

ORIGINAL ARTICLE

Substantial SNP-based heritability estimates for working memory performance

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Working memory (WM) is an important endophenotype in neuropsychiatric research and its use in genetic association studies is thought to be a promising approach to increase our understanding of psychiatric disease. As for any genetically complex trait, demonstration of sufficient heritability within the specific study context is a prerequisite for conducting genetic studies of that trait. Recently developed methods allow estimating trait heritability using sets of common genetic markers from genome-wide association study (GWAS) data in samples of unrelated individuals. Here we present single-nucleotide polymorphism (SNP)-based heritability estimates (h_{SNP}^2) for a WM phenotype. A Caucasian sample comprising a total of $N = 2298$ healthy and young individuals was subjected to an N -back WM task. We calculated the genetic relationship between all individuals on the basis of genome-wide SNP data and performed restricted maximum likelihood analyses for variance component estimation to derive the h_{SNP}^2 estimates. Heritability estimates for three 2-back derived WM performance measures based on all autosomal chromosomes ranged between 31 and 41%, indicating a substantial SNP-based heritability for WM traits. These results indicate that common genetic factors account for a prominent part of the phenotypic variation in WM performance. Hence, the application of GWAS on WM phenotypes is a valid method to identify the molecular underpinnings of WM.

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INTRODUCTION

Working memory (WM) has a pivotal role in human cognition and cognitive performance, allowing the integration of information from instantly perceived stimuli, long-term-memory and thought-processes. A wide variety of psychological testing procedures have been developed to render WM performance quantifiable.^{1–4} Assessment of WM performance along with brain imaging techniques have been used to elucidate and delimit its different components, aiming at a more circumscribed understanding of the neuronal processes at the basis of WM.⁵ The integration of extensive research on WM yields a common consensus that it constitutes a complex trait and that the buffer size for the transiently stored content varies interindividually, which is partly due to genetic factors. WM is an important endophenotype in neuropsychiatric research and its use in genetic association studies is thought to be a promising approach to increase our understanding of psychiatric disease.^{6–11} Namely, two recent studies have corroborated the genetic link between schizophrenia and WM, demonstrating the validity of this endophenotype for schizophrenia research: Stefansson *et al.*¹² report that control subjects carrying Copy Number Variants, which predispose to schizophrenia and autism, perform at a level that is in between patients and population controls in cognitive tasks including a spatial WM test. A genome-wide gene set enrichment study conducted by our group, identified a set of voltage-gated cation channel activity genes that were robustly linked to performance in WM tasks in healthy individuals and also to risk for schizophrenia

in a large case–control sample.¹³ Both these studies suggest that the findings of cognitive deficits are translatable between healthy subjects and cohorts of psychiatric patients. Improving our understanding of the molecular basis of this endophenotype might be key for future drug discovery and treatment options in psychiatry.^{14,15} As for any genetically complex trait, demonstration of sufficient heritability within the specific study context is a prerequisite for conducting genetic studies of that trait. Heritability is a concept that summarizes how much of the phenotypic variation in a given trait is attributable to heritable factors, the majority of them being genetic. Since inter-individual trait differences attributable to genetic variability are a prerequisite for quantitative trait loci mapping, estimation of trait heritability is important to demonstrate the validity of a quantitative trait loci study of a given trait. Conventionally, heritability estimates in humans are derived from phenotypic data by comparing correlations between relatives, where the extent of genetic relatedness is derived from the degree of relationship. Results from previous twin and family studies that used a variety of tasks to measure WM performance have shown heritability estimates ranging between 15 and 72%.^{16–19} Recently developed methods propose inferring genetic identity from high-throughput SNP data and correlating these estimates with phenotypic resemblance among unrelated individuals.^{20,21} This allows the estimation of an SNP-based heritability measure (h_{SNP}^2) for any specific genome-wide association study data set. Importantly, the h_{SNP}^2 value quantifies the amount of phenotypic variation that can be

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Table 1. Descriptive statistics of task performance measures

	2-Back – 0-back	2-Back	d-Prime	MRT 2-back
Total (N = 2298)	–0.077 (0.07)	0.891 (0.07)	2.436 (0.84)	558.224 (128.12)
Females (N = 1471)	–0.075 (0.07)	0.895 (0.07)	2.485 (0.83)	568.890 (131.09)
Males (N = 827)	–0.082 (0.07)	0.885 (0.07)	2.347 (0.85)	539.252 (120.43)

Abbreviations: MRT, mean reaction time; WM, working memory. Performance metrics for WM (*N*-back derived) and RT in milliseconds: mean (s.d.).

explained by the common SNPs represented in genome-wide association study data sets. Of note, h_{SNP}^2 hereby represents a lower bound heritability estimate, because causal variants that are neither genotyped nor tagged by the used set of markers are completely disregarded. In the present study we show that a substantial part of phenotypic variance of WM performance can be explained by using the common marker set represented on the Affymetrix 6.0 Human SNP array to estimate h_{SNP}^2 values for *N*-back-derived WM phenotypes.

MATERIALS AND METHODS

Ethics statement

The experiments were approved by the ethics committee of the Cantons of Basel-City and Basel-Country. Written informed consent was obtained from all subjects before participation.

Participants and genotyping procedure

A sample of 2703 young healthy Swiss individuals (1721 females, 982 males; mean age: 22.5 years; median age: 22 years; range: 18–38 years) was assessed for WM performance using an *N*-back task. Saliva samples were obtained from each study participant, using an Oragene DNA Self-Collection Kit (DNA Genotek, Ottawa, Ontario, Canada). DNA was extracted from saliva using standard protocols. All subjects were individually genotyped using the Affymetrix Human SNP assay 6.0 according to the manufacturer's recommendation.

N-back task

All subjects completed the 0-back and 2-back version of the *N*-back task, after they were instructed and trained on the task. The 0-back condition served as a non-memory-guided control condition, measuring general attention, concentration and reaction time. The *N*-back task was presented on a computer screen and consisted of 12 blocks (six 0-back and six 2-back blocks). Per block, 14 stimuli consisting of 3 targets and 11 non-targets, were presented in a randomized order. Each stimulus was presented for 500 ms, followed by a black screen for 1500 ms. For each stimulus participants had to indicate as fast as possible whether it was a target or a non-target by pressing the corresponding button. At the beginning of each block the instruction was shown for 5 s. There was a 20 s break after every second block. The two blocks between the breaks consisted of a 0-back and a 2-back block, which were presented in a randomized order. Each block lasted for 33 s. The *N*-back task had a total duration of roughly 10 min, including instructions presented at the beginning of the task. Performance in the 0-back and the 2-back tasks was assessed by the mean correct response accuracy. The difference in mean accuracy between 2-back and the 0-back condition served as main phenotype (2-back mean accuracy attention corrected: 2-back–0-back). We also tested the uncorrected 2-back mean accuracy and the d-prime for the 2-back condition. The d-prime was calculated according to the following formula:

$$d' = \text{Probit}(\text{hit rate}) - \text{Probit}(\text{false alarm rate})$$

The maximal number of hits (that is, correct responses to targets) was $N = 36$ and the maximal number of false alarms (that is, incorrect responses to non-targets) was $N = 132$. To allow for a probit-transformation, the hit and false-alarm-rates of 0 or 1 had to be avoided by replacing these extreme values, which was done as follows: 100% of hits were set to $1 - 1/36$ and 0% were set to $1/36$. Accordingly, 100% of false alarms were set to $1 - 1/132$ and 0% of false alarms were set to $1/132$.²² In addition, we also estimated h_{SNP}^2 for the mean reaction time of the 2-back task (2-back

mean reaction time). See Table 1 for descriptive statistics of uncorrected task performance measures.

Genotypic outlier analysis

We identified and subsequently excluded subjects with technical biases or non-Caucasian ancestry. A Bayesian clustering algorithm was applied to genome-wide summary statistics to identify and exclude samples affected by a potential technical bias. Briefly, considering a combination of genome-wide call rate and heterozygosity rate, the algorithm infers each sample's posterior probability to belong to the outliers' class, as extreme values for these summary statistics may be indicative of a genotyping bias. Similarly, the Bayesian clustering algorithm was applied on the coordinates of the subjects on the first two PCA components inferred from HapMap data using the YRI, CEU and CHB-JPT populations. Thus, samples of non-Caucasian ancestry were identified and removed, excluding $N = 272$ individuals.²³

Phenotypic and genetic quality controls

To adjust for sex and age, all *N*-back derived performance measurements (accuracy and reaction time) entered a linear model and residuals were extracted, which were used for all further calculations. As the presence of outliers in the phenotypic data can affect heritability estimation for complex traits,²⁴ all subjects whose performance measurements in any of the four *N*-back performance measurements differed more than 3.5 standard deviations from the sample mean were excluded ($N_{\text{excluded}} = 40$).

Due to this procedure, the exact same number of subjects was included in all subsequent analyses for all investigated phenotypes.

The genotype data set was filtered (MAF ≥ 0.01 ; HWE $p_{\text{Fisher}} \geq 0.001$; per SNP call rate $\geq 95\%$; per individual call rate $\geq 95\%$) to obtain a set of 702,744 autosomal and 27,265 X-chromosomal SNPs for further analysis.

Estimation of the pairwise genetic similarity using all autosomal markers and subsequently removing one of each pairs showing genetic relatedness > 0.025 (~ second-degree cousins) led to the exclusion of $N = 93$ subjects, yielding a sample size of $N = 2298$ for h_{SNP}^2 estimation.

h_{SNP}^2 Estimation

To obtain the genome-wide heritability estimates h_{SNP}^2 , we calculated the genetic relationship between all individuals on the basis of the autosomal SNP data and performed restricted maximum likelihood analyses for variance component estimation using the GCTA software package.²⁰ In a second step, h_{SNP}^2 estimates were calculated for all chromosomes separately including the X-chromosome. The genetic relationship matrix for the X-chromosome was obtained using the designated option in the GCTA toolset.

RESULTS

Heritability estimates for the three 2-back derived WM performance measures on the basis of autosomal chromosomes ranged between 31 and 41%, indicating substantial SNP-based heritabilities (Figure 1). The proportion of phenotypic variance explained by all autosomal SNPs for difference in response accuracy between the 2-back and the 0-back condition was 41% (s.e. = 0.139; P -value = 0.0008). h_{SNP}^2 for the mean response accuracy in the 2-back alone (that is, without correction for 0-back performance) and the false-response corrected d-prime condition were 31% with s.e. = 0.138; P -value = 0.006 and s.e. = 0.140; P -value = 0.01, respectively. Due to several reports linking processing speed to WM-related cognitive abilities,^{25,26} we also investigated heritability of the mean reaction time in the 2-back condition (h_{SNP}^2 : 24%; s.e. = 0.142; P -value = 0.04). A

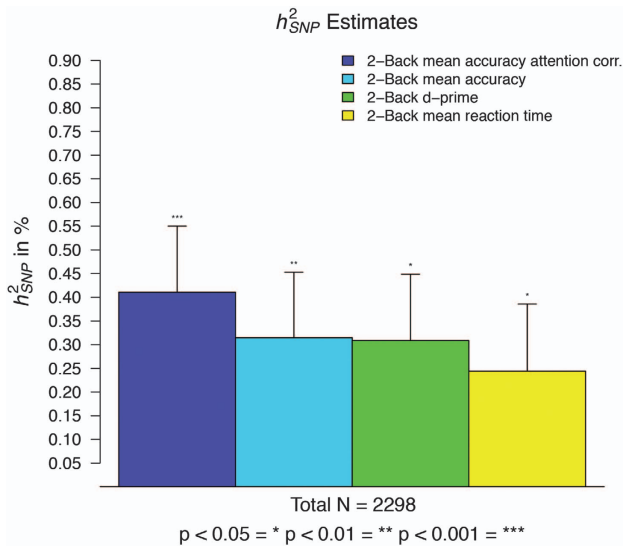


Figure 1. h^2_{SNP} estimates for 2-back derived WM measures in percent for a total of $N=2298$. The error bars represent standard errors. 2-Back mean accuracy attention corrected (corr.) h^2_{SNP} 41%, s.e. 14%, P -value=0.0008; 2-back mean accuracy h^2_{SNP} 31%, s.e. 14%, P -value=0.006; 2-back d-prime h^2_{SNP} 31%, s.e. 14%, P -value=0.01; 2-back mean reaction time h^2_{SNP} 24%, s.e. 14%, P -value=0.04. SNP, single-nucleotide polymorphism; WM, working memory.

descriptive analysis of correlations between phenotypes shows strong intercorrelations between the three accuracy-related 2-back WM phenotypes ($r^2 > 0.65$), whereas correlation coefficients between the mean reaction time in the 2-back condition and the WM phenotypes are negligible ($r^2 < 0.01$) by means of shared phenotypic variance (Table 2).

Chromosomewise h^2_{SNP} estimates

In a further step, we partitioned heritability into contributions from single chromosomes, including the X-chromosome. Figure 2 shows the h^2_{SNP} values per chromosome, presenting an approximation to the amount of phenotypic variance explained by the single chromosomes. For each phenotype, we derived a vector containing h^2_{SNP} estimates per chromosome. To investigate whether the correlational pattern of the phenotypes is reflected also in a similar chromosomal heritability profile, we calculated the Pearson's correlation coefficients for these vectors. The highly correlated WM phenotypes show a similar profile for the chromosomewise h^2_{SNP} estimates. Regarding the single chromosome h^2_{SNP} values for the mean reaction time in the 2-back condition, we observe a different distribution of h^2_{SNP} estimates per chromosome. Table 3 depicts the descriptive Pearson's correlation coefficients between the chromosomewise h^2_{SNP} estimates for all phenotypes. We also investigated whether the chromosomal length and the number of SNPs are correlated with the phenotypic variance that each chromosome explains. We observed significant correlations (Pearson's r in the range between 0.53 and 0.68) for the WM phenotypes with the chromosomal length and number of SNPs, whereas no significant correlation was observed for the mean reaction time of the 2-back task (See Table 4).

DISCUSSION

The present data demonstrate that a substantial proportion of variance in WM performance is captured by common genome-wide association study SNPs in a sample of healthy young

Table 2. Correlation of phenotypes

	2-Back – 0-back	2-Back	d-Prime
2-Back – 0-back			
2-Back	0.91***		
d-Prime	0.83***	0.94***	
MRT 2-back	–0.08***	0.01	0.06**

Abbreviation: MRT, mean reaction time. Pearson's correlation coefficients, $df = 2296$; * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$.

unrelated individuals. The h^2_{SNP} estimates for the N -back-derived WM phenotypes range from 31 to 41% with a mean standard error of 0.14. Thus, the h^2_{SNP} estimates are consistent with the previously reported heritability for WM on the basis of twin-studies.²⁷ Taken together, these findings add further support for the hypothesis that WM is a highly heritable trait. The chromosomal partitioning analysis (Figure 2), which depicts h^2_{SNP} estimates for all chromosomes analyzed individually, provides a clear hint for the pronounced polygenicity of the investigated WM phenotype. This finding is in line with the previously reported ubiquitous polygenicity of human complex traits.²⁸ The amount of genetic variation that explains the variance of WM performance is proportional to the chromosomal length and the number of investigated SNPs per chromosome (see Table 4). The correlational pattern for the investigated phenotypes (see Table 2) indicates that the WM performance measures and the mean reaction time are independent behavioral metrics. The h^2_{SNP} estimate based on genome-wide data (see Figure 1) are lower for the mean reaction time and the h^2_{SNP} estimates per chromosome also show a different distribution compared with the WM performance derived estimates (see Figure 2). Furthermore, although there is an observable trend for the proportionality of h^2_{SNP} estimates with chromosomal length, the correlation fails to reach statistical significance (see Table 2), which may be due to a lower overall heritability of this trait. Hence, we conclude that the WM performance measured with the 2-back task is independent of the mean response time under the cognitive load of performing the 2-back test.

Of note, the heritability estimation for complex traits using genome-wide data sets is rather a complement than a substitution to studies on twin- and family-based heritability. Marker-based heritability estimation represents a lower bound for the true trait heritability as it relies only on the effects of common variants assuming an additive variance model. On one hand, the investigation of large pools of unrelated individuals allows to assess heritability without the undermining effects due to shared environment or familiarity. Yet, on the other hand, it will not take the potential effects of rare variants into account. The SNP-based heritability estimates for WM suggest that a large share of phenotypic variance can be explained by common SNPs rendering well-powered genome-wide association study data sets a promising tool to discover molecular players that act in concert to form this complex trait. It has been repeatedly shown that familial risk for psychiatric diseases like schizophrenia is often accompanied by reduced cognitive abilities.^{29–31} Results from a long-term study suggest that people who reported psychotic-like experiences in late adulthood performed poorer in cognitive tasks during childhood and adolescence.³² In a recent twin study investigating healthy twins, Goldberg *et al.*⁶ report that the phenotypic correlation between intelligence quotient and WM can be almost entirely attributed to shared genetic variance. In an effort to investigate dimensions of observable behavior and neurobiological measures that can be used to classify psychopathology, the National Institute of Mental Health established the Research Domain Criteria project. The N -back task used in the present study

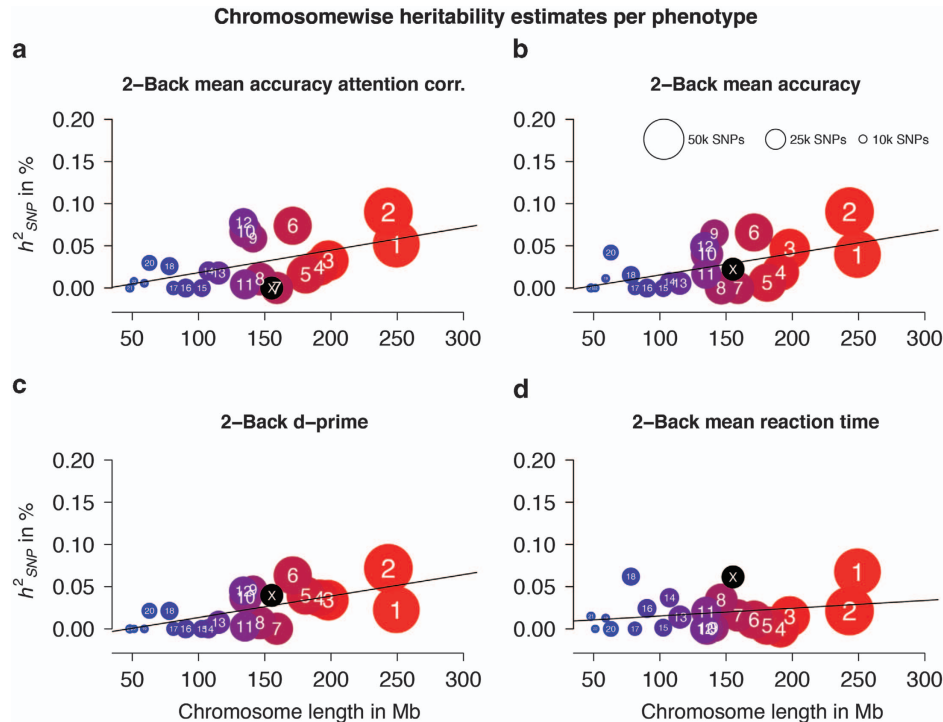


Figure 2. Chromosomewise h^2_{SNP} estimates for N -back phenotypes and mean reaction time h^2_{SNP} estimates per chromosome are plotted on the y axis. The x axis depicts the chromosomal length in Mb. Circle size indicates the number of SNPs used in the analysis after quality control. Color scheme from red to blue reflects the chromosomal ordering from chromosome 1 to 22, with the X-chromosome colored in black. The black line depicts the regression line for chromosomal length and explained variance (regression coefficients (df = 21): (a) $r = 0.53$, P -value = 0.009, (b) $r = 0.56$, P -value = 0.006, (c) $r = 0.65$, P -value = 0.0009, (d) $r = 0.25$, P -value = 0.3). SNP, single-nucleotide polymorphism.

	2-Back – 0-back	2-Back	d-Prime
2-Back – 0-back			
2-Back	0.91***		
d-Prime	0.83***	0.87***	
MRT 2-back	–0.09	–0.04	–0.04

Abbreviations: MRT, mean reaction time; SNP, single-nucleotide polymorphism. Pearson's correlation coefficients, df = 21; * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$.

	2-Back – 0-back	2-Back	d-Prime	MRT 2-back
Chromosomal length	0.53*	0.56*	0.65**	0.25
Number of SNPs	0.61**	0.60**	0.68***	0.15

Abbreviations: MRT, mean reaction time; SNP, single-nucleotide polymorphism. Pearson's correlation coefficients, df = 21; * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$.

is deemed appropriate to measure the sub-constructs of WM of active maintenance, limited capacity and with some, albeit not definitive evidence, for flexible updating according to the Research Domain Criteria project. Given the implication of cognitive and especially WM deficits in schizophrenia and other psychiatric disorders, the genetically guided decomposition of WM-related molecular pathways might pave the way for a better understanding of the genetic architecture implicated in these mental disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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