Biol Psychol. Author manuscript; available in PMC 2012 April 04.

Published in final edited form as:
Biol Psychol. 2011 March ; 86(3): 193–202. doi:10.1016/j.biopsycho.2010.11.008.

Whole genome association scan for genetic polymorphisms influencing information processing speed

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Abstract

Processing speed is an important cognitive function that is compromised in psychiatric illness (e.g., schizophrenia, depression) and old age; it shares genetic background with complex cognition (e.g., working memory, reasoning). To find genes influencing speed we performed a genome-wide association scan in up to three cohorts: Brisbane (mean age 16 years; $N = 1659$); LBC1936 (mean age 70 years, $N = 992$); LBC1921 (mean age 82 years, $N = 307$), and; HBCS (mean age 64 years, $N = 1080$). Meta-analysis of the common measures highlighted various suggestively significant ($p < 1.21 \times 10^{-5}$) SNPs and plausible candidate genes (e.g., *TRIB3*). A biological pathways analysis of the speed factor identified two common pathways from the KEGG database (cell junction, focal adhesion) in two cohorts, while a pathway analysis linked to the GO database revealed common pathways across pairs of speed measures (e.g., receptor binding, cellular metabolic process). These highlighted genes and pathways will be able to inform future research, including results for psychiatric disease.

Keywords

Information processing speed; Cognitive ability; Genes; Biological pathways

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Appendix A. Supplementary data Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.biopsycho.2010.11.008.

Information processing speed is considered a lower level cognitive process, although it shares a large portion of its genetic variance with higher order abilities (e.g., reasoning, working memory) (Luciano et al., 2003; Neubauer, 1997). It is a cognitive domain that is particularly prone to deterioration with ageing (Salthouse, 1996); for example, simple reaction time (RT) slows at around 50 years of age and choice RT slows throughout the adult range (Der and Deary, 2006). However, similar to complex cognition with which it is correlated, the genes influencing speed are expected to be stable across the lifespan (Lyons et al., 2009). Speed is affected (slowed) in psychiatric conditions such as schizophrenia, depression and substance use disorder (Andersson et al., 2010; Jahshan et al., 2009) and RT has even been shown to account for the relationship between IQ and mortality in a cohort followed up until age 70 (Deary and Der, 2005; Latvala et al., 2009). It is therefore an important trait to understand, and in this study, we aim to locate genes influencing chronometric and psychometric processing speed measures via genome wide association. These genes may underlie complex cognition or reflect genetic influences specific to speed because a large portion of genetic variance in processing speed is independent of higher order ability.

Processing speed as measured by elementary cognitive tasks has been used to understand the genetic structure of human mental ability (Baker et al., 1991; Ho et al., 1988; Rijsdijk et al., 1998; Wright et al., 2000). Reaction time measures and measures without a RT component (such as inspection time) demonstrate phenotypic correlations ranging between −.30 to −.50 with IQ (Deary, 2001; Deary et al., 2001; Deary and Stough, 1996). More complex elementary cognitive tasks correlate more strongly with IQ, for example, choice RT confers a greater correlation with IQ than does simple RT (Deary et al., 2001; Larson et al., 1988). Psychometric speed measures, such as digit symbol, contribute to the estimation of a person's full scale IQ, typically forming part of a first-order perceptual speed factor. Multivariate genetic analyses have found evidence for genetic pleiotropy among varied measures of processing speed (chronometric and psychometric) and, importantly, among speed and more complex cognitive abilities, notably IQ (Luciano et al., 2004; Posthuma et al., 2001; Rijsdijk et al., 1998). For chronometric speed measures, common genes have been shown to influence the variation in processing speed and IQ rather than there being a causal relationship between the two (Luciano et al., 2005), although in an older sample (50–89 years) and using psychometric speed measures a directional relationship from speed to spatial and memory abilities explained the genetic covariance (Finkel et al., 2009). Thus, the possibility exists that some information processing components serve as the bases for complex cognition, with the slowing of processing speed accounting for the ageing of other cognitive abilities.

The search for genetic polymorphisms influencing information processing speed variables has been unimpressive: the first whole genome linkage scan (in 378 families) of a collection of speed measures reported no linked chromosomal regions at a genome-wide significance criterion (Wright et al., 2008). However, there were regions of suggestive significance reported for 8-choice RT mean (on chromosomes 1 and 11), 4-choice RT mean (chromosome 8), and a delayed response RT measure (chromosome 14). It was noted that some of these linkage peaks overlapped with peaks observed for IQ, although most of the peaks were specific to individual speed measures. Specific candidate genes influencing processing speed measures have been largely unsubstantiated, but there have been findings of association with the TNF-alpha-308G→A polymorphism and a speed factor in the elderly (Baune et al., 2008), *BDNF* and a psychometric speed measure (alphabet-coding task) (Miyajima et al., 2008), and between *APOE* e4 allele variation and both chronometric and psychometric speed measures in a sample of 70 year olds (Luciano et al., 2009).

The present study uses the technique of genome wide association (GWA) to identify genetic variants influencing processing speed measures. Four cohorts from Australia, Scotland, and Finland were genotyped on the Illumina 610k Quad array and had been measured on information processing speed measures, some of which overlapped in, at most, three cohorts (e.g., choice RT, inspection time, and digit symbol), enabling meta-analysis of these measures. While the cohorts varied widely in age, processing speed has been shown to be fairly stable from childhood to age 70 (Deary et al., 2010), therefore, our study will be able to detect genetic variants influencing stable variation in processing speed.

1. Methods

1.1. GWA study subjects

1.1.1. Brisbane adolescent twin sample – Australia—Twins and their non-twin siblings were initially recruited as part of ongoing studies of melanoma risk factors and cognition (McGregor et al., 1999; Wright et al., 2001). For the current study, processing speed and genotypic data, following quality control described below, were available for a maximum of 1659 individuals (from 730 families), of whom 266 were monozygotic twin pairs and for whom phenotypic data were averaged. When data were collected, participants ranged in age from 15.4 to 28.7 (mean = 16.4 years, SD = .8) with the sample being Caucasian, predominantly Anglo-celtic (i.e., ethnic outliers were excluded (Medland et al., 2009)). Fifty-three percent of the sample was female. Written informed consent was obtained from each participant and their parent/guardian (if younger than 18 years) prior to testing.

1.1.2. Lothian Birth Cohort 1936 (LBC1936) – Scotland—This cohort consists of 1091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age. They were all born in 1936 and most took part at age 11 in the Scottish Mental Survey of 1947. They were Caucasian and almost all lived independently in the Lothian region (Edinburgh city and surrounding area) of Scotland. A full description of participant recruitment and testing can be found elsewhere (Deary et al., 2007). Genomic DNA was isolated from 1071 participants by standard procedure at the Wellcome Trust Clinical Research Facility (WTCRF) Genetics Core, Western General Hospital, Edinburgh. Twenty-nine samples failed quality control preceding the genotyping procedure. A reduced sample of 992 individuals had both genotype and phenotype data; their mean age was 69.55 years (SD = .84, range = 67.6–71.3 years) at data collection.

1.1.3. Lothian Birth Cohort 1921 (LBC1921) – Scotland—This cohort comprises 550 individuals, who were tested on cognitive and medical indices on multiple occasions; at first test wave participants were aged ~79 years (Deary et al., 2004b; Houlihan et al., 2010). They were all born in 1921 and most took part at age 11 in the Scottish Mental Survey of 1932. They were Caucasian and almost all lived independently in the Lothian region (Edinburgh city and surrounding area) of Scotland. The data for this analysis was based on the second test occasion, when they were measured on all three relevant speed traits. Genomic DNA was isolated from whole blood from 542 participants by standard procedure at Medical Research Council Technology, Western General Hospital, Edinburgh. Sixteen samples failed quality preceding the genotyping procedure. A reduced sample of 302 individuals had both genotype and phenotype data; their mean age was 83.35 years (SD = .54, range = 82.0–84.6 years) at data collection.

1.1.4. The Helsinki Birth Cohort Study (HBCS) – Finland—The HBCS cohort is composed of 8760 individuals born between the years 1934 and 1944 in Helsinki University Central Hospital. Between 2001 and 2003, a randomly selected sample of 928 males and

1075 females participated in a clinical study with a focus on cardiovascular, metabolic and reproductive health, cognitive function and depressive symptoms. For the sub-study on cognitive performance we invited those subjects from the original sample, who were still living in the greater Helsinki area (n = 1586). The 1279 subjects who attended were administered a test of cognitive performance in the years 2004–2006. After exclusion of subjects with a history of stroke (n = 29), type 1 diabetes (n = 1) and invalid test results (n = 3), the sample with valid phenotype and genotype data available for analyses consisted of 1080 men (n = 472) and women (n = 608). The mean age of the subjects at time of assessment was 63.9 (SD = 2.8) years. The mean age of the men was 63.6 (SD = 2.6) and of the women was 64.1 (SD = 3.0) years. The subjects who attended the cognitive test were similar in age, sex, educational attainment and prevalence and duration of diabetes to those who did not attend. Detailed information on the selection of the HBCS participants and on the study design can be found elsewhere (Barker et al., 2005; Eriksson et al., 2006; Paile-Hyvarinen et al., 2009; Raikkonen et al., 2008).

1.2. Measures

1.2.1. Brisbane adolescent twin sample—Psychometric speed was measured by the digit symbol substitution test, a performance subtest of the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981) which requires the participant to pair random digits with their matching symbols. Inspection time and choice RT were the elementary cognitive tasks administered. Inspection time was measured using a backward masked, line discrimination task. A parameter estimation by sequential testing procedure was employed (Findlay, 1978; Pentland, 1980) to vary stimulus duration. To minimise bias from random responses and lapses in attention/interest factors, inspection time was estimated by fitting post hoc a cumulative normal curve (mean = 0) to accuracy as a function of stimulus onset asynchrony. See Luciano et al. (2001b) for more details. Mean RT of correct responses on a visual reaction time task with three choice conditions (two, four, and eight) was performed on a computer using a keyboard response pad. The number of trials presented in each of the two, four, and eight choice conditions was 96, 48, and 96, respectively. RT trials less than 150 ms or greater than 2000 ms were excluded from the calculation of the mean. See Luciano et al. (2001a) for a fuller description of this task. A general factor, explaining 51% of variance, was calculated from a principal components analysis of digit symbol, 4-choice RT and inspection time.

1.2.2. LBC1936—The information processing speed battery comprised two psychometric tests from the WAIS-III^{UK} (digit symbol coding and symbol search) and two elementary cognitive tasks, RT and inspection time, which will be described briefly here; a full account of each test is given in Deary et al. (2007). Mean of correct trials on a simple RT (20 trials) and 4-choice RT (40 trials) task were used to assess speed of information processing. For simple RT, the participant is required to press a response key as fast as possible following the occurrence of a zero on the LCD screen. Four-choice RT requires the participant to press the corresponding response key when a target of 1, 2, 3 or 4 appears on the screen. The inspection time task is a two-alternative, forced choice, backward masking, visual discrimination task, requiring participants to make a discrimination, with no pressure on response time, regarding which of two parallel, vertical lines of markedly different lengths was longer. The stimuli and psychophysical procedure were the same as those used in Deary et al. (2004a), with a prescribed number of trials given at different stimulus durations. The correctness of each response across the 150 trials was recorded as the outcome variable. A general factor, explaining 59% of variance, was calculated from a principal components analysis of digit symbol, 4-choice RT mean and inspection time.

1.2.3. LBC1921—Digit symbol, simple RT, 4-choice RT and inspection time were measured as per the protocol described for the LBC1936. A general factor, explaining 63% of variance, was calculated from a principal components analysis of digit symbol, 4-choice RT mean and inspection time.

1.2.4. HBCS—Psychomotor speed was measured with two tests being part of a standardised language independent computerized battery of cognitive tests (CogState1, version 3.0.5). This battery has been validated and shown to be a sensitive indicator of mild impairments in the following cognitive domains: psychomotor speed, attention, working memory and episodic learning and memory (Collie et al., 2001, 2003; Darby et al., 2002). In the tasks participants were asked to pay attention to playing cards on a computer screen. The test battery takes approximately 15 min to complete and is preceded by a practice round. In the simple RT task, which assesses psychomotor function and speed of processing, a single card is presented face-down on the computer screen. The subject is asked to press the spacebar as soon as the card turns face-up. This is repeated 35 times with random time intervals. This task is administered twice – first and last in the test battery – and the mean RT is calculated. In the 2-choice RT task, subjects are asked to indicate whether the turning playing card on the screen is red by pressing either K (“yes”) or D (“no”). The stimulus is repeated 30 times and the mean RT is calculated.

1.3. Genotyping, quality control and imputation

DNA was extracted from blood samples and SNP genotyping was performed with the Illumina 610k Quad Bead chip either by deCODE Genetics (Brisbane cohort) or WTCRF (LBC1921 and LBC1921 cohorts) or with a modified Illumina 610k chip by the Wellcome Trust Sanger Institute, Cambridge, UK (HBCS). In the Brisbane adolescent twin cohort, genotype data (1817 samples) were checked for pedigree, sex, and Mendelian errors, and for ancestry (using HapMap3 and GenomeEUTwin individuals as a reference panel). Five individuals were removed because of gender inconsistencies, and 28 individuals (14 twin pairs) because of non-European ancestry. Quality control filters, as previously described (Medland et al., 2009), ensured no samples had a call rate ≤.95, and that all SNPs included in analyses had the following characteristics: call rate ≥.95, minor allele frequency ≥.01, and HWE test with $P \geq 1 \times 10^{-6}$. In the LBC cohorts (LBC1936 = 1042 and LBC1921 = 526 samples), individuals were checked for disagreement between genetic and reported gender ($n = 12$ in LBC1936 and $n = 1$ in LBC1921). Relatedness between subjects was investigated and, for any related pair of individuals, one was removed ($n = 8$, LBC1936; $n = 1$, LBC1921). Samples with a call rate ≤.95 ($n = 16$, LBC1936; $n = 6$, LBC1921), and those showing evidence of non-caucasian ascent, were also removed ($n = 1$, LBC1936; $n = 2$, LBC1921). SNPs were included in the analyses if they met the following conditions: call rate ≥.98, minor allele frequency ≥.01, and HWE test with $P \geq .001$. Thus after quality control procedures 1005 and 517 samples remained for the LBC1936 and LBC1921 cohorts respectively. In the HBCS, none of the participants showed non-European ancestry. Relatedness of the participants was examined with the pair-wise IBD estimates and closely related individuals were excluded from the analyses. Moreover, participants with X-chromosomal genotypes discrepant with the reported sex were removed ($N = 8$). After quality control procedures 1728 samples remained for the analyses. SNPs were included in the analyses if they met the following conditions: call rate ≥.95, minor allele frequency ≥.01, and HWE test with $p \geq 1 \times 10^{-5}$.

Because all cohorts used the same genotyping chip, the genotyped marker panel was analysed, but in the Australian and Scottish cohorts imputed genotypes were used where cases and SNPs were missing within samples. This ensured that the full panel of markers was available in each cohort. The HapMap phase II CEU data (NCBI build 36 (UCSC

hg18)) was used as the reference sample for imputation using MACH software. In the Australian and Scottish cohorts, SNPs with low imputation ($r^2 < .30$) were excluded, and in all cohorts, SNPs with low minor allele frequency (MAF < .01) were excluded.

1.4. Statistical analyses

Genome-wide association analyses were conducted in each study independently using linear regression (under an additive model) of standardised measures and including sex and age as covariates. We used the family based score test implemented in Merlin for the Brisbane cohort, and PLINK software for the Scottish and Finnish cohorts.

METAL (Abecasis, 2010) was used to perform meta-analysis of the results; it uses the weighted inverse variance method, computing a pooled effect estimate (ln(beta)), its standard error and its *p*-value by weighting the effect estimates of each cohort by the inverse of its variance and by incorporating the direction of effect. Automatic correction for any population stratification effects, if necessary, was done by applying genomic control, although individual cohort lambda values for each variable ranged between .97 and 1 (see Appendix CSupplementary Fig. 1 for genomic control inflation values for reported results). A chi-square test for heterogeneity tested whether the regression coefficients differed significantly between the cohorts contributing to the meta-analysis.

We used a genome-wide significance level of $p < 1.21 \times 10^{-8}$ and a suggestive level of significance of $p < 1.21 \times 10^{-5}$ as proposed for the Illumina 317K panel of markers (adjusted for SNP non-independence) (Duggal et al., 2008). While this is a liberal criterion because we used a larger chip, no SNPs reached genome-wide significance. Using the genome-wide significance alpha level, power calculations for our maximum sample were 36% to detect an effect size of 1% which increased to 80% for an effect size of 1.5%; the more liberal suggestive significance level gave a power of 83% to detect an effect size of 1%. We also present supplementary results of our top 100 SNPs because evidence is accumulating that for complex traits (e.g., height) effect sizes are too small to pass the stringent significance tests of genome-wide association (Yang et al., 2010).

Biological pathways analysis was undertaken for all variables using ALIGATOR (Holmans et al., 2009) and for the speed factor only using the SNPratio test (O'Dushlaine et al., 2009). Because ALIGATOR can use meta-analysis *p*-values to generate results, all variables were run through this program. SNPratio, on the other hand, is computer intensive requiring raw genotype data, therefore, only one variable was analysed (the composite speed factor) and this was done separately by cohort. In brief, ALIGATOR counts the number of significant genes (based on a nominal SNP association) in Gene Ontology (GO) categories that arise more often than would be expected by chance (empirical *p*-values of GO category membership are established via permutation of randomly drawn genes). We used a *p*-value of .01 for inclusion of nominally significant SNPs, 5000 replicate gene lists and 1000 replicate studies (used to judge study-wide significance levels for individual categories). The SNPratio test compares the proportion of nominally significant ($p < .05$) SNPs within genes to all SNPs within genes that relate to a specific biological pathway (from 220 experimentally validated pathways described in the Kyoto Encyclopaedia of Genes and Genomes (KEGG)). The NCBI definition of gene boundaries (including the 5 kb upstream and 2 kb downstream flanking region), was used to define a gene. An empirical *p*-value is estimated from the comparisons to ratios in datasets where the trait score has been randomised (1000 permutations). Because PLINK output was used for this analysis, the Brisbane cohort was re-run using PLINK on a randomly selected single member from each family. It should be noted that pathway categories differ between GO and KEGG databases. The GO categories are descriptors of gene products that fall into three broadly defined groups: biological process, cellular component and molecular function, whereas the KEGG

database contain pathways that have been constructed through knowledge of molecular interaction and reaction networks.

2. Results

Descriptive statistics of the measures, including their correlation with age and with other variables, are shown in Table 1. No SNPs exceeded the genome-wide significance level for any of the traits; q-q plots with their 95% confidence intervals for all measures can be found in the Appendix CSupplementary Fig. 1.

The results for SNPs exceeding suggestive significance level are shown in Table 2; see Appendix CSupplementary Table 1 for top 100 SNPs. For digit symbol, six SNPs showed suggestive significance with three of these SNPs in strong linkage disequilibrium (LD) with each other; they were located in or nearby two known genes, *ATRNL1* and *KRTAP7-1*, although none were exonic. Eight SNPs in three genes were shown to be associated (at suggestive levels) with symbol search in the LBC1936 cohort. The effect sizes of these SNPs were relatively large, ranging between .21 and .43, but larger standard errors accompany these estimates demonstrating the reduced power of the analysis for individual cohorts. There were five SNPs that passed the suggestive significance criterion for inspection time, and two of these were located in a single known gene, *CRTC3*. For simple RT, 11 SNPs were identified at the suggestive level of significance, with a SNP on chromosome 3 located in *MYRIP*. For 2-choice RT mean, 10 SNPs (on 6 chromosomes and two in *DCDC2*) showed suggestive association. The beta weights for all top SNPs for each trait were homogenous between cohorts ($p > .05$). For 4-choice RT, five SNPs showed suggestive significance, they were located in *FAM110C*, *DIP2C* and *KCTD2*. In the Australian cohort, the majority of SNPs showing suggestive association with 8-choice RT mean were in almost perfect LD with each other. SNPs on five chromosomes were identified and two known genes were implicated (*RAB11F1P2*, *LAPTM4A*). Minor allele frequencies were above .07 and effect sizes ranged between .18 and .41. Six SNPs were suggestively significant for the processing speed factor; some were located in *PDE1C* and *PKNOX1* genes. Only one SNP (rs1375785) showed suggestive association with multiple measures (2- and 8-choice RT).

2.1. Biological pathways analysis

The results of the biological pathways analysis of all the speed measures – using ALIGATOR software – are shown in Appendix CSupplementary Table 2. Pathways which overlapped across measures are shown in Table 3. Most of these were part of the biological process category: the three terms associated with inspection time and the speed factor related to vascular process; the two terms associated with simple RT and 4-choice RT were related to biosynthetic process; while the term associated with inspection time and 8-choice RT was a renal system process involved in regulation of systemic arterial blood pressure. The cellular component associated with the choice RT measures comprised terms that were all related to organelle and cell components. The three terms represented in the molecular function category associated with simple RT, choice RT, inspection time and digit symbol were in different pathways.

Table 4 shows the results of the SNPratio pathways analysis undertaken for the speed factor in the Brisbane and LBC1936 cohorts. Two pathways, focal adhesion and cell junction, were identified in both cohorts. Interestingly, the ALIGATOR results for the speed factor also showed an association with the regulation of focal adhesion formation category ($p = .004$). We searched these two pathways for SNPs that were nominally significant in both cohorts. No SNPs were identified that were exclusively tied to the cell junction pathway, that is, they were also linked with the focal adhesion pathway. There were twenty-seven of these (in five

known genes: *LAMB4*, *COL5A1*, *COL4A1*, *VTN*, and *LAMA1*). Seventeen SNPs in six genes (*MAPK10*, *ITGA2*, *PIK3R1*, *TLN2*, *PRKCA*, and *PARVB*) were identified only in the focal adhesion pathway. This included one non-synonymous coding SNP (rs704) on chromosome 17 in the *VTN* gene. The two significant biological pathways identified in the Brisbane and LBC1936 cohorts were not significant in the smaller LBC1921: focal adhesion pathway, $p = .85$; cell junction pathway, $p = .99$. Nor were any of the nominally significant SNPs identified within these pathways replicated ($p > .05$).

3. Discussion

This was the first genome-wide association scan of chronometric information processing speed measures with a number of SNPs showing suggestive association with various traits in both the adolescent and elderly cohorts. Some of these SNPs were in genes that appeared to be theoretically relevant to cognitive processing. Furthermore, a biological pathways analysis revealed SNPs in the cell junction and focal adhesion pathways to be overrepresented at a nominal significance level for the speed factor. Pathways analysis of the other traits showed that biological process pathways (sets of molecular events with a defined beginning and end) were overrepresented among the associations of pathways with multiple variables.

Up to 11 (for 2-choice RT) mostly independent SNPs were identified for the measures at a suggestive significance level. For every SNP located in or nearby a gene a NCBI database search was performed to check the gene function and any previously reported associations with cognition-related traits. A number of candidate genes were suggested by this bioinformatics search (see Table 5). Some of these have been associated with psychiatric diseases characterised by cognitive impairment of some sort (e.g., dyslexia, Alzheimer's disease (AD)), while others are involved in metabolic syndromes which are known to have negative effects on cognition. The association with immune system related disorders is also interesting because a polymorphism in *TNF-alpha* (which encodes a proinflammatory cytokine) has been associated with processing speed in the elderly (Baune et al., 2008).

The speed measures were inter-correlated, and in the Brisbane sample have been shown to be genetically related (Luciano et al., 2004), we therefore expected some overlap between these measures in the GWA results. Only one of the top hits overlapped across measures (2-choice and 8-choice RT) and this SNP was not located near any known gene. Importantly, most of the top hits for each measure showed nominally significant associations with other speed measures. The top hits for digit symbol, symbol search and 4-choice RT were all nominally significant with other speed measures; and one of the top hits for inspection time, simple RT, and all choice RT conditions each showed nominal association with four other speed measures. It is interesting to note that for symbol search, which was only measured in the LBC1936, there were associations with variables that were unmeasured in this cohort (i.e., 2-choice and 8-choice RT) suggesting that not all the common associations can be attributed to correlated type 1 error. The speed factor was most frequently nominally associated with the top hits from other variables and these were not restricted to the measures of which it was composed, suggesting that it was tapping reliable variance related to general speed processes.

Like our study, a previous genome-wide association study of digit symbol and symbol search did not uncover any genome-wide significant associations (Cirulli et al., 2010). This study was less powered than ours with a sample size of 1086 and 414 for the respective measures; none of their 100 top SNPs for each analysis overlapped with our top 100. However, for digit symbol eight of their top 100 SNPs (rs9302365, rs2280645, rs10500956, rs1874989, rs17572757, rs4880535, rs9310772, rs9883639) were significant at a nominal

level from 89 that we had results for; two of these SNPs were in the *ADARB2* gene. For symbol search, three of their top 100 SNPs from 92 that we had results for were nominally significant, these included: rs11812109, rs16896091, and rs4723454. Our study agrees with theirs in that common genes do not influence psychometric speed measures with large effect size.

Biological pathways analysis linked to the GO database uncovered a number of pathways common to multiple measures, in particular, the choice RT measures. Across the measures, there was a recurrence of associations with gene products related to vascular and biosynthetic processes and to organelle and cell components. Using the manually defined pathways from KEGG to investigate the speed factor, two pathways – cell junction and focal adhesion – were identified in the Australian and Scottish LBC1936 cohorts, and when we traced the significant SNPs in these pathways, 44 SNPs were identified in 11 genes. These genes were all in the focal adhesion pathway, although five of these were also involved in cell junction. Focal adhesions are structures consisting of proteins at cell-extracellular matrix (ECM) adhesions, and they are involved in controlling cell behaviour. This pathway was also implicated for the speed factor in the ALIGATOR analysis using GO terms. Of the significant genes we identified in this pathway, several are particularly interesting due to their link with AD. The alpha 1 laminin isoform is over-expressed in AD frontal cortex and presents as punctate deposits in the senile plaques, and in the astrocytes of grey and white matter (Palu and Liesi, 2002), providing a basis for linking *LAMA1* to the aetiology of AD. Type 4 collagen (*COL4A1* is part of the gene family coding for this protein) has also been localised within the senile plaques as punctuate deposits (Kiuchi et al., 2002); and integrins (e.g., *ITGA2* gene product) have been identified immunohistochemically in cerebal amyloid plaques (Eikelenboom et al., 1994), again suggesting that variation in these relevant genes might be important. By the same logic, reduced levels of protein kinase C alpha (e.g., *PRKCA* gene product) have been linked to an altered amyloid precursor protein secretion in fibroblasts from AD patients (Benussi et al., 1998). The only gene (of those we identified in the focal adhesion pathway) to be directly tested for association with AD is *PIK3R1* (Liolitsa et al., 2002). Here, the Met326Tyr polymorphism showed association with risk of late-onset AD in women and in patients where the *APOE* e4 allele was not present; this was argued to relate to impaired insulin mediated signal transduction.

In summary, our study used two approaches to help localise genetic variants influencing information processing speed: association with single SNPs and association within significant biological pathways. Our speed measures shared common variance, and this overlap was demonstrated for most of the top association signals in the SNP analysis, where at least one, and up to four, other variables were nominally associated. Only one SNP reached suggestive association levels for multiple traits (i.e., 2- and 8-choice RT), suggesting that pleiotropic genes have different strengths of association with correlated traits. Further, it might be that much smaller gene effects (and not detectable in our study at genome-wide level) influence pleiotropy among speed traits and, conversely, genes with larger effect influence the unique genetic variance also known to influence speed measures. Five of the candidate genes identified from the biological pathways analysis of the speed factor were implicated in the pathophysiology of AD. Several genes (e.g., *APOE*, *APP*) predisposing to AD have been associated with variation in normal cognition, and there is some indication that the effect of these genes may be stronger for processing speed than for general intelligence or even memory (Harris et al., 2007; Luciano et al., 2009). Thus, the pursuit of AD genes in normal cognition, and especially processing speed traits, might prove worthwhile.

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Supplementary Material

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Acknowledgments

QIMR: We especially thank the twins and their families for participation; Marlene Grace, Ann Eldridge, and Kerrie McAloney for phenotype collection; Anjali Henders, Megan Campbell, Lisa Bowdler, Steven Crooks and staff of the Molecular Epidemiology Laboratory for DNA sample processing and preparation; Harry Beeby, David Smyth and Daniel Park for IT support; and Drs Dale R Nyholt and Scott Gordon for their substantial efforts involving the QC and preparation of the GWA datasets. The research was supported by the Australian Research Council (A7960034, A79906588, A79801419, DP0212016, DP0343921), with genotyping funded by the National Health and Medical Research Council (Medical Bioinformatics Genomics Proteomics Program, 389891). The Genetic Cluster Computer (http://www.geneticcluster.org) which is financially supported by the Netherlands Organization for Scientific Research (NWO 480-05-003), was used for statistical analyses.

LBC: We thank the LBC1921 and LBC1936 participants. We thank the LBC1936 study Secretary Paula Davies. We thank Michelle Taylor, Janie Corley, Caroline Brett, Alison Pattie, Martha Whiteman and Caroline Cameron for data collection and data entry. We thank the staff at Lothian Health Board, and the staff at the SCRE Centre, University of Glasgow; and Jenny Huffman for performing some of the genotyping. The LBC1921 data described here were collected in waves funded by the BBSRC and the Chief Scientist Office of the Scottish Executive. The LBC1936 was supported by a programme grant (to IJD and JMS) from Research Into Ageing, which continues with funding from Help the Aged as The Disconnected Mind. The work was undertaken by The University of Edinburgh Centre for Cognitive Aging and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative. Funding (to IJD and JMS) from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged. ML is a Royal Society of Edinburgh/Lloyds TSB Foundation for Scotland Personal Research Fellow.

HBCS: We thank all study participants as well as everybody involved in the Helsinki Birth Cohort Study. Helsinki Birth Cohort Study has been supported by grants from the Academy of Finland, the Finnish Diabetes Research Society, Folkhälsan Research Foundation, Novo Nordisk Foundation, Finska Läkaresällskapet, Signe and Ane Gyllenberg Foundation, University of Helsinki, European Science Foundation (EUROSTRESS), Ministry of Education, Ahokas Foundation, Emil Aaltonen Foundation, Juho Vainio Foundation, and Wellcome Trust (grant number WT089062).

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Table 1

Mean scores of the processing speed measures in the Australian, Scottish and Finnish studies, stratified across sex, and their correlations with age and with other variables.

	N	Total sample		Men		Women		Correlation with age	Inter-trait correlations (all significant $p < .001$)				
		Mean	SD	Mean	SD	Mean	SD		1. DS	2. IT	3. 2CRT	4. 4CRT	5. 8CRT
Brisbane													
1. Digit Symbol (no. correct in 90 s)	1659	59.25	11.05	54.66	10.22	63.39	10.10	.05*	1				
2. Inspection Time (ms)	1388	92.40	65.79	92.41	75.26	92.39	56.19	−.05*	−.21	1			
3. 2-Choice RT mean (ms)	1531	308.61	39.97	311.20	41.93	306.32	38.04	−.02	−.33	.15	1		
4. 4-Choice RT mean (ms)	1532	487.69	107.47	490.56	108.35	485.16	106.68	−.07**	−.34	.21	.46	1	
5. 8-Choice RT mean (ms)	1382	602.66	100.47	602.85	105.39	602.49	95.93	−.06*	−.35	.20	.62	.64	1
6. G speed factor	1172	.00	1.00	.20	.99	−.18	.94	−.08**	–	–	–	–	–
	N	Total sample		Men		Women		Correlation with age	Inter-trait correlations (all significant $p < .001$)				
		Mean	SD	Mean	SD	Mean	SD		1. DS	2. SS	3. IT	4. SRT	5. 4CRT
LBC1936													
1. Digit Symbol (no. correct in 120 s)	990	56.82	12.81	54.97	13.05	58.65	12.30	−.17**	1				
2. Symbol Search	991	24.82	6.28	24.85	6.48	24.79	6.09	−.23**	.61	1			
3. Inspection Time	952	112.19	11.00	113.99	10.62	110.37	11.10	−.03	.30	.32	1		
4. Simple RT mean (ms)	991	275.33	53.44	275.85	57.29	274.81	49.36	.06*	−.27	−.24	−.19	1	
5. 4-Choice RT mean (ms)	990	640.51	83.93	639.39	91.46	641.63	75.78	.12**	−.50	−.46	−.36	.47	1
6. G speed factor	949	.00	.98	.03	1.01	−.03	.95	−.17**	–	–	–	–	–
	N	Total sample		Men		Women		Correlation with age	Inter-trait Correlations (all significant $p < .001$)				
		Mean	SD	Mean	SD	Mean	SD		1. DS	2. IT	3. SRT	4. 4CRT	
LBC1921													
1. Digit Symbol (no. correct in 120 s)	307	41.83	12.84	42.54	12.44	41.27	13.15	.03	1				
2. Inspection Time	305	101.48	13.59	102.05	14.18	101.01	13.12	−.02	.36	1			
3. Simple RT mean (ms)	307	312.69	84.34	307.57	63.76	316.77	97.66	−.02	−.43	−.27	1		
4. 4-Choice RT mean (ms)	307	792.36	146.29	782.59	150.14	800.13	143.13	.04	−.61	−.34	.53	1	
5. G speed factor	309	.01	1.01	.08	1.00	−.05	1.02	−.01	–	–	–	–	
	N	Total sample		Men		Women		Correlation with age	Inter-trait correlations (all significant $p < .001$)				
		Mean	SD	Mean	SD	Mean	SD		1. SRT	2. 2CRT			

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	N	Total sample		Men		Women		Correlation with age	Inter-trait correlations (all significant $p < .001$)				
		Mean	SD	Mean	SD	Mean	SD		1. DS	2. IT	3. 2CRT	4. 4CRT	5. 8CRT
HBCS													
1. Simple RT mean (ms)	1080	349.42	88.81	332.84	74.22	362.25	96.76	$.12^{***}$	1				
2. 2-Choice RT mean (ms)	1071	580.58	117.62	564.79	93.77	592.66	131.80	$.09^{**}$	.63	1			

$^{*}p < .05$.

$^{**}p < .001$.

$^{***}p < .0001$.

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Biol Psychol. Author manuscript; available in PMC 2012 April 04.

Table 2

Description and results (beta, SE, *p*) of the top SNPs associated with digit symbol, symbol search, inspection time, simple RT, choice RT measures and the speed factor ($p < 1.21\times10^{-5}$); bolded gene name indicates that the SNP lies in the gene/locus.

SNP	Ch	Position	Allele		MAF Range	Results				Individual-analysis *p*				Nominally significant p of other measures
			1	2		Beta	SE	Meta-*p*	Gene/Locus	Brisbane	LBC1936	LBC1921	HBCS	
Psychometric														
Digit symbol (DS)														
Rs10490919	10	117512588	T	G	.46–.49	−.12	.03	1.88E-06	***ATRNL1***	4.20E–03	6.98E–05	4.59E–01	–	SS (.007); CRT4 (.048)
Rs4247092	15	96225221	T	G	.46–.48	−.12	.03	5.59E–06	AC015574.1	4.50E–02	8.38E–06	2.65E–01	–	SS (.003); Factor (.048)
Rs2567426	15	96332861	A	G	.33–.35	.13	.03	3.23E–06	AC015574.2	3.90E–02	5.69E–06	2.45E–01	–	SS (.002); Factor (.031)
Rs7283316	21	32216253	A	G	.38–.39	−.37	.08	8.71E–06	KRTAP7-1	–	8.53E–01	1.23E–05	–	IT (.007)
Symbol search (SS)														
Rs6707697	2	109940324	G	T	.07	−.43	.08	–	***SH3RF3***	–	2.29E–07	–	–	CRT8 (.008)
rs2255798	6	31629281	C	G	.11	.31	.07	–	***NFKBIL1***	–	1.66E–06	–	–	DS (.027); Factor (.005)
rs2230365	6	31633427	T	C	.13	.28	.06	–	***NFKBIL1***	–	6.57E–06	–	–	Factor (8.38E–05)
rs7087965	10	16689683	A	G	.32	−.21	.05	–	***RSU1***	–	4.93E–06	–	–	CRT2 (.008); DS (.014)
Chronometric														
Inspection time (IT)														
rs2392362	7	35401447	T	C	.27–.31	−.14	.03	2.40E–06	AC007652.1	3.90E–03	2.46E–03	1.97E–02	–	–
rs12915189	15	91114376	A	G	.29–.33	.14	.03	2.97E–06	***CRTC3***	2.30E–03	8.85E–05	8.56E–01	–	–
rs3743401	15	91185994	T	C	.21–.24	.15	.03	7.10E–06	***CRTC3***	8.00E–04	1.22E–03	7.64E–01	–	–
rs7219585	17	72268208	A	G	.13–.14	.20	.04	1.03E–06	*DNAI2*	4.10E–02	2.70E–04	7.12E–04	–	SS (.007); CRT4 (.039); DS (.004); Factor (.003)
rs1884136	20	10850464	T	G	.09–.11	.20	.05	8.65E–06	RP4-697P8.2	9.60E–05	8.11E–02	6.08E–02	–	SRT (.03)
Simple RT (SRT)														
rs7566934	2	176654738	A	G	.29–.32	−.13	.03	7.03E–06	*EXTL2P1*	–	5.23E–03	7.92E–02	2.40E–03	Factor (.038)
rs1446829	2	176677084	A	G	.31–.32	−.13	.03	7.09E–06	*EXTL2P1*	–	2.14E–02	6.38E–02	6.34E–04	Factor (.015)
rs9985399	3	40008634	T	C	.05–.07	−.26	.06	8.79E–06	***MYRIP***	–	4.87E–02	3.20E–01	6.66E–05	CRT2 (.005); CRT4 (.012); IT (.007); SS (.024)
rs523340	9	111854246	A	G	.10–.12	.21	.04	2.43E–06	**C9orf5**	–	5.83E–04	8.61E–03	2.52E–02	DS (.019); IT (.026)
rs2908835	12	11648418	T	C	.23–.24	.14	.03	6.51E–06	AC007450.3	–	1.21E–01	4.85E–02	5.54E–05	–
rs10148969	14	90968374	T	C	.38–.42	−.12	.03	1.08E–05	*TTC7B*	–	1.03E–04	7.46E–01	7.20E–03	CRT4 (.025); Factor (.012)
rs17291845	16	55245037	A	G	.13–.14	.19	.04	4.70E–06	AC109462.1	–	4.48E–03	1.05E–01	1.43E–03	IT (.022)
2-choice RT														
rs6801136	3	55265321	T	C	.33–.34	−.13	.03	9.97E–06	RP11-889D3.262	2.10E–04	–	–	1.17E–02	Factor (.045)
rs6922632	6	24107093	A	C	.10–.16	.19	.04	4.18E–06	*NRSN1*	7.50E–03	–	–	5.79E–05	SRT (.002)

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SNP	Ch	Position	Allele		MAF Range	Results				Individual-analysis *p*				Nominally significant p of other measures
			1	2		Beta	SE	Meta-*p*	Gene/Locus	Brisbane	LBC1936	LBC1921	HBCS	
rs9460980	6	24233288	A	G	.35–.39	−.13	.03	4.34E–06	***DCDC2***	2.60E–02	–	–	1.22E–05	–
rs793834	6	24234933	A	G	.18–.25	.15	.03	2.85E–06	***DCDC2***	8.70E–04	–	–	8.97E–04	SRT (.041)
rs1375785[a]	8	83991231	A	C	.08–.12	−.20	.05	8.41E–06	–	2.60E–05	–	–	6.78E–02	CRT8 (1.00E–06); CRT4 (.016)
rs11212364	11	97574984	A	G	.03–.11	−.26	.05	2.96E–06	AP005434.1	2.10E–03	–	–	2.82E–04	SRT (.008); SS (.036)
rs17124581	14	88826682	T	C	.06	−.27	.06	2.71E–06	*SPATA7*	4.90E–04	–	–	1.77E–03	Factor (.034)
rs4815868	20	5840539	A	G	.19	.16	.04	8.21E–06	**C20orf196**	2.90E–03	–	–	9.17E–04	CRT4 (.004); CRT8 (.027); DS (.008); SRT (.006)
4-Choice RT														
rs11542478	2	38938	A	C	.10–.12	.19	.04	8.89E–06	***FAM110C***	8.70E–03	6.57E–04	1.98E–01	–	SRT (.018); IT (.04)
rs6961611	7	67426323	T	C	.02	−.63	.14	7.33E–06	RP11-358M3.1	–	5.83E–05	5.04E–02	–	DS (.038); Factor (.0005)
rs16939046	8	76147954	T	C	.09–.10	.22	.05	3.71E–06	**AC022274.1**	7.70E–03	2.83E–03	9.54E–03	–	CRT2 (.042); CRT8 (.048); IT (.017); SRT (.04)
rs17293454	10	633495	T	C	.08–.13	−.19	.04	1.20E–05	***DIP2C***	4.20E–03	8.46E–04	3.98E–01	–	SS (.018)
rs11077773	17	73060073	T	C	.06–.08	.24	.05	8.33E–06	***KCTD2***	3.00E–04	1.21E–02	2.94E–01	–	IT (.011); SRT (.043)
8-Choice RT														
rs1191812	2	20224999	C	A	.25	.22	.05	–	*LAPTM4A*	1.00E–05	–	–	–	CRT2 (.006); DS (.0008); SS (.014)
rs11694170	2	20260512	T	C	.21	.23	.05	–	AC098828.2	7.00E–06	–	–	–	CRT2 (.006); DS (.029); IT (.0322)
rs13170576	5	8467174	C	T	.07	.41	.09	–	RP11-480D4.3	1.20E–05	–	–	–	–
rs11156429	6	105364421	G	T	.46	−.18	.04	–	C6orf220	1.10E–05	–	–	–	CRT2 (.003); CRT4 (.00002); DS (.0001); SRT (.031)
rs1375785[a]	8	83991231	C	A	.12	.30	.06	–	–	1.00E–06	–	–	–	CRT2 (8.41E–06); CRT4 (.016)
rs1419141	10	119694504	A	G	.34	−.19	.04	–	*RAB11FIP2*	5.80E–06	–	–	–	–
Speed Factor														
rs10475598	5	173648438	T	C	.32–.34	.15	.03	8.10E–07	CTC-430J12.2	2.30E–02	9.55E–04	5.41E–04	–	DS (.02)
rs4710758	6	170455060	T	C	.32–.34	.14	.03	9.77E–06	RP11-302L19.1	5.30E–04	8.52E–03	2.35E–01	–	CRT8 (.031)
rs4723127	7	32225283	T	G	.43–.44	−.13	.03	9.54E–06	***PDE1C***	2.30E–03	3.92E–03	1.58E–01	–	–
rs6051520	20	351944	T	G	.21–.24	.18	.03	1.68E–07	*TRIB3*	3.40E–05	6.61E–03	6.63E–02	–	CRT8 (.002)
rs2839627	21	44448718	T	C	.11–.12	−.27	.06	6.17E–06	***PKNOX1***	2.00E–05	8.05E–02	1.18E–01	–	IT (.0002)

SNP = single nucleotide polymorphism. Ch = chromosome. A1 = allele 1 (effect allele); A2 = allele 2. MAF=minor allele frequency.

Note: The following SNPs were in LD (r^2 > .80) with significant SNPs reported in the table: Digit Symbol: rs10490919 with rs2804161, rs1157117; Symbol Search: rs2255798 with rs2857708, rs2736189, rs2009658, rs2844482; Inspection Time: rs3743401 with rs8028854, rs13379889; rs12915189 with rs6496696; Simple RT: rs523340 with rs1519466; rs17291845 with rs12926302, rs12918335; rs9985399 with rs6791790; 2-choice RT: rs9460980 with rs9295619, rs793842; 8-choice RT: rs1375785 with rs1449811; rs1375785 with rs4739919, rs896010; rs11694170 with rs1513831; rs11156429 with rs4946651, rs314262, rs31428; Speed Factor: rs10475598 with rs4295404.

[a]Overlapping SNP.

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Biol Psychol. Author manuscript; available in PMC 2012 April 04.

Table 3

Enriched GO categories ($p < .01$) for multiple speed measure.

GO number	Type	Genes in category	# genes on list	Expected # genes on list	*p*	Expected hits/study
GO:0008373	**Sialyltransferase activity**					
2-choice RT	FUNCTION	20	7	2.72	.0066	19.59
8-choice RT	FUNCTION	20	8	2.54	.0000	.7
GO:0030173	**Integral to Golgi membrane**					
2-choice RT	CELLULAR	41	12	5.48	.0014	4.43
8-choice RT	CELLULAR	41	12	5.17	.0008	2.73
GO:0031228	**Intrinsic to Golgi membrane**					
2-choice RT	CELLULAR	44	12	5.51	.0018	5.57
4-choice RT	CELLULAR	44	12	5.19	.0008	2.73
GO:0031301	**Integral to organelle membrane**					
2-choice RT	CELLULAR	100	16	8.69	.007	20.81
8-choice RT	CELLULAR	100	15	8.28	.0068	19.86
GO:0044237	**Cellular metabolic process**					
2-choice RT	PROCESS	4200	297	259.16	.001	3.37
8-choice RT	PROCESS	4179	278	244.93	.0036	10.65
GO:0016226	**Iron-sulfur cluster assembly**					
Simple RT	PROCESS	8	2	.16	.008	23.65
4-choice RT	PROCESS	8	2	.15	.008	24.07
GO:0031163	**Metallo-sulfur cluster assembly**					
Simple RT	PROCESS	8	2	.16	.008	23.65
4-choice RT	PROCESS	8	2	.15	.008	24.07
GO:0003071	**Renal system process involved in regulation of systemic arterial blood pressure**					
Inspection Time	PROCESS	4	2	.19	.0096	28.09
8-choice RT	PROCESS	4	3	.18	.0000	.7
GO:0008889	**Glycerophosphodiester phosphodiesterase activity**					
Inspection Time	FUNCTION	7	3	.51	.0076	22.12
Simple RT	FUNCTION	7	3	.52	.0066	19.5

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GO number	Type	Genes in category	# genes on list	Expected # genes on list	*p*	Expected hits/study
GO:0005102	**Receptor binding**					
Digit Symbol	FUNCTION	655	68	51.68	.0054	15.69
Inspection Time	FUNCTION	655	68	51.83	.0054	15.7
GO:0001568	**Blood vessel development**					
Inspection Time	PROCESS	191	29	18	.0022	6.63
Speed Factor	PROCESS	191	29	18.37	.0044	12.8
GO:0001944	**Vasculature development**					
Inspection Time	PROCESS	195	29	18.18	.0026	7.74
Speed Factor	PROCESS	195	30	18.55	.0032	9.32
GO:0048514	**Blood vessel morphogenesis**					
Inspection Time	PROCESS	162	28	15.73	.0000	.77
Speed Factor	PROCESS	162	27	16.03	.0022	6.58

Note: Results from ALIGATOR using association *p* values.

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Table 4

Enriched KEGG Pathways ($p < .05$) for the Speed Factor. Common pathways between cohorts have been bolded.

Brisbane	***p***	**LBC1936**	***p***
Human diseases, immune disorders	.003	Primary immunodeficiency	.006
Cellular processes, immune system	.003	Tight junction	.009
Environmental information processing, signal transduction	.007	**Focal adhesion**	.011
Metabolism, metabolism of other amino acids	.014	Valine, leucine and isoleucine biosynthesis	.014
Metabolism, glycan biosynthesis and metabolism	.019	**Cell junction**	.02
Cellular processes, endocrine system	.019	Extracellular matrix-receptor interaction	.035
Focal adhesion	**.022**	Peroxisome proliferator-activated receptors signalling pathway	.039
Cell junction	**.03**		
Genetic information processing, replication and repair	.046		
Complement and coagulation cascades	.046		
Glycan structures – biosynthesis 1	.05		

Note: Results from SNPratio using observed genotypes.

Table 5

Genes with Known Function from the List of Best Hits in Table 2.

Gene function	Gene, Chr, Chr-Band ● ***Meta-analysis association*** ○ ***Single study association***[a]	Literature supporting gene function
Neurological	*DCDC2*, 6, 6p22.2 ● *2-Choice RT, p = 2.9E−06* ● *Simple RT, p = .041*	*DCDC2* is thought to play a role in neuronal migration, and has been associated with dyslexia in multiple independent studies (e.g., Meng et al., 2005; Schumacher et al., 2006; Wilcke et al., 2009) (*p* values = .0003, .004, and <.05 respectively). It has been associated with variation in reading and spelling ability in a general population (*p* values <.001) (Lind et al., 2010), with inattention and hyperactivity/impulsivity symptoms of ADHD (Couto et al., 2009), and with the distribution of grey matter in language-related brain regions in healthy individuals (*p* < .01 for volumetric differences between genotype groups) (Meda et al., 2008).
Metabolic	*TRIB3*, 20, 20p13-p12.2 ● *Speed factor, p = 1.7E–07* ○ *8-Choice RT, p = .002*	*TRIB3* is a member of the Tribbles family of pseudokinases. Numerous studies point to its involvement in metabolic processes, e.g., in a US Caucasian case-control sample, the functional TRIB3 Q84R polymorphism has been nominally associated with: type 2 diabetes (T2D) (OR = 1.17, *p* = .04), early-onset of T2D (OR = 1.32, *p* = .002), and among a non-diabetic subset, R84 carriers had higher glucose levels (*p* = .005) and lower insulinogenic (*p* = .03) and disposition index (*p* = .02) during an oral glucose tolerance test (Prudente et al., 2009). Further, in two independent Italian samples, R84 carriers were found to be at higher risk of impaired glucose regulation (OR = 1.54, *p* = .004 and OR= 1.63, *p* = .027) (Prudente et al., 2010). In a Chinese cohort, individuals with the same variant were found to be at risk for metabolic syndrome (OR = 2.349, *p* = .018), with a particular predisposition to carotid atherosclerosis, in part due to the effects of abdominal obesity (OR = 2.351, *p* = .012), hypertriglyceridemia (OR = 2.314, *p* = .00003), and insulin resistance (OR-1.697, *p* = .023) (Gong et al., 2009). The same gene has shown nominal association with AD in a cohort of Swedish men (*p* = .044) – a finding replicated in a Canadian cohort of males and females (*p* = .001) (Giedraitis et al., 2009). *TRIB3* has also been implicated in the control of stress response (Ord et al., 2009).
Immune	*NFKBIL1*, 6, 6p21.3 ○ *Symbol search, p = 6.6E–06, p = 1.66E–6* ● *Digit symbol, p = .027* ● *Speed factor, p = .005, P = 8.38E–05*	*NFKBIL1* is located on the human leukocyte antigen locus, which is the major histocompatibility complex in humans and contains a large number of genes involved in immune system function. It has been associated with rheumatoid arthritis in case-control Japanese (*p* = .006) (Okamoto et al., 2003) and Taiwanese cohorts (*p* = .004) (Lin et al., 2006). Functional characterisation of the gene supports a role in the pathogenesis of rheumatoid arthritis, and further, indicates that NFKBIL1 proteins may be involved in mRNA processing or the regulation of translation (Greetham et al., 2007). *NFKBIL1* has also been associated with other inflammation-related disorders: chronic thromboembolic pulmonary hypertension in a Japanese cohort (*p* = .0002) (Kominami et al., 2009), and the development of chronic Chagas' cardiomyopathy among Trypanosoma cruzi-infected individuals in a Brazilian cohort (*p* = .009) (Ramasawmy et al., 2008).

Note: Gene selection was based on searches conducted using the Genetic Association Database (geneticassociationdb.nih.gov). Only genes with multiple, independent indicators of function were included.

a Phenotype available for one cohort only.