ADHD and executive functioning measures at 26 years and are thus included in this study. Of the 194 VP/VLBW participants and 197 controls, 172 (89%) and 181 (93%) also had data available for parent-reported ADHD symptoms at 26 years of age. The participant flow chart for the BLS is presented in Supplemental Digital Content 1. Informed consent was obtained from parents and participants, ethical approval was obtained from University Hospital Bonn Ethical Committee.

EPICure. Details of the design of EPICure have been previously reported[12] as have the details of the assessments at 19 years of age.[13] Briefly, EPICure included EP infants who were born in the United Kingdom and Ireland from March through to December 1995. Of the 315 alive at hospital discharge, 306 EP participants were eligible for the 19-year follow-up assessment of which 129 (42%) participated. Of these, 107 (35%) completed measures of self-reported ADHD symptoms and tests of executive functioning. A stratified comparison group of 160 children were initially recruited at age 6 with 43 further recruited at 11 years. Of the full-term control group at 11 years (N: 153), 65 (42%) took part at 19 years of age, with 60 (39%) completing measures of self-reported ADHD symptoms and tests of executive functioning. The participant flow chart for EPICure is presented in Supplemental Digital

Content 1. Informed consent was obtained from participants, ethical approval was obtained from the South Central – Hampshire A Research Ethics Committee.

Measures

Adult ADHD Symptoms. Both EPICure and BLS participants completed Kooij's DSM-IV based ADHD adult rating scale.[14] This 23 item scale is considered a valid and reliable measure of ADHD in adulthood.[14] The scale determines a participant as having a symptom if the participant responds 'often' or 'very often' to items such as 'I fail to give close attention to details in work'. Two subscores assessing 9 ADHD-I symptoms and 9 ADHD-H symptoms, ranging from 0 (no ADHD sub score symptoms present) to 9 (maximum number of ADHD sub score symptoms present) are calculated with the combined ADHD symptoms (ADHD-C) calculated by totalling the two subscores. In both cohorts, the self-reported ADHD scales had good internal reliability (BLS α= 0.75, EPICure α= 0.85). In the BLS cohort only, parents also assessed their child's ADHD symptoms using the same questionnaire, with a similarly good internal reliability (α= 0.88). All ADHD-I, ADHD-H and ADHD-C symptom scores were then converted into Z scores based upon the mean and standard deviation of each cohort's respective control group.

Tester Rating of Adult Behaviour - Attention Span (TRAB-AS). In both cohorts, psychologists rated the individual's attention on a scale from 1 (very short attention span) to 9 (very long attention span).[15] Assessments were made three times across the assessment day: (1) during the cognitive assessment, (2) during the afternoon session, and (3) at the end of the assessment day. The means of these three time points were then combined to produce an overall assessment of attention span which were then converted into Z scores based upon the mean and standard deviation of each cohort's respective control group. Within the BLS, Tester Rating of Adult Behaviour - Attention Span (TRAB-AS) showed moderate inter-rater reliability (Kappa=0.67). For EPICure, all assessments were made by a single psychologist.

Adult Executive Functioning: Inhibitory control. Inhibitory control was measured using the Attention Network Task (ANT).[16] The ANT measures alerting, orienting and executive control. For this study, executive control was of interest as a measure of inhibitory control. Consisting of 128 trials, the ANT requires participants to determine the direction of a central target arrow as accurately and as quickly as possible while ignoring flanker arrows. Inhibitory control was calculated by taking the mean reaction time on trials when the flanker arrows were incongruent and subtracting the mean reaction time when the flanker arrows were congruent. Scores were measured in milliseconds with a larger inhibitory control score indicating greater difficulty with inhibiting extraneous stimuli. See Supplemental Digital Content 2 for a diagram demonstrating the sequence of events in an ANT trial and a detailed description of how the ANT was performed in both cohorts using identical procedure.

Adult Executive Functioning: Working Memory. For BLS participants, the working memory assessment comprised a Letter-Number Sequencing task, a subtest of Wechsler Adult Intelligence Scale III.[17] Participants heard sequences of numbers and letters and then repeated back the numbers in ascending order and the letters in alphabetical order. EPICure participants partook in a different verbal working memory assessment, the backwards digit recall task a subtest of Wechsler Adult Intelligence Scale IV.[18] Participants listened to sequences of numbers and then repeated them back in reverse order, a working memory assessment found to be closely related to the Letter-Number Sequencing task.[19] Scores in both cohorts were standardised based upon each cohort's respective control group with a mean of 100 and a standard deviation of 15.

Childhood IQ. At 6 years of age, the IQ of participants was assessed with the Kaufman Assessment Battery for Children Mental Processing Component, comprising of 8 subtests, 5 subtests to measure simultaneous processing and 3 subtests to sequential processing.[20–22] Scores in both cohorts were standardised based upon each cohort's respective control group with a mean of 100 and a standard deviation of 15. If IQ data were missing at 6 years, IQ scores from the next available cognitive assessment at either 8 years (BLS) or 11 years (EPICure) were used (N:41, 7% of all participants).

Statistical Analysis

SPSS version 24 (IBM Corp., Armonk, NY) and R version 3.4.2 were used to analyse the data. The comparison of demographic data in VP/VLBW or EP and control samples were assessed using chi-squared tests in both cohorts. Participants with complete data for measures of executive functioning, self-reported ADHD symptoms and TRAB-AS were included for analysis. All analyses were performed separately for each cohort; first in the BLS and then subsequently replicated in EPICure, allowing for the robustness of findings to be explored.

To test for differences between VP/VLBW participants or EP participants and controls, independent samples t-tests were first used to compare self-reported ADHD symptoms, parent-reported ADHD symptoms (BLS only), TRAB-AS, inhibitory control, working memory and IQ at 6 years for each cohort. Adjustment for multiple comparisons were made using Hochberg's procedure.[23] Effect sizes are reported as Cohen's d: 0.20 = small, 0.50 = medium, 0.80 = large.[24]

When significant differences in attention problems were found between VP/VLBW or EP participants and controls, hierarchical regressions were performed to identify which factors reduced and explained these differences. This was performed first in the discovery sample of the BLS and replicated when possible in EPICure. Hierarchical regressions were used to determine whether deficits in executive function explained the greater attention problems in VP/VLBW and EP individuals, above and beyond the effect of IQ or sex. Each hierarchical regression added at step 1 the binary variable of birth group (VP/VLBW or control for BLS, EP or control for EPICure). At step 2, measures of executive function were added. IQ at 6 years was added at step 3 while male sex, a common risk factor for attention problems, was added at step 4. At each step in the hierarchical regression, the importance of each variable was assessed in two ways. Firstly, by the R-square change of the overall model fit for the ADHD-I symptoms or TRAB-AS outcome, determining how each step improves the prediction of attention problems in adulthood. At step 4, the final model was assessed to determine the predictive ability of each variable upon consideration of all other variables in the model and the total variance explained. Additionally, the estimated adjusted means for VP/VLBW(or EP) and controls were calculated at each step in the hierarchical regression. This assessed the importance of inhibitory control, working memory, IQ at 6 years and sex by their effect on the differences in means between the VP/VLBW(or EP) groups and their respective controls. If for example, the reason for poor attention in VP/VLBW and EP adults was a result of poor executive functioning, then the adding of executive functioning measures at step 2 should cause the difference in estimated adjusted means between VP/VLBW and controls to diminish, becoming no longer statistically significant.

RESULTS

Demographic Data and Drop-out Analysis

Information regarding demographic data and loss to follow-up into adulthood have been reported previously for the BLS[11] and in EPICure.[13] VP/VLBW and EP participants in both cohorts were more likely to be of higher socioeconomic status than dropouts from their respective cohorts (*p* = 0.003 in BLS, *p* = 0.004 in EPICure). Participating EPICure EP individuals were also more likely to be female than EP participants lost to follow up (*p* = 0.039). The only significant difference within both cohorts comparing demographic data of VP/VLBW and EP to controls was that BLS controls were more likely to have higher socioeconomic status than BLS VP/VLBW individuals (*p* = 0.030).

Differences between EP/VP/VLBW adults and controls in ADHD symptoms, executive function and IQ

Between group differences in ADHD symptoms, attention span, executive function and IQ are shown in Table 1. In the discovery sample, the BLS, VP/VLBW participants did not self-report significantly higher ADHD-I, ADHD-H or ADHD-C symptoms than controls. Similarly, after adjustments for multiple comparisons were made,[23] there were no significant differences in self-reported ADHD between EP and controls in the replication sample of EPICure. Parents of the BLS VP/VLBW participants reported their adult children as having significantly higher ADHD-C symptoms than controls, which was primarily due to differences in ADHD-I symptoms rather than ADHD-H symptoms. Finally, in the BLS VP/VLBW participants were found to have considerably shorter attention spans than controls when rated by observers using the TRAB-AS, which was replicated in EPICure (Table 1).

For executive function, BLS's VP/VLBW participants demonstrated poorer performance in both domains, with larger response times for inhibitory control and lower working memory scores in comparison to controls. On the measure of IQ at 6 years of age, VP/VLBW participants scored considerably lower than their respective control group. In the replication sample of EPICure, a robustly similar set of findings regarding executive and general cognitive functions were found. However, the magnitude of difference between the EP participants and controls was slightly larger than the difference found between the VP/VLBW and controls in the BLS (Table 1). A correlation matrix for attention measures, executive functioning and general cognitive functioning is also provided in supplementary digital content 3.

Hierarchical regressions explaining TRAB-AS and ADHD-I symptoms differences in VP/VLBW or EP adults and controls

For TRAB-AS in the BLS, the estimated adjusted means between groups at each hierarchical step are shown in figure 1. Initially at step 1, the VP/VLBW groups' attention span ratings were z= -0.48 (-0.70, -0.25) lower than controls. At step 2, both inhibitory control and working memory were found to be significantly associated with TRAB-AS rating, with the difference in adjusted means between groups reducing to z=-0.21 (-0.43, 0.01) and no longer statistically significant. At step 3, IQ at 6 years old was also found to be significantly associated with TRAB-AS rating, further reducing the estimated adjusted means to a difference of z=-0.04(-0.26, 0.19). While at step 1, the difference in estimated adjusted means between VP/VLBW and controls was found to be 0.48, this reduced to 0.04 at step 4, (see figure 2). The final model for predicting TRAB-AS in the BLS explained 23% of the variance with working memory and IQ at 6 years old the only factors remaining significantly associated with attention span rating (Table 2).

For TRAB-AS in EPICure, the estimated adjusted means between groups at each hierarchical step are shown in figure 1. Initially at step 1, the EP groups' attention span ratings were z= -1.14 (-1.73, -0.55) lower than controls. At step 2, working memory and inhibitory controls significantly diminished the effect of birth group on attention span rating to z= -0.58(-1.21,0.06). At step 3, adding the measure of IQ at 6 years old, both executive functioning variables were no longer statistically significant and resulted in controls having an adjusted attention span of z=0.14 (-0.55, 0.83) lower than EP participants. While at step 1, the estimated difference in adjusted means found the EP group to have a deficit of z= -1.14, at step 4 with sex also introduced the difference had switched to controls having a deficit of z= 0.11 (see figure 2). The final model for TRAB-AS in EPICure explained 26% of the variance, with IQ at 6 years of age being the only remaining significant predictor (Table 2).

For BLS parent-reported ADHD-I symptoms, the estimated adjusted means for VP/VLBW and controls at each hierarchical step are shown in figure 2. Initially at step 1, the VP/VLBW group had an ADHD-I symptom z score 0.95 greater than the controls, 95% confidence interval 0.49 to 1.41. When inhibitory control and working memory were entered at step 2, both executive functioning measures were significantly associated with ADHD-I symptoms, with the difference in estimated adjusted means between VP/VLBW and controls reducing to z=0.50 (0.04, 0.95). It was not until step 3, when IQ at age 6 years was added, that the estimated mean differences between groups became statistically insignificant, reducing to a difference of z=0.03 (-0.43, 0.50). At step 4, the variable of sex did not significantly increase R^2 and only minimally influenced the estimated adjusted means 0.01(-0.46, 0.48). From the initial differences between VP/VLBW and controls at step 1 being z=0.95, the difference in estimated adjusted means between VP/VLBW and controls in the final model was reduced to a difference of z=0.01. The final model for BLS parent-reported ADHD-I symptoms explained 22% of the variance and was predominantly explained by IQ at 6 years of age and inhibitory control in adulthood (Table 2).

DISCUSSION

In the discovery sample of the BLS, we observed evidence of greater attention problems for VP/VLBW adults, as demonstrated by poorer observed attention span in comparison to controls, further validated by greater parent-reported ADHD-I symptoms. In contrast, we found no self-reported difference in ADHD between VP/VLBW and controls. These results were found to be robust, being replicated in the EPICure sample in which EP adults had shorter observer rated attention span but no self-reported differences in ADHD either. Our hypothesis, that differences in attention would be explained by executive functioning was only partially supported. In the BLS, measures of inhibitory control and working memory in adulthood partially explained the effect of VP/VLBW birth. However, after childhood IQ was accounted for, inhibitory control only remained significantly associated with parent-reported ADHD-I symptoms, while working memory only remained significantly associated with TRAB-AS ratings. For EPICure, while the effect of EP birth on TRAB-AS rating was explained by inhibitory control and working memory, neither factor remained significant after accounting for childhood IQ. The results from both cohorts indicate that while specific executive functioning measures can aid in explaining why VP/VLBW or EP adults show more attention problems than controls, childhood IQ explains a larger amount of the difference between groups.

The pattern of results from adulthood is largely in concordance with past research looking at attention problems in preterm children, suggesting specific problems of inattention rather than hyperactivity/impulsivity. Additionally, the greater relative differences found between EP and controls in EPICure than between the VP/VLBW and controls in the BLS may result from a "gestational gradient", whereby the risk of attention problems increases as gestational age at birth decreases.[1] The EPICure EP group were born on average 6 weeks more preterm than the BLS VP/VLBW group. Also consistent with this interpretation is the relatively poorer performances on measures of executive functioning and the larger deficits in general cognitive ability between EPICure's EP adults and controls than between BLS's VP/VLBW adults and controls. Alternatively, or additionally, year of birth (1985 vs 1995) and age of assessment (26 vs 19 years old) differed between the discovery sample (BLS) and the replication sample (EPICure). Regarding era of birth, previous studies[25,26] found that while survival of very preterm born babies has increased, there is little evidence of improved cognitive outcome across eras. Age of assessment may also be important if deficit in executive function and attention is due to developmental delay that may narrow with age. As the BLS' VP/VLBW participants were older than EPICure's EP participants, they may have had more time to 'catch up' in comparison to their respective control group. Nevertheless, our results were remarkably similar across cohorts despite differences in degree of prematurity and age of assessment, indicating generalisability of findings.

Within the general population and in VP/VLBW children, attention problems have been primarily associated with deficits in executive functioning,[5,8,27] however, we found inconsistent evidence for this after we controlled for childhood IQ. Our results are in line with Willcutt, Doyle and Nigg et al's (2005) postulation that deficits in executive function are important but are not the sole factor causing ADHD symptoms.[5] Alternatively, as our VP/VLBW and EP participants demonstrated a behaviourally distinct phenotype, composed primarily of inattention rather than hyperactivity/impulsivity, it may be that this phenotype has a different primary factor. The attention problems of VP/VLBW and EP adults, as shown here, would appear to be due to a general cognitive deficit rather than the specific executive functioning deficit seen in the general population. However, if inattention is a result of a specific executive functioning deficit it is also possible that our measures were not sensitive to those specific deficits. In childhood, inattention within the general population but also in VP/VLBW and EP participants has been found to be more closely related to visuo-spatial working memory rather than verbal working memory.[27–29] As our measures of working memory were verbal, it may be that we failed to assess the correct specific measures of executive functioning. While future studies should look to address this, the current results are in line with recent research suggesting the limited efficacy of working memory interventions on attention and working memory performance itself for VP/VLBW children.[30] If verbal working memory is both impervious to intervention and only partially related to inattention in VP/VLBW and EP adults, it suggests that interventions for VP/VLBW and EP children may be focused elsewhere.

The fact that childhood IQ was significantly related to attention problems in adulthood in both cohorts, regardless of how attention was assessed, and partially explained the effect of being born VP/VLBW or EP is pertinent. Intelligence is unlikely to be assessed independent of executive function in childhood. For example, the IQ test used (the K-ABC) , has some tasks that are related to executive functioning. However, the K-ABC is strongly correlated with the widely used Wechsler Intelligence Scale for Children, at r=.79 and .70 throughout childhood.[20,31] Thus, our results are unlikely to differ depending on the child IQ test used. Regardless, failing to control for general cognitive ability might lead to the potentially erroneous conclusion that a specific executive functioning is responsible for attention problems when it is instead part of a more general cognitive deficit. If early identification of VP/VLBW or EP children at risk of long-term attention problems is of primary importance, then IQ testing appears a relatively straightforward approach to do so. VP/VLBW and EP individuals have been found to be at increased risk of brain injury, such as reduced cholinergic basal forebrain integrity and decreased white and grey matter, which has been found to mediate the relationship between preterm birth and poorer IQ.[32,33] It may be that IQ scores in childhood act as an indicator of overall poor brain growth. This poor brain growth may result in long term behavioural deficits in domains such as inattention, but less so for behaviours regarding hyperactivity and impulsivity. The finding of a strong association between general cognitive ability and inattention are consistent with evidence from EPICure in childhood,[2] as well as other research finding strong links between general cognitive performance and behavioural difficulties for VP/VLBW children.[8,34]

Another important finding is that the method for assessing attention problems is key, with non-significant differences by self-report but larger differences when assessed through parent report or observer rating. When BLS VP/VLBW behaviour was rated by their parents or observer, more attention problems were found but this was not found for self-report. In EPICure parent report was unavailable but the results found a similar disparity between self-report and observer ratings. Overall, our results support other research into attention in extremely low birthweight adults and controls, finding no significant difference for self-reported ADHD of any subtype.[35,36] We can speculate that the VP/VLBW group's reporting of fewer symptoms as compared to parents is compatible with Festinger's theory of social comparison.[37] VP/VLBW and EP adults have been found to have a lower educational level and are more likely to be in manual employment.[38] An individual's primary comparison is with those they socialise with mostly, i.e. peers. Compared to peers in their social circle, VP/VLBW and EP adults may not consider themselves to have attention problems. In contrast, parents are more likely to compare their offspring to their birth cohort (i.e. all adults) and thus use a different comparison level and report more attention problems, similar to observation measures of attention. Regardless of why EP and VP/VLBW adults under report their own symptoms, these results are in concordance with studies in the general population. In both childhood and into adulthood, there is substantive evidence that individuals with attention problems report less symptoms than their parents or independent observers do.[39,40] Overall, self-report measures of ADHD may underestimate symptoms in VP/VLBW and EP adults and as such multi informants should be assessed.

There are clear strengths to this study. These include the use of two prospectively studied cohorts allowing for replication of findings. The use of identical measures for ADHD symptoms, observer rating of attention span, inhibitory control and child IQ in both cohorts reduces the influence of methodological issues in interpreting results. However, there are also limitations. Firstly, the rate of attrition was moderate to high, with remaining participants found to be of higher socioeconomic status in both cohorts. This potential bias is unlikely to have had an impact on our results, as regressions models may be only marginally affected by selective dropout;[41] nevertheless, bias cannot be excluded. The lack of parent report in EPICure and the difference in working memory assessments limited direct replication of some of the findings from the BLS. Though the two measures of verbal working memory have been found to be closely related,[19] the letter number sequencing task may be more associated with attention ratings due to its greater complexity.[42] Future research should look to address the importance of task complexity as well as assessing visuo-spatial working memory, which as previously noted may be more linked to attention deficits. Finally, while our study was able to assess multiple possible predictors of inattention, it had the limitation that we were unable to directly assess other important cognitive factors such as processing speed equivalently for both cohorts, as it has been noted as a core deficit for inattention in the general population and VP/VLBW children.[28,43] While working memory performance is thought to be at least partially reliant on processing speed,[44] directly testing whether this lower level ability is key to adult inattention could be pivotal for future interventions.

To conclude, this study provides further evidence for specific attention problems in early adulthood for VP/VLBW and EP in comparison to controls, replicating findings from childhood. While we found that adult executive functioning measures were associated with attention problems in adulthood, childhood IQ was a stronger and more consistent predictor in both the discovery and replication sample. Early assessment of cognitive ability would allow for early identification of VP/VLBW and EP children at risk for long term attention problems.

Abbreviations

ADHD Attention-Deficit/Hyperactivity Disorder

ADHD-I Attention-Deficit/Hyperactivity Disorder- Inattention

ADHD-H Attention-Deficit/Hyperactivity Disorder- Hyperactive/impulsivity

VP/VLBW Very preterm/Very low birthweight

EP Extremely Preterm

IQ Intelligence Quotient

ANT Attention Network Task

TRAB-AS Tester Rating of Adult Behaviour – Attention Span

References

1. Johnson S, Wolke D. Prematurity and low birthweight. In: Hopkins B, Geangu E, Linkenauger S, eds. The Cambridge Encyclopedia of Child Development. 2nd ed. Cambridge University Press; 2017:705-716. doi:10.1017/9781316216491.112

2. Johnson S, Kochhar P, Hennessy E, et al. Antecedents of Attention-Deficit/Hyperactivity Disorder symptoms in children born extremely preterm. J Dev Behav Pediatr JDBP. 2016;37(4):285-297. doi:10.1097/DBP.0000000000000298

3. Nadeau L, Boivin M, Tessier R, et al. Mediators of behavioral problems in 7-year-old children born after 24 to 28 weeks of gestation. J Dev Behav Pediatr JDBP. 2001;22(1):1-10.

4. Breeman LD, Jaekel J, Baumann N, et al. Attention problems in very preterm children from childhood to adulthood: the Bavarian Longitudinal Study. J Child Psychol Psychiatry. 2016;57(2):132-140. doi:10.1111/jcpp.12456

5. Willcutt EG, Doyle AE, Nigg JT, et al. Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Biol Psychiatry. 2005;57(11):1336-1346. doi:10.1016/j.biopsych.2005.02.006

6. Diamond A. Executive Functions. Annu Rev Psychol. 2013;64(1):135-168. doi:10.1146/annurev-psych-113011-143750

7. Burnett AC, Scratch SE, Anderson PJ. Executive function outcome in preterm adolescents. Early Hum Dev. 2013;89(4):215-220.

8. Aarnoudse-Moens CSH, Weisglas-Kuperus N, Duivenvoorden HJ et al. J. Executive Function and IQ Predict Mathematical and Attention Problems in Very Preterm Children. PLOS ONE. 2013;8(2):e55994. doi:10.1371/journal.pone.0055994

9. Engelhardt LE, Mann FD, Briley DA, et al. Strong genetic overlap between executive functions and intelligence. J Exp Psychol Gen. 2016;145(9):1141-1159. doi:10.1037/xge0000195

10. Wolke D, Schmid G, Schreier A, et al. Crying and Feeding Problems in Infancy and Cognitive Outcome in Preschool Children Born at Risk: A Prospective Population Study. J Dev Behav Pediatr. 2009;30(3):226. doi:10.1097/DBP.0b013e3181a85973

11. Eryigit Madzwamuse S, Baumann N, Jaekel J et al. Neuro-cognitive performance of very preterm or very low birth weight adults at 26 years. J Child Psychol Psychiatry. 2015;56(8):857-864. doi:10.1111/jcpp.12358

12. Costeloe K, Hennessy E, Gibson AT et al. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics. 2000;106(4):659-671.

13. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. Arch Dis Child. 2018;103(4):363-370. doi:10.1136/archdischild-2017-313414

14. Kooij JJS, Buitelaar JK, van den Oord EJ et al. Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med. 2005;35(6):817-827.

15. Wolke D. TRAB Tester's Rating of Adult Behavior (in German). Available from author upon request; 2012.

16. Fan J, McCandliss BD, Sommer T et al. Testing the Efficiency and Independence of Attentional Networks. J Cogn Neurosci. 2002;14(3):340-347. doi:10.1162/089892902317361886

17. von Aster M, Neubauer A, Horn R von. Wechsler Intelligenztest Für Erwachsene: WIE; Übersetzung Und Adaption Der WAIS-III. Harcourt Test Services; 2006.

18. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). San Antonio, TX: The Psychological Corporation; 2008.

19. Crowe SF. Does the Letter Number Sequencing Task Measure Anything More Than Digit Span? Assessment. 2000;7(2):113-117. doi:10.1177/107319110000700202

20. Kaufman AS, Kaufman NL. K-ABC: Kaufman Assessment Battery for Children: Interpretive Manual. American Guidance Service; 1983.

21. Marlow N, Hennessy EM, Bracewell MA, et al. Motor and Executive Function at 6 Years of Age After Extremely Preterm Birth. Pediatrics. 2007;120(4):793-804. doi:10.1542/peds.2007-0440

22. Wolke D, Meyer R. Cognitive status, language attainment, and prereading skills of 6-year-old very preterm children and their peers: the Bavarian Longitudinal Study. Dev Med Child Neurol. 1999;41(2):94-109.

23. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-802. doi:10.1093/biomet/75.4.800

24. Cohen J. A power primer. Psychol Bull. 1992;112(1):155.

25. Cheong JLY, Anderson PJ, Burnett AC, et al. Changing Neurodevelopment at 8 Years in Children Born Extremely Preterm Since the 1990s. Pediatrics. June 2017. doi:10.1542/peds.2016-4086

26. Twilhaar ES, Wade RM, Kieviet JF de, et al. Cognitive Outcomes of Children Born Extremely or Very Preterm Since the 1990s and Associated Risk Factors: A Meta-analysis and Meta-regression. JAMA Pediatr. 2018;172(4):361-367. doi:10.1001/jamapediatrics.2017.5323

27. Retzler J, Johnson S, Groom M, et al. Cognitive predictors of parent-rated inattention in very preterm children: The role of working memory and processing speed. Child Neuropsychol. 2018;0(0):1-19. doi:10.1080/09297049.2018.1510908

28. Mulder H, Pitchford NJ, Marlow N. Inattentive behaviour is associated with poor working memory and slow processing speed in very pre-term children in middle childhood. Br J Educ Psychol. 2011;81(1):147-160. doi:10.1348/000709910X505527

29. Martinussen R, Hayden J, Hogg-johnson S, et al. A Meta-Analysis of Working Memory Impairments in Children With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(4):377-384. doi:10.1097/01.chi.0000153228.72591.73

30. Anderson PJ, Lee KJ, Roberts G, et al. Long-Term Academic Functioning Following Cogmed Working Memory Training for Children Born Extremely Preterm: A Randomized Controlled Trial. J Pediatr. 2018;202:92-97.e4. doi:10.1016/j.jpeds.2018.07.003

31. Zins JE, Barnett DW. A validity study of the K-ABC, the WISC-R, and the Stanford-Binet with nonreferred children. *J Sch Psychol*. 1984;22(4):369-371. doi:10.1016/0022-4405(84)90024-4

32. Grothe MJ, Scheef L, Bäuml J, et al. Reduced Cholinergic Basal Forebrain Integrity Links Neonatal Complications and Adult Cognitive Deficits After Premature Birth. *Biol Psychiatry*. 2017;82(2):119-126. doi:10.1016/j.biopsych.2016.12.008

33. Nosarti C, Giouroukou E, Healy E, et al. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain*. 2008;131(1):205-217. doi:10.1093/brain/awm282

34. Burnett AC, Youssef G, Anderson PJ, et al. Exploring the “Preterm Behavioral Phenotype” in Children Born Extremely Preterm: *J Dev Behav Pediatr*. 2019;40(3):200-207. doi:10.1097/DBP.0000000000000646

35. Boyle MH, Miskovic V, Lieshout RV, et al. Psychopathology in young adults born at extremely low birth weight. *Psychol Med*. 2011;41(8):1763-1774. doi:10.1017/S0033291710002357

36. Johnson S, O'Reilly H, Ni Y, et al. Psychiatric Symptoms and Disorders in Extremely Preterm Young Adults at 19 Years of Age and Longitudinal Findings From Middle Childhood. *J Am Acad Child Adolesc Psychiatry*. 2019;58(8):820-826.e6. doi:10.1016/j.jaac.2019.02.020

37. Festinger L. A theory of social comparison processes. *Hum Relat*. 1954;7(2):117-140.

38. Mathiasen R, Hansen BM, Anderson A-MN, et al. Socio-economic achievements of individuals born very preterm at the age of 27 to 29 years: a nationwide cohort study. *Dev Med Child Neurol*. 2009;51(11):901-908. doi:10.1111/j.1469-8749.2009.03331.x

39. Owens JS, Hoza B. The role of inattention and hyperactivity/impulsivity in the positive illusory bias. *J Consult Clin Psychol*. 2003;71(4):680.

40. Knouse LE, Bagwell CL, Barkley RA,et al. Accuracy of self-evaluation in adults with ADHD: Evidence from a driving study. *J Atten Disord*. 2005;8(4):221-234.

41. Wolke D, Waylen A, Samara M, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *Br J Psychiatry*. 2009;195(3):249-256. doi:10.1192/bjp.bp.108.053751

42. Engle RW. Role of Working-Memory Capacity in Cognitive Control. *Curr Anthropol*. 2010;51(S1):S17-S26. doi:10.1086/650572

43. Diamond A. Attention-deficit disorder (attention-deficit/ hyperactivity disorder without hyperactivity): A neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). *Dev Psychopathol*. 2005;17(3):807-825. doi:10.1017/S0954579405050388

44. Fry AF, Hale S. Relationships among processing speed, working memory, and fluid intelligence in children. *Biol Psychol*. 2000;54(1):1-34. doi:10.1016/S0301-0511(00)00051-X

Figure Legends

Figure 1: Differences in Tester Rating of Adult Behaviour-Attention span (TRAB-AS) between VP/VLBW and EP with their respective control group at each step of the hierarchical regression for the Bavarian Longitudinal Study and EPICure. Error bars represent 95% confidence intervals

*Figure 2: D*ifferences in parent reported ADHD-Inattention symptomology between VP/VLBW and controls at each step of the hierarchical regression for the Bavarian Longitudinal Study. Error bars represent 95% confidence intervals

List of Supplemental Digital Content

- Supplementary digital content 1: Flow chart of participants (.docx)
- Supplementary digital content 2: Attention network task figure and description(.docx)
- Supplemental digital content 3:Correlation matrices between attention measures, executive and general cognitive functioning for the Bavarian Longitudinal Study and EPICure(.docx)

Table 1: Univariate differences between VP/VLBW or EP participants and controls

	Bavarian Longitudinal Study				EPICure			
	Mean difference (VP/VLBW-Control)	Mean difference 95% CI	Adjusted P-Value	Cohen's D	Mean difference (EP- Control)	Mean difference 95% CI	Adjusted P-Value	Cohen's D
ADHD- Inattention Self-Reported symptoms – Z scored	0.12	[-0.09, 0.34]	0.522	0.11	0.39	[0.03, 0.75]	0.084	0.34
ADHD- Hyperactivity/impulsivity Self-Reported– Z scored	-0.16	[-0.36, 0.03]	0.340	-0.17	-0.06	[-0.40, 0.29]	0.739	-0.05
ADHD- Combined Self-Reported –Z scored	-0.05	[-0.26, 0.15]	0.597	-0.05	0.19	[-0.16, 0.54]	0.543	0.17
ADHD- Inattention Parent Reported – Z scored	0.95	[0.49, 1.41]	<0.001	0.44	-	-	-	-
ADHD-Hyperactivity/impulsivity Parent Reported – Z scored	0.20	[-0.05, 0.44]	0.34	0.17	-	-	-	-
ADHD- Combined Parent Reported – Z scored	0.51	[0.19, 0.84]	0.01	0.33	-	-	-	-
Observer rating of attention span(TRAB-AS) – Z scored	-0.48	[-0.70, -0.25]	<0.001	-0.42	-1.14	[-1.73,-0.55]	0.001	-0.62
Inhibitory Control (ms)	27.53	[17.04, 38.01]	<0.001	0.52	41.86	[22.4, 61.33]	<0.001	0.69
Working Memory	-8.98	[-12.72, -5.24]	<0.001	-0.48	-10.37	[-14.77,-5.96]	<0.001	-0.75
IQ at 6 years	-16.49	[-19.81, -13.17]	<0.001	-0.99	-26.24	[-31.69, -20.79]	<0.001	-1.54

Note: ADHD(attention deficit hyperactivity disorder). Inhibitory Control as measured by the Attention Network Task. Working memory as measured by the letter number sequencing task in the BLS and backwards digit recall task in EPICure. IQ at 6 years as measured by the K-ABC task. P values are Adjusted using Hochberg's correction. Z- scored indicates that raw scores are standardised based upon the mean and standard deviation of the respective control group.

Table 2: Final multiple regression models (step 4) predicting standardised parent reported ADHD-I symptoms and TRAB-AS ratings in the Bavarian Longitudinal Study (BLS) and EPICure.

Predictor	BLS ADHD-I PR		BLS TRAB-AS		EPICure TRAB-AS	
	Beta	P-Value	Beta	P-Value	Beta	P-Value
Birth Group(0 = Control, 1 =EP/VP/VLBW)	0.00	0.971	-0.02	0.712	0.03	0.759
Inhibitory Control	0.14	0.006	-0.07	0.149	-0.11	0.114
Working Memory	-0.07	0.213	0.24	<0.001	0.12	0.165
IQ at 6 years	-0.35	<0.001	0.26	<0.001	0.39	<0.001
Sex (0 = Female, 1=Male)	0.06	0.218	0.03	0.566	-0.11	0.119
Total R^2	0.22		0.23		0.26	

Note: ADHD-I PR: Parent reported ADHD-inattention symptoms , TRAB-AS: observer rating of attention span. Inhibitory Control as measured by the Attention Network Task, working memory as measured by the letter number sequencing task in the BLS and backwards digit memory task in EPICure. IQ at 6 years as measured by the K-ABC task.

Figure 1

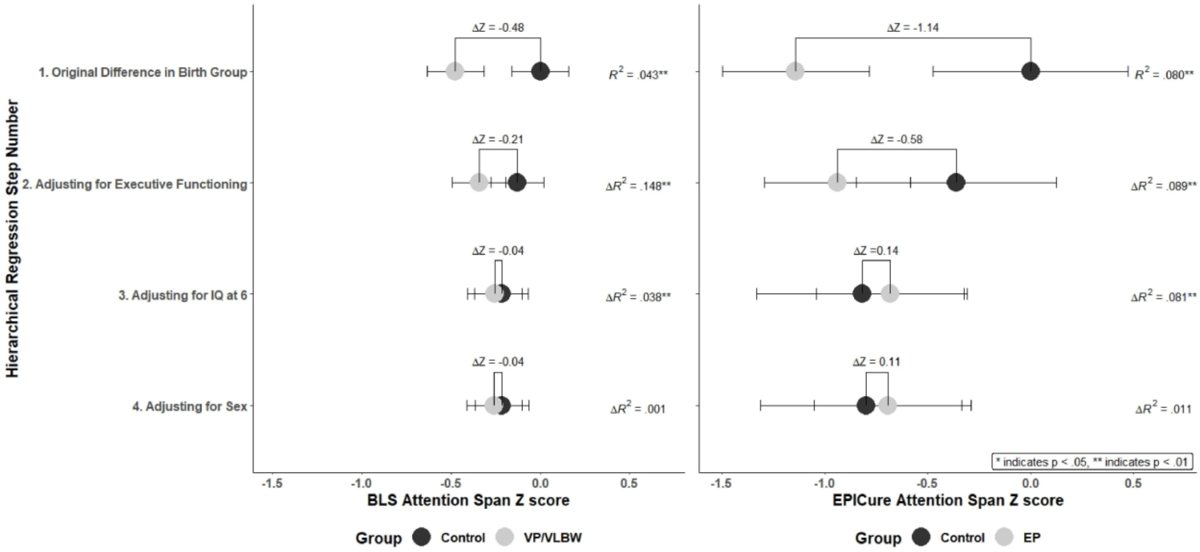
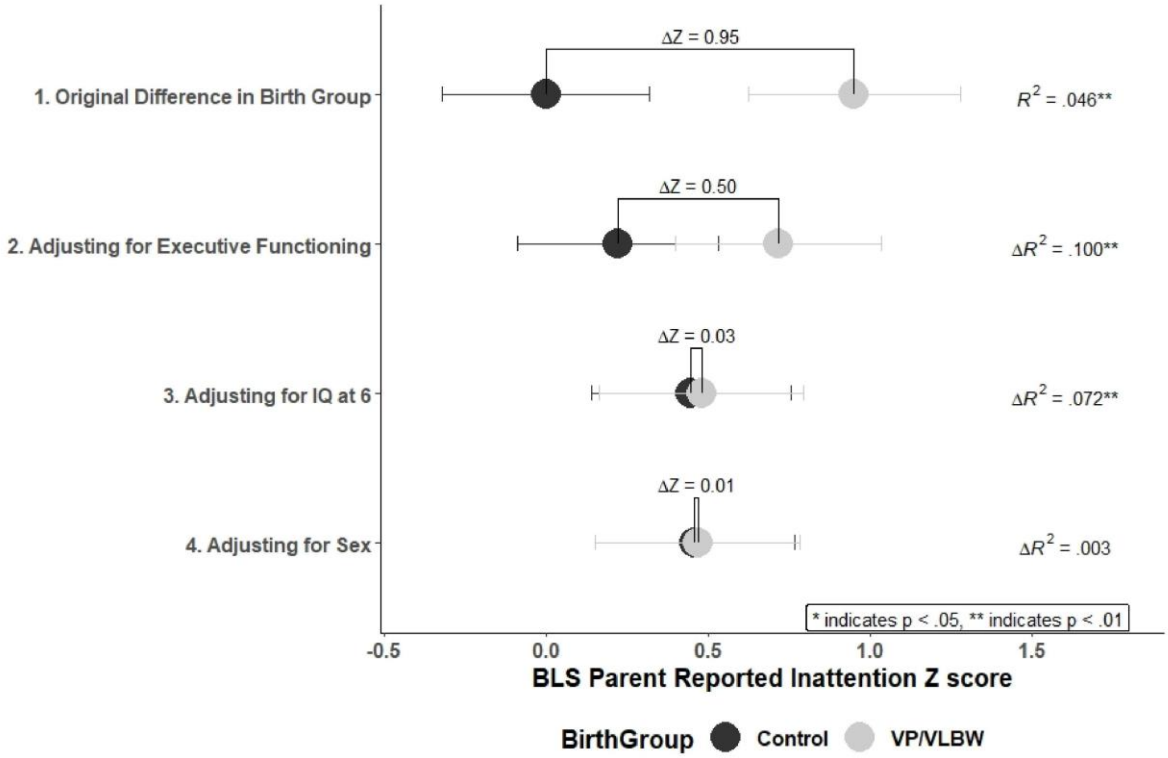


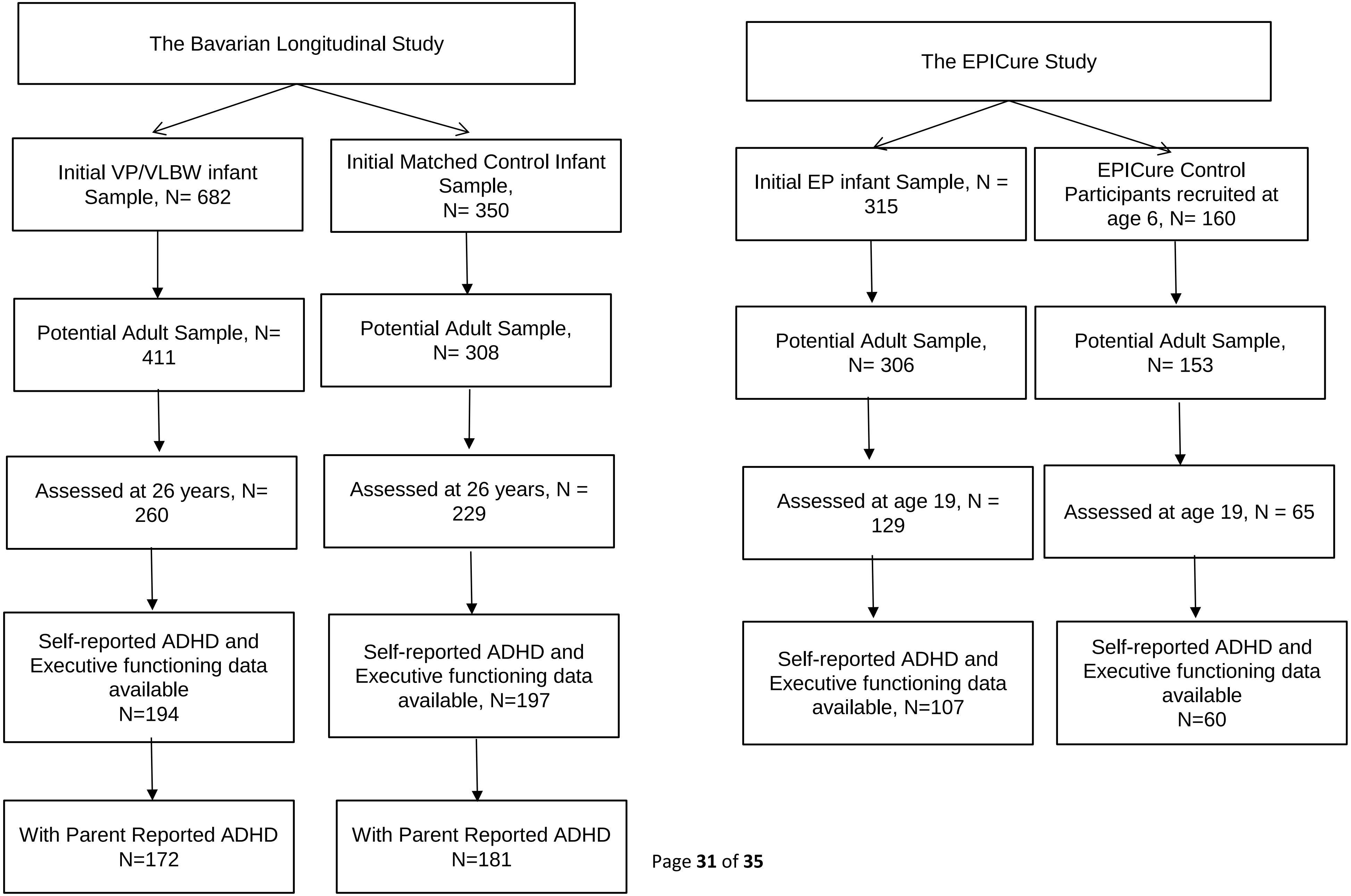
Figure 2



Supplementary Digital Content

Contents

Supplemental Digital Content 1



Supplemental Digital Content 2

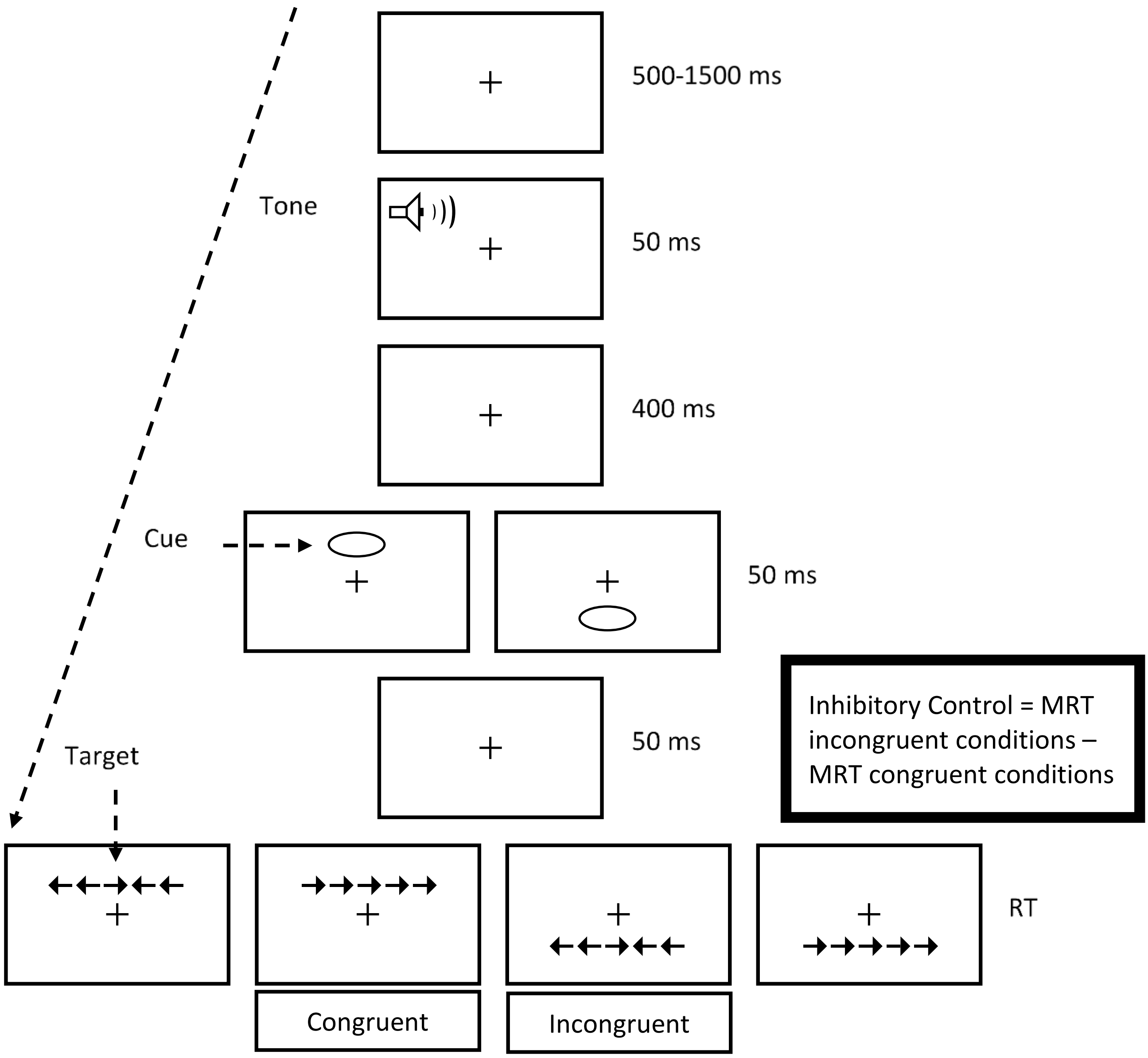


Figure 1. *Sequence of events in the ANT. A tone (present or absent) was followed by a spatial cue (top or bottom). The subsequent target arrow in the middle was either at the cued or uncued location and surrounded by congruent or incongruent flanker arrows. MRT = mean reaction time*

The ANT (Fan et al., 2002) was presented utilizing identical computers in both cohorts. Stimuli were presented on a 19” LCD monitor at approximately 57 cm and responses were recorded using the left and right arrow keys of a computer keyboard. Stimuli consisted of lines (thickness: 0.18° visual angle) and triangles drawn in grey (RGB values: 128, 128, 128) on a black background. The sequence of events in each trial is depicted in Figure 1 Each trial started with the presentation of a fixation cross (1.5°) at the centre of the screen. After a random duration of 500 to 1500 ms, an auditory tone (~400Hz) was either played for 50 MS or not played. 400 MS later the spatial cue – a horizontal non-filled oval (1.5° x 0.75°) – was presented 5.4° above or below fixation for 50 Ms. After a short gap of 50 MS, five arrows (2.25° x 1.06°) were presented also 5.4° above or below fixation. The target arrow in the middle (i.e., aligned with fixation) was enclosed by flanker arrows 5.4° and 2.7° to the left and to the right of the target (see Figure 1). The participant's task was to indicate the direction of the middle arrow by pressing the corresponding key. All stimuli were re-moved after the participant responded, and feedback was given after an erroneous response by presenting “error” for 1000 ms. Participants were instructed to respond as quickly and accurately as possible making less than 5% errors overall. The inter-trial interval was 1s.

Supplemental Digital Content 3

BLS Correlation Matrix of measures

	Self-Reported Inattention	Self-Reported Hyperactivity	Parent-Reported Inattention	Parent-Reported Hyperactivity	Observer Rating of Attention	Inhibitory Control	Working Memory
Self-Reported Inattention							
Self-Reported Hyperactivity	0.43****						
Parent-Reported Inattention	0.26****	0.08					
Parent-Reported Hyperactivity	0.20***	0.19***	0.61****				
Observer Rating of Attention	-0.10	-0.03	-0.32****	-0.17**			
Inhibitory Control	0.07	-0.03	0.29****	0.11*	-0.23****		
Working Memory	-0.13*	0.05	-0.29****	-0.15**	0.40****	-0.24****	
IQ at 6 Years	-0.09	0.03	-0.44****	-0.22****	0.43****	-0.37****	0.54****

p < .0001****, p < .001*** , p < .01**, p < .05*

EPICure Correlation Matrix of measures

	Self-Reported Inattention	Self-Reported Hyperactivity	Observer Rating of Attention	Inhibitory Control	Working Memory
Self-Reported Inattention					
Self-Reported Hyperactivity	0.58****				
Observer Rating of Attention	-0.33****	-0.31***			
Inhibitory Control	0.12	0.13	-0.21**		
Working Memory	-0.11	-0.11	0.35****	-0.10	
IQ at 6 Years	-0.28***	-0.11	0.48****	-0.23**	0.57****

p < .0001****, p < .001*** , p < .01**, p < .05*