Cognitive Performance and BMI in Childhood: Shared Genetic Influences Between Reaction Time But Not Response Inhibition

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Objective: The aim of this work is to understand whether shared genetic influences can explain the association between obesity and cognitive performance, including slower and more variable reaction times (RTs) and worse response inhibition.

Methods: RT on a four-choice RT task and the go/no-go task, and commission errors on the go/no-go task for 1,312 twins ages 7-10 years were measured. BMI was measured at 9-12 years. Biometric twin models were run to give an estimate of the genetic correlation ($r_G$) between body mass index (BMI) and three cognitive measures: mean RT (MRT), RT variability (RTV; the standard deviation of RTs), and commission errors (a measure of response inhibition).

Results: Genetic correlations indicated that 20%-30% of the genes underlying BMI were shared with both RT measures. However, only small phenotypic correlations between MRT and RTV with later BMI ($r_{Ph} = \sim 0.1$) were observed. Commission errors were unassociated with later BMI ($r_{Ph} = -0.03$, ns).

Conclusions: Our results are the first to demonstrate significant shared genetic effects between RT performance and BMI. Our findings add biological support to the notion that obesity is associated with slower and more variable RTs. However, our results also emphasize the small nature of the association, which may explain previous negative findings.

Introduction

Obesity now affects 20% of the US child/adolescent population, and is associated poorer academic achievement, suggesting that obesity affects cognitive development, as well as physical health (1-3). As academic achievement has been associated with cognitive control (4-6), accuracy on tasks which require response inhibition have been examined as a possible mediator of the association between BMI and academic success (7). Slower reaction times (mean reaction time, RT) is another aspect of cognitive performance associated with weight status (8,9). The meaning of slower RTs for underlying cognition is not clear and likely task-dependent. Slower RTs in situations requiring response inhibition may be a behavioral indicator of increased recruitment of cognitive resources related to the implementation of cognitive control, however on simple RT tasks longer RT can reflect slower motor response speed, and when seen with and a more variable pattern of RT may reflect attentional lapses (10,11). Thus, accuracy and RT data from neuropsychological tasks can provide insights into the cognitive profile associated with weight status.

Empirical evidence for the association between response inhibition and BMI in adolescents and children over 8 years is mixed, with some studies reporting associations between greater inhibition errors and higher BMI using the Stroop and five-digit task (12,13), others showing associations on some tasks (e.g., Stop Task) but not others (Circle Drawing task, Opposite Worlds task) (14), and others showing associations (with Go/No-Go commission errors) only when an interaction term with age was included (9). Evidence is also mixed in younger (<8 years) children, with some studies reporting lower

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Abbreviations

BMI, body mass index; MRT, mean reaction time; RTV, reaction time variability; SAIL, Study on Activity and Impulsivity Levels in Children; TEDS, Twins Early Development Study

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Go/No-Go response accuracy in obese compared with lean children (15) but others reporting no differences using either the Go/No-Go task (8) or a modified stop signal task (16). A smaller body of literature has been more consistent in reporting a positive association between BMI and mean RT (8,16), with one study additionally reporting more variable RTs with higher weight status (9).

The conflicting data observed could reflect true differences attributable to the nature of these tasks, or measurement error. Previous results from our group on mean reaction time (MRT) and reaction time variability (RTV) on the go/no-go task and a four-choice RT task (the Fast Task) have highlighted the importance of reducing task-specific variance (which subsumes some error) through aggregation. Aggregation is justified only where data share etiological variance (17), and our data show that MRT and RTV indeed share their underlying etiology on the go/no-go task and fast task (a four-choice RT task), with a genetic correlation between MRT and RTV of \( r_G = 0.62-0.64 \) (18). Aggregating data across several tasks can also reduce task-specific variance, increasing the detectable heritability (18-20). The power of aggregation to reduce error has previously been operationalized to test the association between BMI and task performance across the go/no-go and incompatibility tasks (9). Here, task-specific measures of MRT and RTV were not associated with BMI, but a latent factor from all four measures derived by principal component analysis was associated with BMI, with the effect moderated by age (9).

As illustrated above, relationships between measures of response inhibition, MRT, RTV, and BMI in young children are inconclusive, likely due to between-study differences in tasks, wide sample age ranges, and modest sample sizes. We therefore aimed to conduct an examination of genetic association between response inhibition, MRT and RTV, and BMI, in a large sample of twins (\( N = 1,312 \)), using a tightly defined age range of 7-10 years, and BMI reported at 9-12 years. BMI measured at the same time as cognitive performance is not available in our study; however, by incorporating BMI at a later time point we are able to take the additional, novel step of going beyond cross-sectional associations to see whether any associations between cognitive performance and BMI hold over time. Our design allowed us to examine BMI correlations in the largest child sample to date, and to conduct the first analysis of genetic association between BMI and response inhibition on the go/no-go task, and MRT and RTV across two tasks (the go/no-go and the fast task), as well as to examine longitudinal associations between the measures.

Methods
Sample and procedure
Participants were members of the Study of Activity and Impulsivity Levels in children (SAIL), a general population sample of twins aged between 7 and 10 years old. All twins were recruited from the Twins’ Early Development Study (20), a birth cohort study in which parents of all twins born in England and Wales during 1994-1996 were invited to enroll. The TEDS families are representative of the UK population with respect to parental occupation, education and ethnicity (22).

TEDS families were invited to take part if they fulfilled the following SAIL project inclusion criteria: twins’ birthdates between September 1, 1995 and December 31, 1996; lived within a feasible traveling distance from the research center; white European ethnic origin (to reduce population heterogeneity for molecular genetic studies); participation in previous TEDS follow-up studies, as indicated by return of questionnaires at either 4- or 7-year data collection point; no extreme pregnancy, perinatal difficulties, specific medical syndromes, chromosomal anomalies, or epilepsy; not participating in other current TEDS substudies; and not on stimulant or other neuropsychiatric medications.

Of the 1,230 suitable families contacted, 672 families (55%) agreed to participate, considered reasonable for a study requiring families to spend a day at the London research center. Thirty-two children were excluded due to: IQ < 70, epilepsy, autism, obsessive-compulsive, or other neurodevelopmental disorder, illness during testing or placement on stimulant medication for attention deficit hyperactivity disorder. The final sample consisted of 1,312 individuals: 257 monozygotic (MZ) twin pairs, 181 same-sex dizygotic (DZ), and 206 opposite-sex DZ twin pairs, as well as 24 singletons coming from pairs with one of the twins excluded.

Participants were invited to the research center for cognitive assessments. Two testers assessed the twins simultaneously in separate testing rooms. The tasks were administered in a fixed order as part of a more extensive test session, which in total (including breaks) lasted approximately 2.5 hours. The mean age of the sample was 8.83 (SD = 0.67), and half of the sample was female (\( N = 663, 50.5\% \)). Children’s IQs ranged from 70 to 158 (\( M = 109.34, \) SD = 14.72). Parents of all participants gave informed consent following procedures approved by the Institute of Psychiatry Ethical Committee.

Measures
Wechsler Intelligence scales for children, third edition [WISC-C-III (23)]. Vocabulary, similarities, picture completion and block design subtests from WISC-III were used to obtain an estimate of the child’s IQ, pro-rated following procedures described by (24).

The go/no-go task (25,26). On each trial, one of two possible stimuli appeared for 300 milliseconds (ms) in the middle of a computer screen. The child was instructed to respond only to the “go” stimuli and to react as quickly as possible, but to maintain a high level of accuracy. The proportion of “go” stimuli to “no-go” stimuli was 4:1. Three conditions were presented; we present data from the slow condition since this condition was the baseline condition (other conditions altered event rates and incentives to examine the effect on baseline performance). The slow condition had an inter-stimulus interval (ISI) of 8 seconds and consisted of 72 trials. Our response variables of interest were MRT to the “go” stimuli, RTV (the standard deviation of RTs) and errors of commission (an index of inhibition). Omission errors (not responding) were measured, but not frequent enough in our sample to analyze [see Ref. [20]].

The fast task (20,25). The baseline condition, with a fore period of 8 seconds and consisting of 72 trials, followed a standard warned four-choice RT task (27). A warning signal (four empty circles, arranged side by side) first appeared on the screen. At the end of the fore period of 8 seconds (presentation interval for the warning signal), the circle designated as the target signal for that trial was filled.
Reaction Time and BMI in Twins

**BMI.** BMI was calculated from parents’ reports of child height and weight, ascertained by questionnaire as part of the TEDS study when the twins were 9-12 years.

Within the parent TEDS study, for a subsample of 228 children not included in SAIL, children’s weights and heights were measured by researchers during home visits at ages 8-11 years. These researcher-measured metrics correlated with self-report metrics of height and weight measured within a year of each other at 0.90, and 0.92, respectively. Discrepancies were likely the result of a time lag between the two measures. Since data in biometric models are regressed for age and gender, to avoid over-correction we did not use BMI z-scores. When we compared results between BMI regressed for age and gender, to avoid over-correction we did not use BMI z-scores.

**Phenotype selection.** We include data from the baseline conditions only (i.e., go/no-go slow condition and fast baseline condition). Cross-task phenotypic correlations were moderate across the go-no/go and fast task data [MRT \( r = 0.44 \), 95% confidence interval (CI) 0.40-0.49; RTV \( r = 0.35 \), 95% CI 0.30-0.40]. Initial bivariate analyses indicated that across both cognitive indices, the underlying genetic etiology was largely shared [MRT genetic correlation \( r_G = 0.62 \), 95% CI 0.37-0.92; RTV \( r_G = 0.64 \), 95% CI 0.25-1.00] (18). In addition MRT and RTV largely share their etiology [\( r_G \) between mean score MRT across tasks and mean RTV across tasks = 86, 95% CI 0.73-1.00] (18). Given our previous analyses supporting the creation of composite RT scores across two independent samples (18,19), and work showing that the greatest associations between RT and BMI were for composite scores (9), we also ran additional models specifying a latent factor which loaded onto both MRT and RTV across both conditions, in order to capture the common cross-task cross-construct variation (18).

**Analyses**

The structural equation modeling program Mx (30) was used to conduct the genetic analyses and estimate correlations. Models were fit to age- and sex-regressed residual scores and the unstandardized residuals were transformed using a natural log transformation for all variables except commission errors, for which the residuals were normally distributed. As Mx provides a method for handling incomplete data by using raw maximum likelihood estimation, in which a likelihood statistic (\(-2\text{LL}\)) of the data for each observation is calculated, participants with incomplete data were included in the analyses.

**Genetic models.** Genetic models using the classical twin design operate under the assumptions that monozygotic (MZ) twins share 100% of their segregating alleles and dizygotic (DZ) twins share 50% of additive genetic influences (A), members of both MZ and DZ twins are 100% concordant for common environment (C), and do not correlate at all for child-specific influences (E).

**Univariate models.** Univariate analyses use within-pair correlations on a single trait to partition the variance of the trait into A, C, and E effects. Any possible measurement error is subsumed under the E effects (31). Twin correlations did not indicate the possibility of sex differences in the etiology of traits along the lines of previous analysis (18,19). Parameter estimates are presented from multivariate models, due to their increased power (32).

**Bivariate genetic models between BMI and cognitive data.** Bivariate genetic analyses use the power given by the MZ:DZ ratio of cross-twin trait correlations to decompose the covariance between traits into A, C, and E influences (i.e., one twin’s score on one phenotype; e.g., BMI with their co-twin’s score on a different phenotype such as response inhibition).

**Phenotypic correlations.** Phenotypic correlations (rPh) between traits are presented from bivariate genetic models, which accurately specify the family structure of the data, allowing generalizations to be made to non-twins. These yield highly similar point estimates to Pearson correlations, but allow adjustment to standard errors to reflect the non-independence of data points.

**Latent factor model (Figure 1).** Here the variance in variables is decomposed into that shared between RTV and MRT across the two tasks (a phenotypic latent factor), and that which is unique to each task or phenotype. A triangular, or Cholesky, decomposition is used to decompose the variance in each latent phenotype, and covariance between the phenotypes, into A, C, and E influences. This is mathematically converted to a correlated factors solution, which gives a direct estimate of the genetic and environmental correlations between a latent factor of MRT and RTV across tasks and BMI.

**Results**

**Phenotypic associations between commission errors, MRT, and RTV with BMI**

For means and standard deviations, see Table 1. Task-specific measures showed that in the biometrical model, the number of commission errors was not significantly associated with BMI (\( r_{\text{Ph}} = -0.03, 95\% \text{ CI} -0.09 \) to 0.04). MRT was significantly associated with BMI in the go/no-go task (\( r_{\text{Ph}} = 0.07, 95\% \text{ CI} 0.01-0.14 \)) and the fast task (\( r_{\text{Ph}} = 0.11; 95\% \text{ CI} 0.04-0.18 \)). RTV was not significantly associated with BMI in the go/no-go task (\( r_{\text{Ph}} = 0.06, 95\% \text{ CI} -0.01 \) to 0.12) but showed a significant positive association in the fast task (\( r_{\text{Ph}} = 0.09, 95\% \text{ CI} 0.02-0.16 \)). A latent factor approach revealed similar phenotypic associations between cognitive performance and BMI (\( r_{\text{Ph}} = 0.12, 95\% \text{ CI} 0.05-0.19 \); Figure 1).

**Genetic associations between MRT and RTV and BMI**

Cross-trait twin correlations for cognitive data, are presented in Table 1. As there was no phenotypic association between response inhibition score and BMI, the genetic association between these variables was not analyzed. Heritabilities for MRT and RTV (Table 2) replicate our previous findings, and have been presented extensively.
elsewhere (18,20,33). Variance components for BMI were A \(\approx 0.83\) (95% CI 0.66-0.89); C \(\approx 0.03\) (95% CI 0.00-0.18); E \(\approx 0.14\) (95% CI 0.11-0.17). Task-specific measures showed significant genetic correlations between MRT and BMI in the fast task (\(r_G = 0.25\), 95% CI 0.01-0.50) and go/no-go task (\(r_G = 0.31\), 95% CI 0.08-0.64), but not between RTV and BMI in either task (fast task \(r_G = 0.18\); 95% CI \(-0.04\) to 0.47; go/no-go task \(r_G = 0.19\), 95% CI \(-0.06\) to 0.62).

Although phenotypic correlations were small, power is increased in multivariate analysis, so we continued to multivariate genetic modeling (32). A latent factor loading onto all MRT and RTV measures showed a significant heritability of 54% (30%-67%), with the majority of the remaining variance being attributable to child-specific environmental effects. The latent factor showed significant genetic overlap with BMI (\(r_G = 0.27\), 95% CI 0.05-0.52), which, due to the very small child-specific environmental overlap with BMI (\(r_E = 0.04\), 95% CI \(-0.20\) to 0.13) indicated that genes accounted for almost 100% of the covariance between the latent factor and BMI.

All analyses were conducted controlling for IQ; as parameter estimates only changed minimally (\(\pm 0.01\)) and not in a consistent direction, these results are presented in the online supplementary material (Supporting Information Table 1).

**Table 1**

|                     | Fast task |           | Go/no-go task |           | Response inhibition |
|---------------------|-----------|-----------|---------------|-----------|---------------------|
|                     | MRT       | RTV       | MRT           | RTV       |                     |
| Mean (±SD), MZ twins| 954.69 (233.77) | 412.15 (280.93) | 587.64 (134.01) | 217.23 (138.94) | 8.11 (3.41) |
| Mean (±SD), DZ twins| 946.98 (243.42) | 412.88 (392.96) | 582.17 (128.69) | 255.15 (153.97) | 8.30 (3.45) |
| Phenotypic correlation with BMI | 0.11 (0.04-0.18) | 0.09 (0.02-0.16) | 0.07 (0.01-0.14) | 0.06 (0.01-0.12) | –0.03 (–0.09-0.04) |
| Cross-trait twin correlation with BMI, MZ twins | 0.12 (0.04-0.20) | 0.09 (0.02-0.17) | 0.10 (0.03-0.18) | 0.08 (0.01-0.16) | –0.06 (–0.14-0.01) |
| Cross-trait twin correlation with BMI, DZ twins | 0.04 (–0.06-0.12) | 0.03 (–0.06-0.11) | –0.02 (–0.10–0.07) | 0.01 (–0.07-0.10) | 0.07 (–0.01-0.15) |

Note: Mean BMI (±SD) was 17.18 (2.63) for MZ twins and 17.11 (2.52) for DZ twins.
**Discussion**

The current study addressed the issue of whether response inhibition, MRT and RTV share etiological pathways with BMI in children. We present the largest study to date to examine the association between computerized cognitive task data and BMI, and the first study to explicitly address the question of genetic correlations between the cognitive data and BMI. RT measures showed phenotypic correlations with later BMI, and for the first time shared genetic influences were identified between RT performance and BMI. However, the phenotypic and correlations were small, which, if confirmed, could limit clinical utility and partly explain previous conflicting results.

Since response inhibition in the go/no-go task did not show a significant association with later BMI, we cannot support its use in understanding the pediatric obesity at this time. Previous literature has shown conflicting results on the association between response inhibition and BMI in children with some data supporting an association (9,12,13,16) and other data refuting it (7,9). Since data both supporting the association and failing to show an association are available within the same study, a task-dependent nature (as opposed to an entirely sample-dependent nature) is likely. In addition, there may be an age effect, with stronger associations as children pass into adolescence (7,9). Since our own conclusions are limited to go/no-go task performance in 7- to 10-year-olds, we would encourage studies examining response inhibition on alternative tasks and investigating both task-specific and task-general effects.

Our observation of slower and more variable RTs with increasing BMI in both tasks, as well as when using RT data aggregated across tasks, is supported by a small but relatively consistent body of literature (8,9,16). Associations were small but small associations can still be informative on cognitive differences associated with weight status. In addition, associations were independent of IQ at both the phenotypic and genetic levels. This is not surprising given previous work by our group showing that cognitive performance does not share substantial genetic influences shared with IQ (18). Slower RTs may reflect slower motor speed, but the joint association with more variable RTs suggests lapses in attention may be part of the cognitive profile associated with obesity.

The mechanisms by which altered RTs are associated with BMI increases are beyond the scope of this study. Previous data have shown that the physiological changes accompanying increased adiposity, such as increased glycaemia and decreased blood flow to the prefrontal cortex are associated a particular cognitive profile, characterized by reduced motor speed (34-36), in addition to impairments on measures of executive function. However, more variable RTs have been shown to predict weight status, implying increased RTV may also precede the development of obesity, which is hypothesized to occur through a link with impulsive tendencies (37). We are unable to distinguish causal pathways using our current design and only emphasize a change in cognitive performance associated with BMI, which if replicated, may give insights into other aspects of cognition, such as attentiveness.

Our study provides the first evidence for shared genetic effects between RT data and BMI. Specifically, MRT and RTV showed small-to-moderate genetic correlations with BMI (rG = 0.19-0.31), suggesting that up to around 30% of the genetic variance between RT performance and BMI are shared. Given that our estimates are likely conservative (due to the time lag between the RT and BMI data collection points); these results lend significant biological support to the notion that altered RT is a component of the pediatric obesity phenotype. Our results may also explain data suggesting that ADHD (a disorder strongly associated with altered slower and more variable RTs) and BMI share a common genetic background in pediatric populations (38).
The shared genetic variance between RT measures and BMI raises the potential of RT indices as endophenotypes for childhood obesity. Endophenotypes are intermediate traits lying on the pathways between genes and disease outcome and may lie closer to the underlying genotype than the more distal disease measure, making them more etiologically homogenous than more complex disease measure (39), and potentially increasing the power to identify genes. Several criteria have been proposed for a trait to qualify as an endophenotype the most agreed upon being that: (1) the intermediate trait is heritable, (2) the intermediate trait is associated with the outcome of interest, and (3) the intermediate trait shares genetic variance with the outcome (39,40). Our previous analyses in a general population of 7- to 10-year-olds have demonstrated the heritability of MRT and RTV (18,20). Although phenotypic correlations are small, if replicated, the shared genetic influences between RT data and BMI indicate that genetic associations with RT phenotypes may also associate with pediatric obesity.

Our study had several limitations. First, although our neuropsychological data are strong and collected using a standardized protocol, the BMI was parent-reported and not collected concurrently with the cognitive data. Data on a group of twins from the parent study who are not part of the current sample support the use of self-reported BMI in our sample, but associations could have been stronger, and point estimates more accurate, given objectively measured BMI. However, the fact that we observed significant effects despite these limitations argues strongly for a true link between RT data and BMI. Finally, our conclusions regarding the lack of an association between response inhibition and BMI are hindered by having only go/no-go task data. Future research examine other tasks, and aggregate across multiple measures of response inhibition where this is supported by theoretical or empirically demonstrated shared variance across measures.

To our knowledge, this is the first twin study to examine the etiological relationship between BMI, and response inhibition and RT data. We were unable to support an association between response inhibition and BMI in the current dataset, but MRT and RTV emerged as promising phenotypes that could explain a modest portion of population variance in BMI, and demonstrated shared genetic effects with BMI. Our results argue for continued investigation of cognitive indices as endophenotypes for obesity, and support the need for future studies which can give insight into the biological and behavioral mechanisms underlying associations between BMI and cognitive performance.

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