Title: Computational modeling of the N-Back task in the ABCD study: associations of drift diffusion model parameters to polygenic scores of mental disorders and cardiometabolic diseases

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Abstract

Background Cognitive dysfunction is common in mental disorders and represents a potential risk factor in childhood. The nature and extent of associations between childhood cognitive function and polygenic risk for mental disorders is unclear. We applied computational modeling to gain insight into mechanistic processes underlying decision making and working memory in childhood and their associations with PRS for mental disorders and comorbid cardiometabolic diseases.

Methods We used the drift diffusion model to infer latent computational processes underlying decision-making and working memory during the N-back task in 3707 children aged 9-10 from the ABCD Study. SNP-based heritability was estimated for cognitive phenotypes, including computational parameters, aggregated N-back task performance and neurocognitive assessments. PRS was calculated for Alzheimer's disease (AD), bipolar disorder, coronary artery disease (CAD), major depressive disorder, obsessive-compulsive disorder, schizophrenia and type 2 diabetes.

Results Heritability estimates of cognitive phenotypes ranged from 12 to 39%. Bayesian mixed models revealed that slower accumulation of evidence was associated with higher PRS for CAD and schizophrenia. Longer non-decision time was associated with higher PRS for AD and lower PRS for CAD. Narrower decision threshold was associated with higher PRS for CAD. Load-dependent effects on non-decision time and decision threshold were associated with PRS for AD and CAD, respectively. Aggregated neurocognitive test scores were not associated with PRS for any of the mental or cardiometabolic phenotypes.

Conclusions We identified distinct associations between computational cognitive processes to genetic risk for mental illness and cardiometabolic disease, which could represent childhood cognitive risk factors.

Introduction

Mental disorders are highly complex, heritable, and polygenic (1). Aggregating many small effects of common single-nucleotide polymorphisms (SNPs) on mental disorders from genome-wide association studies (GWAS) allow for the construction of polygenic risk scores (PRS), reflecting an individual's cumulative genetic risk for a given trait or disorder. Mapping PRS for adult-onset disorders to relevant phenotypes in childhood represents an opportunity for discovering the expression of genetic liability in premorbid phases.

Cognitive functions are also heritable traits (2–4), and cognitive deficits are frequent in patients with mental disorder (5,6). Working memory dysfunction is commonly reported in mental disorders including schizophrenia (7), bipolar disorder (8) and major depressive disorder (MDD) (9), while impaired decision making is observed in, among other, obsessive-compulsive disorder (10), MDD (11) and schizophrenia (12,13).

Deficits in cognition have been found to precede the onset of illness, in some cases during childhood (14–17). Whether cognitive aberrations during childhood are associated with genetic liability for mental disorders is currently being explored. Recent studies have found PRS for schizophrenia to be positively (18), negatively (19) and not (20,21) associated with general cognitive function in childhood and adolescence, while others have reported negative associations between PRS for AD and memory (22) and between PRS for schizophrenia and emotion identification and verbal reasoning (23). It is currently unclear how cognitive variability in childhood is reflected in genetic liability for other mental disorders. Further, it is unclear how cognitive function relates to polygenic risk for cardiometabolic disease, which is highly comorbid with mental disorders (24). Taken together, an improved understanding of cognitive deficits during childhood for mental and cardiometabolic diseases with adult onset could give insight into the mapping between cognition and disease, and ultimately aid individual prediction.

Cognitive abilities are often inferred from observed behavior such as task accuracy or response time. Although identifying associations between mental disorders and observed behavior can have predictive value, measures of task accuracy and response time are inherently agnostic about their computational origins. Poor accuracy could for

example result from impulsive decision-making or from a low signal-to-noise ratio in information accumulation. Computational approaches, in contrast, allow for model-based delineations of latent cognitive processes (25), and have provided insight into the computational cognitive processes underlying aberrant learning and decision-making in clinical groups (e.g. (26–29)). Further, individual-level parameters from computational models have been shown to be more sensitive to diagnosis (30) and clinical outcome (31) than task accuracy and response time.

Computational modeling could thus aid in identifying mechanistic cognitive processes associated with genetic liability for mental disorders. To this end we took a computational psychiatry (32) approach to map associations between latent cognitive processes and PRS for mental disorders. We applied the drift diffusion model (DDM) (33) to performance on the N-back task, a decision-making task probing working memory capacity, from 3707 children aged 9 to 10 in the Adolescent Brain Cognitive DevelopmentSM (ABCD) study (34–37) baseline sample. DDM analysis allowed us to estimate individual computational parameters during two load conditions (0-back and 2-back), including evidence accumulation, speed-accuracy tradeoff, response bias and time spent on motor and perceptual processes. PRS were calculated for AD (38), bipolar disorder (39), MDD (40), OCD (41) and schizophrenia (42). In addition, driven by the high occurrence of somatic comorbidity (43), the genetic overlap between cardiometabolic disease and mental illness (44), and associations between cardiometabolic disease and cognition (45), we calculated PRS for coronary artery disease (CAD) (46) and type 2 diabetes (T2D) (47).

We used genome-wide complex trait analysis (GCTA) (48) to assess whether DDM parameters represent heritable traits. Next, we tested for associations between DDM parameters and PRS using Bayesian linear multilevel models, which allowed us to describe uncertainty in estimates. To provide a comparison to DDM parameters we also tested for associations with response time and task accuracy as well as aggregated neuropsychological scores as a proxy for general cognitive ability.

Methods and Materials

Participants

The total sample consists of 11875 children aged 9-10 years. We analyzed data made available through the curated data release 2.0.1 (DOI:10.15 154/1504041). Informed written consent for child and parent was obtained from parents, and child participants separately completed a written assent.

N-back task

The Emotional N-back task (49,50) consisted of 160 trials divided into 2 runs. The task was performed in the scanner while collecting functional MRI data. Each run consisted of 8 blocks, each with 10 trials. The objective was, for each trial, to decide whether the current stimulus matched a target stimulus (Figure 1a). In the 0-back condition the target stimulus was presented before the first trial in each block, and the participants were asked to decide whether the current stimulus matched the target stimulus. In the 2-back condition participants responded whether the stimulus on the current trial matched the stimulus presented 2 trials back. The stimulus and target matched in 20% of the trials. For the remaining trials the stimulus did not match the target, and the stimulus on the current trial either had (lure, 25% of trials) or had not (non-lure, 55%) been presented earlier in the block.

Stimulus-category (house and happy, fearful or neutral faces) varied across blocks, but was not incorporated into the current analyses, as it would result in too many parameters for reliable subject-level estimates. Information regarding the condition (and for the 0-back condition the target stimulus) was presented for 2500 ms at the start of each block. The stimulus was preceded by a plus sign presented for 1000 ms. The stimulus and the stimulus-response mapping were presented for 2000 ms.

The analysis included data from participants with recorded response on at least 50 of the total 160 trials to ensure reliable measures of performance. 8077 participants fulfilled this criterion. Data on one or more variables of interest were missing from 248 participants (Supplemental Table S1), for which data were imputed using the R package mice (51). Participants with a task accuracy below 60% (N=468) were excluded, resulting in a sample of 7609 participants. Next, since the PRSs were derived from samples of

European ancestry we excluded participants of non-European origin. The final sample included 3707 participants.

Figure 1. a, Emotional N-back task. During the 0-back condition (top) participants were instructed to decide whether a stimulus matched the target stimulus presented at the start of each block. During the 2-back condition (bottom) participants were instructed to decide whether currently presented stimulus matched the stimulus presented 2 trials back. Figure adapted from (35). **b**, Illustration of the drift diffusion model applied to the N-back task. The model assumes decision makers accumulate evidence until reaching a threshold to decide whether the current stimulus is a target (upper bound) or non-target (lower bound). Illustrated here are three simulated decisions, one for each stimulus type (lure, non-lure and target). The rate and direction at which evidence is accumulated depends on the drift rate. Here, sample paths were simulated with a drift rate of -2.5 (lure), -2.3 (non-lure) and +3.05 (target). NDT = non-decision time.

Drift diffusion model

We analyzed trial-by-trial choice and response time data on the N-back task with the DDM, a cognitive process model that describes two-alternative forced choice decision-making as a noisy accumulation-to-bound process (Figure 1b). The DDM provides good fits to observed choice and response time distributions (52). The accumulation-to-bound processes proposed by sequential sampling models, including the DDM, have been shown to correlate with neural firing patterns during decision-making in primates, suggesting that the model captures neural implementations of decision-making, providing a link between behavior and neural activity (53).

The DDM has four main parameters. Drift rate (v) reflects the rate of evidence accumulation, where stronger drift rate leads to faster and more accurate decisions, due to less impact of noise. Decision threshold (a) captures the speed-accuracy tradeoff, where

wider decision thresholds require more evidence to be accumulated to reach a decision. This will lead to slower, but more accurate decisions. The starting point bias parameter (z) captures the starting point of the accumulation process. Lastly, non-decision time (ndt) captures the time spent on encoding the stimulus and motor response, where shorter non-decision time reflects that less time is spent on stimulus encoding and motor response. The parameters of the DDM can be estimated using the Wiener first passage time likelihood function (54), and thus allows inference on how parameters vary between groups, individuals, and task manipulations.

N-back DDM: For the N-back task we assumed that participants could be biased towards responding target or non-target, and therefore coded upper bound responses as target responses and lower bound responses as non-target (Figure 1b). We allowed the rate of evidence accumulation to differ across stimulus type, and thus estimated separate drift rates for target, lure and non-lure stimuli. Further, to capture effects of load we estimated all parameters separately for the 0-back and 2-back conditions. In total, 12 parameters were estimated per subject in a mixed model using the Wiener first passage-time distribution to calculate the likelihood of the response times of choices x ,

$$RT(x) \sim Wiener(a_{s,c}, ndt_{s,c}, z_{s,c}, v_{s,c,stim}),$$

where a = decision threshold, c = condition (0-back or 2-back), ndt = non-decision time, RT = response time, s = subject, $stim$ = stimulus (target, lure, non-lure), v = drift rate, x = choice (target or non-target), z = starting point bias. In addition, we estimated group-level variability parameters for non-decision time.

From the 12 parameters we computed overall scores for each of the 4 cognitive processes, i.e., an average individual value for a , ndt , v and z across conditions and stimuli. We further calculated load-effects for each parameter by subtracting estimates for the 0-back from the 2-back condition.

Figure 2a and b show that the model fit was good, and that predicted choice, response time and response time distributions (Supplemental Figure S1) across conditions closely matched the observed data. Briefly, Figure 2c shows that reduced accuracy and

slower response times in the 2-back compared to 0-back condition was reflected as lower drift rate in the 2-back condition, with the strongest effect for lures, likely reflecting a higher propensity to mistake lures for targets. Participants were more biased towards responding target in the 2-back condition, reflected in an increased starting point bias towards the target boundary. Lastly, participants increased the decision threshold in the 2-back compared to 0-back condition, which counteracts the effect of higher difficulty on accuracy but also leads to slower responses.

Figure 2. Model fit and group parameter estimates. Observed (green) and predicted (orange) mean and standard deviation accuracy (a) and response time (b) across condition (0-back and 2-back) and stimuli (lure, non-lure, target). The model slightly overpredicted accuracy for target responses, while accuracy for

non-lures was slightly underpredicted. The model shows a good prediction of the response time distribution, but slightly overpredicts mean response time for targets in the 2-back condition. (c) Mean estimated parameters and their 95 % highest density interval across 0-back (red) and 2-back (blue) conditions and, for drift rate (v), stimuli (lure, non-lure, target). Positive (negative) drift rate (v) values indicate evidence is accumulated toward responding target (non-target). a = decision threshold, ndt = non-decision time, v = drift rate, z = starting point bias.

NIH toolbox

Participants completed the NIH toolbox (<http://www.nihtoolbox.org>), a computerized test battery comprising 7 tasks spanning executive function, working memory, episodic memory, attention, processing speed and language (55). We performed principal component analysis on uncorrected scores from all 7 tasks and included the first component in analyses as a measure of general cognitive ability. See (56) for more details.

Supplemental Figures S2 and S3 show the distribution of the included variables across participants.

Statistical analysis

Drift diffusion model

We used the python package HDDM (57) to model choice and response time data from the N-back task with Bayesian hierarchical estimation. As running all subjects in a single model would be too time-consuming, we randomly assigned subjects to one of 40 groups and ran Bayesian hierarchical models for each of these 40 groups.

Three chains, each with 2000 samples, were estimated for each group. The first 1000 samples were discarded as burn-in, to allow the sampling process to identify the region of best-fitting values in the parameter space. The models were estimated to be reliable, meaning that rerunning the models yielded similar parameter estimates. This was measured with the Gelman-Rubin statistic (58), which was below 1.1 for all group and subject parameters, indicating convergence. Scripts for HDDM analyses can be found at <https://osf.io/ubezy/>.

Genetic data

Genotyping on saliva samples collected at the baseline visit was performed using the Smokescreen array, consisting of 646 247 genetic variants. Following (59) we removed genetic variants that were not called in at least 95% of the sample and individuals with more than 20% missing data. Variant imputation was performed on 517 724 single-nucleotide polymorphisms (SNP) and 10659 participants with the Michigan Imputation Server using hrc.r1.1.2016 reference panel, Eagle v2.3 phasing and multiethnic imputation process. PLINK was used to convert dosage files to plink files, using a best guess threshold of 0.9 for each locus. Further, PLINK was used for post imputation quality control, filtering out variants with an imputation INFO score below .5, a minor allele frequency below .001, failing Hardy-Weinberg equilibrium at $p=10^{-9}$, and missingness above 5%, as well as individuals missing more than 10% of variants. After these steps, 14 754 215 SNPs and 10 660 individuals remained.

Heritability

We used the GCTA-GREML analysis (54) (60,61) in GCTA (48) to estimate SNP-based heritability of DDM parameters, response time, accuracy and NIH toolbox scores using a 0.05 relatedness threshold and 20 ancestry components of the GRM as covariates.

Polygenic Risk Scores

Using PRSice v2 (62) we calculated polygenic scores for AD (38), bipolar disorder (39), CAD (46), MDD (40), OCD (41), schizophrenia (42) and T2D (47). We processed the GWAS summary statistics using a standardized pipeline (https://github.com/precimed/python_convert) and ran PRSice using default settings. We performed principal component analysis on PRS across all p-thresholds and used the first component of this analysis to associate to cognitive phenotypes.

Bayesian linear multilevel models

We tested for associations between cognitive phenotypes (computational parameters, mean response time and accuracy from the N-back task, WM load-effects for

computational parameters, response time and accuracy, and the first principal component calculated from the NIH toolbox) and polygenic scores with Bayesian linear multilevel models using brms (63), built on top of Stan (64). Models were run for all combinations of cognitive phenotypes and polygenic. Further, we tested the effect of load by computing the difference between parameter estimates (and response time and accuracy) between the 2-back and 0-back conditions. All models included sex and age as fixed effects and scanning site, family (siblings and twins) and model group (40 pools of subjects used for DDM analysis) as random effects:

$$\begin{aligned} \text{cognitive phenotype} \sim & PRS + age + sex + (1|site) + (1|family) \\ & + (1|model\ group) \end{aligned}$$

Models also included 10 genetic ancestry PCs and genetic batch as covariates. Priors strongly centered around 0 ($M = 0$, $SD = 0.5$) were used for all coefficients to reduce the likelihood of false positives. All variables were standardized prior to analysis. Scripts for Bayesian linear multilevel model analyses can be found at <https://osf.io/ubezy/>.

Statistical inference

We describe the effect size of predictors as the mean and the 95% highest density interval (HDI) of posterior distributions (65).

Results

SNP-based heritability

Individual differences in DDM parameters showed moderate SNP heritability (*Decision threshold*: $h^2 = 0.16$; $SE = 0.05$; *Non-decision time*: $h^2 = 0.19$; $SE = 0.05$, *Drift rate*: $h^2 = 0.21$; $SE = 0.05$, *Bias*: $h^2 = 0.12$; $SE = 0.06$). Similar results were found for response time ($h^2 = 0.16$; $SE = 0.05$) and accuracy ($h^2 = 0.20$; $SE = 0.05$), while heritability of the first principal component from NIH toolbox was estimated to $h^2 = 0.39$ ($SE = 0.05$).

Table 1. Posterior distributions of associations between cognitive phenotypes and clinical and polygenic scores.

Cognitive Phenotype	PRS AD	PRS BD	PRS CAD	PRS MDD	PRS OCD	PRS SZ	PRS T2D
	mean (95% HDI)	mean (95% HDI)	mean (95% HDI)	mean (95% HDI)	mean (95% HDI)	mean (95% HDI)	mean (95% HDI)
Decision Threshold	-0.005 (-0.037, 0.028)	0.014 (-0.019, 0.047)	-0.018 (-0.053, 0.016)	0.008 (-0.029, 0.043)	0.005 (-0.028, 0.039)	0.012 (-0.021, 0.045)	-0.011 (-0.045, 0.024)
Drift Rate	-0.024 (-0.055, 0.007)	-0.007 (-0.04, 0.025)	-0.043 (-0.075, -0.009)	-0.019 (-0.054, 0.016)	0.005 (-0.026, 0.039)	-0.043 (-0.074, -0.009)	-0.002 (-0.035, 0.032)
Non-Decision Time	0.042 (0.01, 0.073)	0.016 (-0.015, 0.049)	-0.067 (-0.099, -0.033)	0.021 (-0.014, 0.056)	0.017 (-0.016, 0.048)	-0.002 (-0.034, 0.03)	-0.029 (-0.062, 0.004)
Bias	0.011 (-0.019, 0.043)	0.003 (-0.029, 0.034)	-0.008 (-0.041, 0.025)	0.025 (-0.008, 0.061)	-0.021 (-0.054, 0.01)	-0.022 (-0.054, 0.01)	-0.018 (-0.051, 0.015)
WM Accuracy	-0.01 (-0.043, 0.023)	-0.011 (-0.044, 0.021)	-0.001 (-0.035, 0.033)	0.011 (-0.026, 0.046)	-0.01 (-0.043, 0.024)	-0.009 (-0.042, 0.024)	-0.025 (-0.059, 0.01)
WM Reaction Time	-0.024 (-0.056, 0.009)	0.005 (-0.028, 0.038)	-0.02 (-0.054, 0.014)	-0.022 (-0.059, 0.014)	0.007 (-0.026, 0.041)	-0.019 (-0.052, 0.015)	-0.013 (-0.046, 0.023)
WM Drift Rate	0 (-0.032, 0.033)	-0.019 (-0.053, 0.014)	0.021 (-0.013, 0.055)	0.022 (-0.014, 0.057)	-0.014 (-0.048, 0.019)	0.01 (-0.023, 0.043)	-0.021 (-0.056, 0.014)
WM Decision Threshold	0.002 (-0.03, 0.033)	0.008 (-0.024, 0.041)	-0.044 (-0.079, -0.01)	-0.018 (-0.054, 0.018)	0.021 (-0.011, 0.055)	-0.023 (-0.056, 0.01)	-0.021 (-0.054, 0.014)
WM Non-Decision Time	-0.037 (-0.07, -0.005)	-0.028 (-0.061, 0.005)	0.015 (-0.02, 0.049)	-0.003 (-0.039, 0.034)	-0.015 (-0.048, 0.018)	0.006 (-0.026, 0.041)	-0.008 (-0.042, 0.026)
WM Bias	-0.003 (-0.034, 0.03)	0.024 (-0.008, 0.056)	-0.023 (-0.057, 0.01)	0.004 (-0.031, 0.038)	-0.004 (-0.037, 0.028)	-0.021 (-0.053, 0.013)	-0.007 (-0.042, 0.026)
Response Time	0.046 (0.014, 0.077)	0.016 (-0.016, 0.048)	-0.046 (-0.079, -0.014)	0.022 (-0.013, 0.056)	0.012 (-0.02, 0.044)	0.017 (0.016, 0.048)	-0.032 (-0.065, 0.002)
Accuracy	-0.031 (-0.063, 0.002)	-0.004 (-0.037, 0.028)	-0.039 (-0.073, -0.005)	-0.013 (-0.048, 0.023)	0.005 (-0.029, 0.037)	-0.038 (-0.072, -0.007)	-0.004 (-0.038, 0.03)
NIH Toolbox	-0.026 (-0.056, 0.005)	0.008 (-0.023, 0.038)	-0.027 (-0.059, 0.005)	-0.018 (-0.052, 0.015)	-0.003 (-0.034, 0.028)	-0.027 (-0.059, 0.004)	-0.011 (-0.043, 0.021)

AD = Alzheimer's disease, BD = bipolar disorder, CAD = coronary artery disease, HDI = highest density interval, MDD = major depressive disorder, NIH Toolbox = first principal component from the NIH cognitive test battery, OCD = obsessive-compulsive disorder, PRS = polygenic risk score, SZ = schizophrenia, T2D = type 2 diabetes, WM = working memory.

Associations between cognitive phenotypes and polygenic scores

Figure 3 and Table 1 summarize results from the Bayesian linear multilevel models estimating the association between cognitive phenotypes and polygenic scores for mental illness and cardiometabolic disease.

Higher PRS for AD was associated with slower responses (beta = 0.05 95% highest density interval (HDI) [0.01, 0.08]), reflected in longer non-decision time (0.04 [0.01, 0.07]).

Higher PRS for CAD was associated with lower accuracy (-0.04 [-0.07, -0.01]) and faster responses (-0.05 [-0.08, -0.01]), reflected in lower drift rates (-0.04 [-0.08, -0.01]) and faster non-decision times (-0.07 [-0.1, -0.03]).

Higher PRS for schizophrenia was also associated with lower task accuracy (-0.04 [-0.07, -0.01]), reflected in lower drift rates (-0.04 [-0.07, -0.01]).

Working memory contrasts, captured as the difference between 2-back and 0-back conditions in the N-back task, were found to be negatively associated with PRS for AD (-0.04 [-0.07, -0.01]) on non-decision time, and with PRS for CAD on decision thresholds (-0.04 [-0.08, -0.01]).

None of the polygenic scores were associated with the first principal component from the NIH toolbox (Table 1).

Figure 3. Posterior distributions for the association of polygenic scores on cognitive phenotypes. Error bars represent 95% highest density interval. AD = Alzheimer’s disease, BD = bipolar disorder, CAD = coronary artery disease, MDD = major depressive disorder, NIH Toolbox = first principal component from the NIH cognitive test battery, OCD = obsessive-compulsive disorder, PRS = polygenic risk score, SZ = schizophrenia, T2D = type 2 diabetes, WM = working memory.

Discussion

Cognitive impairments are frequently observed in patients with mental disorders, and often precede the emergence of clinical symptoms (66). While not included among the diagnostic criteria, mapping specific cognitive functions to polygenic scores for mental illness in children could provide new knowledge on the cognitive architecture of psychopathology.

We used computational modeling to identify and associate latent variables of decision-making and working memory in 3707 children to polygenic scores for mental

illness and cardiometabolic disease. Individual variation in computational parameters were reflected in genetic variability, suggesting the parameters represent heritable phenotypes. We found small but robust associations between DDM parameters and polygenic scores for mental illness and cardiometabolic disease. The cognitive measures associated with PRS were related to task performance across load-conditions, and to a lesser extent to effects of load, suggesting a link to decision making in general, and not to aberrations in working memory. We did not find any associations of genetic liability to general cognitive function, as reflected in the first principal component of the neurocognitive battery.

Our analyses revealed several associations between DDM parameters and polygenic scores. Despite identifying associations also to response time and accuracy, computational modeling gives insight into the latent computational processes that give rise to alterations in observed behavior. Higher polygenic scores for AD were associated with slower responses, which were captured by the DDM as longer non-decision. Premorbid cognitive dysfunction has been shown in preclinical AD and as a predictor of progression from mild cognitive impairment (MCI) to AD in older adults (16,67). Associations between PRS for AD and non-declarative memory, but not executive memory, in children aged 6-14 has been reported (22). Longitudinal studies could test whether these cognitive profiles are predictive of AD over and above the polygenic scores.

Higher polygenic scores for schizophrenia were associated with slower evidence accumulation and lower accuracy. These results are in line with case-control studies reporting impairment in schizophrenia for decision making (12,13). Previous studies have reported negative (19,68), positive (18) and no associations (21,69,70) between polygenic scores for schizophrenia and cognitive function across age spans in the general population. A longitudinal study showed that polygenic risk for schizophrenia was not associated with childhood cognitive performance, but with the rate of cognitive decline from age 11 to 70 (71). These results were based on general cognitive function, for which we did not find an association. Instead, focusing on domain-specific cognitive functions and their computational processes could be more sensitive to underlying aberrations captured by genetic liability.

Although working memory is strongly linked to mental disorder through case-control studies (7–9), our analyses did not identify associations between reduced working memory capacity, through reduced accuracy or drift rate, and heightened polygenic risks for the included mental and cardiometabolic disorders. The only polygenic associations to working memory load was altered adjustment of speed-accuracy tradeoff for CAD and changes in non-decision time for AD, which was not reflected in task accuracy or response time.

Although the first principal component from the NIH toolbox was estimated to be more than twice as heritable as phenotypes from the N-back task, we found no associations to polygenic scores. These results are in line with previous studies not reporting associations between polygenic risk for mental illness and general cognitive function (21,69,70). Future investigations of follow-up data from the ABCD study can indicate whether speeded decision-making, and not WM capacity or general cognitive ability, are predictive of mental illness in adolescence.

The work described here is not without limitations. First, the computational parameters from the DDM cannot identify the separate contributions of working memory components, including the active maintenance and updating of target stimuli, and the inhibition of non-N stimuli. Although biophysical models of these processes exist (72), to our knowledge, they cannot be used for model fitting on a subject level (although see (73) for computational modeling of an alternative working memory task). Second, due to the block design used for fMRI scans, which does not allow insight into trial-by-trial brain activity, we did not analyze the accompanying fMRI data and therefore cannot describe the association between computational parameters and their neural underpinnings.

In conclusion, we identified associations between computational cognitive processes and polygenic scores for mental illness and cardiometabolic disease in children aged 9-10 years. Recent studies have shown that the associations between psychological variables and mental disorders in large datasets typically are small (74). The results reported here are no different. However, mapping the associations between computational cognitive processes and genetic load for mental disorders can improve our understanding of the small but robust effects that do exist, and in parsing the massive heterogeneity of mental disorders (75,76) and thereby improving prediction of individual vulnerability.

References

1. Kendler KS, Zachar P, Craver C (2011): What kinds of things are psychiatric disorders? *Psychol Med* 41: 1143–1150.
2. Trzaskowski M, Yang J, Visscher PM, Plomin R (2014): DNA evidence for strong genetic stability and increasing heritability of intelligence from age 7 to 12. *Mol Psychiatry* 19: 380–384.
3. Haworth CMA, Wright MJ, Luciano M, Martin NG, Geus EJC de, Bejsterveldt CEM van, *et al.* (2010): The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Mol Psychiatry* 15: 1112–1120.
4. Polderman TJC, Benjamin B, Leeuw CA de, Sullivan PF, Bochoven A van, Visscher PM, Posthuma D (2015): Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* 47: 702–709.
5. Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Færden A, *et al.* (2011): Neurocognitive Dysfunction in Bipolar and Schizophrenia Spectrum Disorders Depends on History of Psychosis Rather Than Diagnostic Group. *Schizophrenia Bull* 37: 73–83.
6. Kuperberg G, Heckers S (2000): Schizophrenia and cognitive function. *Curr Opin Neurobiol* 10: 205–210.
7. Forbes NF, Carrick LA, McIntosh AM, Lawrie SM (2008): Working memory in schizophrenia: a meta-analysis. *Psychol Med* 39: 889–905.
8. Arts B, Jabben N, Krabbendam L, Os J van (2007): Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med* 38: 771–785.
9. Matsuo K, Glahn DC, Peluso MAM, Hatch JP, Monkul ES, Najt P, *et al.* (2007): Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Mol Psychiatry* 12: 158–166.
10. Sachdev PS, Malhi GS (2005): Obsessive–Compulsive Behaviour: A Disorder of Decision-Making. *Aust Nz J Psychiat* 39: 757–763.
11. Lawlor VM, Webb CA, Wiecki TV, Frank MJ, Trivedi M, Pizzagalli DA, Dillon DG (2019): Dissecting the impact of depression on decision-making. *Psychol Med* 1–10.

12. Heerey EA, Bell-Warren KR, Gold JM (2008): Decision-Making Impairments in the Context of Intact Reward Sensitivity in Schizophrenia. *Biol Psychiat* 64: 62–69.
13. Shurman B, Horan WP, Nuechterlein KH (2005): Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. *Schizophr Res* 72: 215–224.
14. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RSE, Murray RM, *et al.* (2010): Static and Dynamic Cognitive Deficits in Childhood Preceding Adult Schizophrenia: A 30-Year Study. *Am J Psychiat* 167: 160–169.
15. Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T (2000): Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: A prospective cohort study. *Schizophrenia Bull* 26: 379–393.
16. Bäckman L, Jones S, Berger A-K, Laukka EJ, Small BJ (2005): Cognitive Impairment in Preclinical Alzheimer’s Disease: A Meta-Analysis. *Neuropsychology* 19: 520–531.
17. Gale CR, Batty GD, Tynelius P, Deary IJ, Rasmussen F (2010): Intelligence in Early Adulthood and Subsequent Hospitalization for Mental Disorders. *Epidemiology* 21: 70–77.
18. Córdova-Palomera A, Kaufmann T, Bettella F, Wang Y, Doan NT, Meer D van der, *et al.* (2018): Effects of autozygosity and schizophrenia polygenic risk on cognitive and brain developmental trajectories. *Eur J Hum Genet* 26: 1049–1059.
19. Hubbard L, Tansey KE, Rai D, Jones P, Ripke S, Chambert KD, *et al.* (2016): Evidence of Common Genetic Overlap Between Schizophrenia and Cognition. *Schizophrenia Bull* 42: 832–842.
20. McIntosh AM, Gow A, Luciano M, Davies G, Liewald DC, Harris SE, *et al.* (2013): Polygenic Risk for Schizophrenia Is Associated with Cognitive Change Between Childhood and Old Age. *Biol Psychiat* 73: 938–943.
21. Kjelkenes R, Wolfers T, Alnæs D, Meer D van der, Pedersen ML, Dahl A, *et al.* (2021): Mapping normative trajectories of cognitive function and its relation to psychopathology symptoms and genetic risk in youth. *PsyArxiv*.
<https://doi.org/10.31234/osf.io/yz8q6>

22. Axelrud LK, Santoro ML, Pine DS, Talarico F, Gadelha A, Manfro GG, *et al.* (2018): Polygenic Risk Score for Alzheimer's Disease: Implications for Memory Performance and Hippocampal Volumes in Early Life. *Am J Psychiat* 175: 555–563.
23. Germine L, Robinson EB, Smoller JW, Calkins ME, Moore TM, Hakonarson H, *et al.* (2016): Association between polygenic risk for schizophrenia, neurocognition and social cognition across development. *Transl Psychiat* 6: e924–e924.
24. Plana-Ripoll O, Pedersen CB, Holtz Y, Benros ME, Dalsgaard S, Jonge P de, *et al.* (2019): Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *Jama Psychiat* 76: 259–270.
25. Kriegeskorte N, Douglas PK (2018): Cognitive computational neuroscience. *Nat Neurosci* 21: 1148–1160.
26. Pedersen ML, Frank MJ, Biele G (2017): The drift diffusion model as the choice rule in reinforcement learning. *Psychon B Rev* 24: 1234–1251.
27. Ulrichsen KM, Alnæs D, Kolskår KK, Richard G, Sanders A, Dørum ES, *et al.* (2020): Dissecting the cognitive phenotype of post-stroke fatigue using computerized assessment and computational modeling of sustained attention. *Eur J Neurosci*. <https://doi.org/10.1111/ejn.14861>
28. Dillon DG, Wiecki T, Pechtel P, Webb C, Goer F, Murray L, *et al.* (2015): A computational analysis of flanker interference in depression. *Psychol Med* 45: 2333–2344.
29. Hauser TU, Fiore VG, Moutoussis M, Dolan RJ (2016): Computational Psychiatry of ADHD: Neural Gain Impairments across Marrian Levels of Analysis. *Trends Neurosci* 39: 63–73.
30. Pedersen ML, Ironside M, Amemori K, McGrath CL, Kang MS, Graybiel AM, *et al.* (2021): Computational phenotyping of brain-behavior dynamics underlying approach-avoidance conflict in major depressive disorder. *Plos Comput Biol* 17: e1008955.

31. Berwian IM, Wenzel JG, Collins AGE, Seifritz E, Stephan KE, Walter H, Huys QJM (2020): Computational Mechanisms of Effort and Reward Decisions in Patients With Depression and Their Association With Relapse After Antidepressant Discontinuation. *Jama Psychiat* 77.
<https://doi.org/10.1001/jamapsychiatry.2019.4971>
32. Huys QJM, Maia TV, Frank MJ (2016): Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci* 19: 404–413.
33. Ratcliff R (1978): A theory of memory retrieval. *Psychol Rev* 85: 59.
34. Cohen AO, Breiner K, Steinberg L, Bonnie RJ, Scott ES, Taylor-Thompson K, *et al.* (2016): When Is an Adolescent an Adult? Assessing Cognitive Control in Emotional and Nonemotional Contexts. *Psychol Sci* 27: 549–562.
35. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, *et al.* (2018): The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Dev Cogn Neuros-neth* 32: 43–54.
36. Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, *et al.* (2018): The conception of the ABCD study: From substance use to a broad NIH collaboration. *Dev Cogn Neuros-neth* 32: 4–7.
37. Luciana M, Bjork JM, Nagel B, Barch DM, Gonzalez R, Nixon SJ, Banich MT (2018): Adolescent Neurocognitive Development and Impacts of Substance Use: Overview of the Adolescent Brain Cognitive Development (ABCD) Baseline Neurocognition Battery. *Dev Cogn Neuros-neth* 32: 67–79.
38. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, *et al.* (2019): Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer’s disease risk. *Nat Genet* 51: 404–413.
39. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* 51: 793–803.
40. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50: 668–681.

41. Arnold PD, Askland KD, Barlassina C, Bellodi L, Bienvenu OJ, Black D, *et al.* (2018): Revealing the complex genetic architecture of obsessive–compulsive disorder using meta-analysis. *Mol Psychiatr* 23: 1181–1188.
42. Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H, Holmans PA, *et al.* (2014): Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511: 421–427.
43. Schwarz E, Alnæs D, Andreassen OA, Cao H, Chen J, Degenhardt F, *et al.* (2021): Identifying multimodal signatures underlying the somatic comorbidity of psychosis: the COMMITMENT roadmap. *Mol Psychiatr* 26: 722–724.
44. Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, *et al.* (2013): Improved Detection of Common Variants Associated with Schizophrenia by Leveraging Pleiotropy with Cardiovascular-Disease Risk Factors. *Am J Hum Genetics* 92: 197–209.
45. McCrimmon RJ, Ryan CM, Frier BM (2012): Diabetes and cognitive dysfunction. *Lancet* 379: 2291–2299.
46. Consortium E-C, CARDIoGRAMplusC4D, group TUBCCC working, Nelson CP, Goel A, Butterworth AS, *et al.* (2017): Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* 49: 1385–1391.
47. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, *et al.* (2018): Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 50: 1505–1513.
48. Yang J, Lee SH, Goddard ME, Visscher PM (2011): GCTA: A Tool for Genome-wide Complex Trait Analysis. *Am J Hum Genetics* 88: 76–82.
49. Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, *et al.* (2013): Function in the human connectome: Task-fMRI and individual differences in behavior. *Neuroimage* 80: 169–189.
50. Cohen, Conley, Dellarco, Casey (2016): The impact of emotional cues on short-term and long-term memory during adolescence.
51. Buuren S van, Groothuis-Oudshoorn K (2011): mice : Multivariate Imputation by Chained Equations in R. *J Stat Softw* 45. <https://doi.org/10.18637/jss.v045.i03>

52. Smith PL, Ratcliff R (2004): Psychology and neurobiology of simple decisions. *Trends Neurosci* 27: 161–168.
53. Gold JI, Shadlen MN (2007): The Neural Basis of Decision Making. *Annu Rev Neurosci* 30: 535–574.
54. Navarro DJ, Fuss IG (2009): Fast and accurate calculations for first-passage times in Wiener diffusion models. *J Math Psychol* 53: 222–230.
55. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, *et al.* (2013): Cognition assessment using the NIH Toolbox. *Neurology* 80: S54–S64.
56. Thompson WK, Barch D, Bjork J, Gonzalez R, Nagel B, Nixon SJ, Luciana M (2018): The Structure of Cognition in 9 and 10 year-old Children and Associations with Problem Behaviors: Findings from the ABCD Study’s Baseline Neurocognitive Battery. *Dev Cogn Neuros-neth* 36: 100606.
57. Wiecki TV, Sofer I, Frank MJ (2013): HDDM: Hierarchical Bayesian estimation of the Drift-Diffusion Model in Python. *Front Neuroinform* 7: 14.
58. Gelman A, Rubin DB (1992): Inference from Iterative Simulation Using Multiple Sequences. *Statistical Science* 7. <https://doi.org/10.2307/2246093>
59. Loughnan RJ, Palmer CE, Thompson WK, Dale AM, Jernigan TL, Fan CC (2020): Polygenic Score of Intelligence is More Predictive of Crystallized than Fluid Performance Among Children. *Biorxiv* 637512.
60. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, *et al.* (2010): Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* 42: 565–569.
61. Zaitlen N, Kraft P, Patterson N, Pasaniuc B, Bhatia G, Pollack S, Price AL (2013): Using Extended Genealogy to Estimate Components of Heritability for 23 Quantitative and Dichotomous Traits. *Plos Genet* 9: e1003520.
62. Choi SW, O’Reilly PF (2019): PRSice-2: Polygenic Risk Score software for biobank-scale data. *Gigascience* 8. <https://doi.org/10.1093/gigascience/giz082>
63. Bürkner P-C (2017): brms: An R Package for Bayesian Multilevel Models Using Stan. *Journal of Statistical Software* 80. <https://doi.org/10.18637/jss.v080.i01>
64. Gelman A, Lee D, Guo J (2015): Stan. *J Educ Behav Stat* 40: 530–543.

65. Kruschke JK (2010): Bayesian data analysis. *Wiley Interdiscip Rev Cognitive Sci* 1: 658–676.
66. Kahn RS, Keefe RSE (2013): Schizophrenia Is a Cognitive Illness: Time for a Change in Focus. *Jama Psychiat* 70: 1107–1112.
67. Belleville S, Fouquet C, Duchesne S, Collins DL, Hudon C, disease-Quebec the C-Q group: C for the EI of A (2014): Detecting Early Preclinical Alzheimer’s Disease via Cognition, Neuropsychiatry, and Neuroimaging: Qualitative Review and Recommendations for Testing. *J Alzheimer’s Dis* 42: S375–S382.
68. Liebers DT, Pirooznia M, Seiffudin F, Musliner KL, Zandi PP, Goes FS (2016): Polygenic Risk of Schizophrenia and Cognition in a Population-Based Survey of Older Adults. *Schizophrenia Bull* 42: 984–991.
69. Shafee R, Nanda P, Padmanabhan JL, Tandon N, Alliey-Rodriguez N, Kalapurakel S, *et al.* (2018): Polygenic risk for schizophrenia and measured domains of cognition in individuals with psychosis and controls. *Transl Psychiat* 8: 78.
70. Harris SE, Davies G, Luciano M, Payton A, Fox HC, Haggarty P, *et al.* (2014): Polygenic Risk for Alzheimer’s Disease is not Associated with Cognitive Ability or Cognitive Aging in Non-Demented Older People. *J Alzheimer’s Dis* 39: 565–574.
71. Hill WD, Davies G, Group TCCW, Liewald DC, McIntosh AM, Deary IJ (2016): Age-Dependent Pleiotropy Between General Cognitive Function and Major Psychiatric Disorders. *Biol Psychiat* 80: 266–273.
72. O’Reilly RC, Frank MJ (2006): Making Working Memory Work: A Computational Model of Learning in the Prefrontal Cortex and Basal Ganglia. *Neural Comput* 18: 283–328.
73. Rac-Lubashevsky R, Frank MJ (2021): Analogous computations in working memory input, output and motor gating: Electrophysiological and computational modeling evidence. *Plos Comput Biol* 17: e1008971.
74. Paulus MP, Thompson WK (2019): The Challenges and Opportunities of Small Effects. *Jama Psychiat* 76: 353–354.
75. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, *et al.* (2018): Mapping the Heterogeneous Phenotype of Schizophrenia and Bipolar Disorder Using Normative Models. *Jama Psychiat* 75: 1146.

76. Marquand AF, Wolfers T, Mennes M, Buitelaar J, Beckmann CF (2016): Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying Psychiatric Disorders. *Biological Psychiatry Cognitive Neurosci Neuroimaging* 1: 433–447.