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Neurocognitive impairment in type 2 diabetes: evidence for shared genetic aetiology

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Abstract

Aims/hypothesis—Type 2 diabetes is associated with cognitive impairments, but it is unclear whether common genetic factors influence both type 2 diabetes risk and cognition.

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Methods—Using data from 1892 Mexican-American individuals from extended pedigrees, including 402 with types 2 diabetes, we examined possible pleiotropy between type 2 diabetes and cognitive functioning, as measured by a comprehensive neuropsychological test battery.

Results—Negative phenotypic correlations (ρ_p) were observed between type 2 diabetes and measures of attention (Continuous Performance Test [CPT d']: $\rho_p = -0.143$, $p=0.001$), verbal memory (California Verbal Learning Test [CVLT] recall: $\rho_p = -0.111$, $p=0.004$) and face memory (Penn Face Memory Test [PFMT]: $\rho_p = -0.127$, $p=0.002$; PFMT Delayed Test: $x_p = -0.148$, $p=2\times10^{-4}$), replicating findings of cognitive impairment in type 2 diabetes. Negative genetic correlations (ρ_g) were also observed between type 2 diabetes and measures of attention (CPT d': $\rho_g = -0.401$, $p=0.001$), working memory (digit span backward test: $\rho_g = -0.380$, $p=0.005$), and face memory (PFMT: $\rho_g = -0.476$, $p=2\times10^{-4}$; PFMT Delayed Test: $\rho_g = -0.376$, $p=0.005$), suggesting that the same genetic factors underlying risk for type 2 diabetes also influence poor cognitive performance in these domains. Performance in these domains was also associated with type 2 diabetes risk using an endophenotype ranking value approach. Specifically, on measures of attention (CPT d': $\beta = -0.219$, $p=0.005$), working memory (digit span backward: $\beta = -0.326$, $p=0.035$), and face memory (PFMT: $\beta = -0.171$, $p=0.023$; PFMT Delayed Test: $\beta = -0.215$, $p=0.005$), individuals with type 2 diabetes showed the lowest performance, while unaffected/ unrelated individuals showed the highest performance, and those related to an individual with type 2 diabetes performed at an intermediate level.

Conclusions/interpretation—These findings suggest that cognitive impairment may be a useful endophenotype of type 2 diabetes and, therefore, help to elucidate the pathophysiological underpinnings of this chronic disease.

Keywords

Cognitive function; Cognitive impairment; Genetic correlation; Genetic overlap; Type 2 diabetes

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Introduction

Over 29 million Americans have diabetes and 90–95% of these have type 2 diabetes [1]. If current trends continue, as many as one in three Americans are predicted to have diabetes by 2050 [1, 2], prompting Zimmet and colleagues to claim that type 2 diabetes is an 'epidemic' with profound societal consequences [3].

From the prospective of pathophysiology, the sevenfold increase in type 2 diabetes prevalence over the past 60 years [2] must be due to environmental factors (or the interaction of environmental factors with genetic background) since genetic variation on such a short timescale is relatively constant. Nevertheless, high concordance rates for type 2 diabetes in identical twins [4, 5] and aggregation of type 2 diabetes in families [6, 7] suggest that genetic factors play an important role in illness liability. However, despite recent progress in delineating the genetic architecture of type 2 diabetes [8], only around 10% of the risk attributable to genetic factors has been identified [9]. A potential reason for the slow progress in demarcating genomic regions that confer type 2 diabetes risk is that the genetic architecture of the illness is highly heterogeneous [10]. One strategy to reduce this heterogeneity is the application of allied phenotypes or endophenotypes [11], defined as

traits that are genetically related to, but not a symptom of, an illness. The endophenotype must show shared genetic aetiology with illness risk, such that the biological mechanisms underlying the endophenotype overlap with those that are disrupted in the disease [12]. Yet, despite the potential utility of the endophenotype strategy, relatively few studies have attempted to identify potential endophenotypes for type 2 diabetes.

While there are many potential medical complications of type 2 diabetes, cognitive impairment and dementia are increasingly recognised as clinically important [13]. Indeed, individuals with type 2 diabetes have a 1.5 times increased risk for Alzheimer's disease and other dementias [14], with longitudinal studies consistently reporting that type 2 diabetes in midlife is associated with increased risk of dementia in later life [14]. A recent meta-analysis of 2.3 million individuals, including more than 100,000 with dementia, found a 60% increased risk of any dementia in men and women with type 2 diabetes (women, pooled relative risk: 1.62; men, pooled relative risk: 1.58) [15]. Moreover, individuals with type 2 diabetes have modest, yet reliable, cognitive decrements when compared with individuals without type 2 diabetes [16, 17]. For example, meta-analyses report small to moderate impairments on measures of processing speed (Cohen's d −0.43 to −0.22 [18–20]), verbal declarative memory (d = −0.51 to −0.27 [18, 20]), visual declarative memory (d = −0.26 [18, 20]), executive functioning (d = −0.52 to −0.25 [18–20]) and motor functioning (d = −0.36 [18]) in individuals with type 2 diabetes. Cognitive impairments are also present in individuals with recent-onset type 2 diabetes [21], adolescents who later develop diabetes [22] and in individuals with impaired glucose tolerance [23]. Thus, at least part of the cognitive impairment associated with type 2 diabetes appears to preceed onset and may be related to risk for the illness.

Unlike other common sequelae of type 2 diabetes (e.g. retinopathy or peripheral neuropathy), cognitive impairments are only weakly associated with peripheral blood glucose levels or glucose regulation [24], suggesting that these impairments are not entirely due to current metabolic dysfunction (e.g. insulin resistance). Poor cognitive functioning also appears to be a risk factor for metabolic dysregulation [13], such as severe hypoglycaemic episodes [25], suggesting a bidirectional association between cognition and type 2 diabetes. Moreover, in a systematic review and synthesis of the literature, Biessels and colleagues [25] noted that effect sizes of cognitive impairment in type 2 diabetes are consistent across the lifespan and similar to those reported in individuals with impaired glucose tolerance [23], suggesting minimal influence of illness duration and/or age. Given evidence that cognitive impairments show relatively little association with clinical state, exist prior to illness onset and show minimal progression [13, 14], it is possible that at least some of the cognitive complications of type 2 diabetes reflect subtle biological changes associated with liability for type 2 diabetes. In other words, cognitive impairment may be an endophenotype of type 2 diabetes.

Using data from a large sample of Mexican-American individuals from extended pedigrees, we sought to find evidence for possible pleiotropy between cognitive functioning and type 2 diabetes, such that the genetic factors influencing these two traits overlap. Specifically, our aims were to: (1) estimate the heritability of type 2 diabetes and cognitive functioning in this

sample; (2) quantify the genetic correlation between these two traits; and (3) test for the effect of duration of type 2 diabetes on cognitive functioning.

Methods

Sample

Participants were from the Genetics of Brain Structure and Function (GOBS) study [26, 27],which is part of the San Antonio Family Heart Study (SAFH). Cognitive data and data on type 2 diabetes status were available for 1892 participants from 96 pedigrees (average [mean] family size, 19.2; range, 2–189). The sample was 60.4% female and had a mean age of 49.9 years (SD, 15.6; range, 18–97). GOBS data collection occurred between 2006 and 2016. Of the 1892 individuals, 402 received a type 2 diabetes diagnosis (see below), 1247 were related to an affected individual and 243 were unrelated to an affected individual (Table 1).

All participants were randomly selected from the community with the constraints that they were of Mexican-American ancestry, part of a large family, and lived in the San Antonio (TX, USA) region. All participants provided written informed consent. The institutional review board (IRB) at the University of Texas Science Center at San Antonio approved the study.

Neurocognitive assessment

Participants completed a 90 min neuropsychological test battery consisting of standard and computerised measures [28], including measures of attention, executive processing, working memory, declarative memory, language processing, intelligence and emotional processing. The vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) [29] provided an estimate of intelligence quotient (IQ). Participants were tested in their choice of language; 132 (7%) participants were tested in Spanish and the remainder were tested in English.

Type 2 diabetes diagnosis

Participants were classified as having type 2 diabetes if they had a fasting glucose concentration   7.0 mmol/l and/or a 2 h glucose level   11.1 mmol/l after OGTT. Participants who did not meet these criteria, but reported current treatment with oral glucose-lowering agents or insulin, and a history of diabetes, were also classified as having type 2 diabetes.

Quantitative genetic analysis

Univariate models—All genetic analyses were performed using the Sequential Oligogenetic Linkage Analysis Routines (SOLAR) software [30]. SOLAR implements a maximum likelihood variance decomposition to determine the proportion of variation in a phenotype due to genetic and environmental influences by modelling the covariance amongst family members as a function of genetic proximity. This approach can handle pedigrees of arbitrary size and complexity and, thus, is optimally efficient with regard to extracting maximal genetic information. The simplest such decomposition is one where the additive genetic contribution of a trait is indexed by the heritability (h^2). All cognitive

measures and type 2 diabetes underwent univariate decomposition analysis to ensure they were significantly heritable. Raw continuous traits were subjected to rank-based inverse-normal transformation to ensure that they were normally distributed. Residualised traits were then generated by entering age, age^2 and sex, and their interactions, as well as testing language and years of education, as fixed-effect covariates in all models. These residualised traits were used in all subsequent analyses. To control for multiple testing, the false discovery rate (FDR) was set at 5% in all genetic and statistical models [31].

Bivariate models—Bivariate polygenic models were used to decompose the phenotypic covariance between each neurocognitive measure and type 2 diabetes status into genetic and environmental constituents to determine the extent by which they were influenced by shared genetic effects. Specifically, bivariate polygenic analyses were performed to estimate phenotypic (ρ_p), genetic (ρ_g) and environmental (ρ_e) correlations, where: $\rho_p = \rho_g$ ($h^2_e h^2_i$) + ρ_e [$(1-h^2_e)(1-h^2_i)$], where h^2_e is the heritability of the endophenotype and h^2_i is the heritability of the illness. The significance of these correlations was tested by comparing the log likelihood for two restricted models (with ρ_p, ρ_g or ρ_e constrained to equal 0) against the log likelihood for the model in which these parameters were estimated. A significant phenotypic correlation is evidence for a phenotypic association (i.e. including both genetic and environmental influences) between neurocognitive measures and a type 2 diabetes diagnosis. A significant environmental correlation is evidence for a non-genetic factor jointly influencing both traits. A significant genetic correlation is evidence for pleiotropy suggesting that a gene or set of genes jointly influences both phenotypes. It is worth noting that there are multiple possible interpretations of genetic correlations. While the same genetic variants may contribute both to type 2 diabetes risk and cognitive functioning (horizontal pleiotropy), genetic variants related to type 2 diabetes risk may also have indirect effects on cognition (vertical pleiotropy) [32]. Nevertheless, the mechanisms underlying the observed genetic correlations between type 2 diabetes and cognitive impairment do not deter from the potential use of cognitive functioning as an endophenotype for type 2 diabetes. We also used bivariate models to decompose the phenotypic covariance between each neurocognitive measure and BMI, as well as between each neurocognitive measure and waist circumference.

Endophenotype Ranking Values—Parameters from these bivariate models were used to calculate endophenotype ranking values (ERVs). The ERV objectively prioritises potential endophenotypes for use in molecular genetics analyses [33]. The ERV represents the standardised genetic covariance between an endophenotype and an illness, defined as ERV = $(h^2_e h^2_i)|\rho_g|$, where h^2_e is the heritability of the endophenotype, h^2_i is the heritability of the illness and ρ_g is their genetic correlation. The ERV provides a measure between 0 and 1, with higher values indicating a stronger combination of genetic signal and relationship to disease.

Mean-based ERV calculation—The mean-based ERV (mERV) is an extension of the ERV. For details on the derivation of the mERV, see Glahn et al [34]. Briefly, the mERV leverages the many coefficients of relationship that exist in extended-pedigree data. The coefficient of relationship refers to the average (mean) number of alleles held in common

between individuals. For example, first-degree relatives (e.g. full siblings or parents) share, on average, 50% of their alleles, whilst second-degree relatives (e.g. grandparents or aunts/ uncles) share 25%, third-degree relatives (e.g. great-grandparents or great aunts/uncles) share 12.5% and so on. Thus, it is possible, given an individual with a disease, to index all other pedigree members by their degree of relatedness to that individual. For non-affected individuals with more than one relative with type 2 diabetes, the highest degree of relatedness is used. This scalar can then be used to perform a fixed-effect single-degree-of-freedom test within the univariate variance components analysis outlined above, providing an estimate of the standardised genetic covariance between the potential endophenotype and illness risk. The mERV can then be used in the same way as the ERV to rank potential endophenotypes by their degree of standardised genetic overlap with illness risk. In the present paper, the mERV was applied to type 2 diabetes and all neurocognitive measures with statistically significant genetic correlations.

Statistical analyses

We used ANOVA models, implemented in the statistical programming language R [35], to test for the effect of duration of type 2 diabetes on neurocognitive functioning. Participants with type 2 diabetes were categorised into two illness duration groups: (1) duration of less than 10 years; and (2) duration of 10 or more years. Neurocognitive scores were residualised in SOLAR for sex and testing language, then subsequently for sex, testing language and age. Finally, the three groups (unaffected, duration <10 years, duration 10 years) were matched by age using the 'MatchIt' package in R.

We also examined the effect of duration of type 2 diabetes on neurocognitive functioning using linear regression models. Duration in years was modelled onto cognitive functioning, both as linear and quadratic functions, the latter to account for potential nonlinearity in the association between type 2 diabetes duration and cognitive functioning.

Results

Evidence for pleiotropy between type 2 diabetes and neurocognition

Table 2 shows results of univariate and bivariate genetic analyses of type 2 diabetes on neurocognitive functioning. All neurocognitive measures were significantly heritable (h^2 range, 0.17–0.59), as was type 2 diabetes ($h = 0.59$; $p = 6 \times 10^{-14}$). Significant phenotypic correlations were observed between type 2 diabetes and measures of attention (Continuous Performance Test [CPT d']: $\rho_p = -0.143$, $p = 0.001$), verbal memory (California Verbal Learning Test [CVLT] recall: $\rho_p = -0.111$, $p = 0.004$), and face memory (Penn Face Memory Test [PFMT]: $\rho_p = -0.127$, $p = 0.002$; PFMT Delayed Test: $\rho_p = -0.148$, $p = 2 \times 10^{-4}$). These statistically significant phenotypic correlations were in line with standardised mean difference effect sizes (Fig. 1). Significant genetic correlations were observed between type 2 diabetes and CPT d' ($\rho_g = -0.401$, $p = 0.001$), digit span backward ($\rho_g = -0.380$, $p = 0.005$), PFMT ($\rho_g = -0.476$, $p = 2 \times 10^{-4}$) and PFMT Delayed Test ($\rho_g = -0.376$, $p = 0.005$), suggesting overlap between the genetic factors influencing type 2 diabetes and performance on measures of attention, working memory and face memory, respectively. Figure 2 shows results of mERV analyses. Standardised genetic covariances were statistically significant for

all cognitive measures: CPT d' ($\beta = -0.219$, $p=0.005$), digit span backward ($\beta = -0.326$, $p=0.035$), PFMT ($\beta = -0.171$, $p=0.023$) and PFMT Delayed Test ($\beta = -0.215$, $p=0.005$). However, the effect of relatedness on cognition differed between these measures; for CPT d', individuals with type 2 diabetes had the lowest scores, followed by their first-degree relatives and then their second- to sixth- degree relatives, whilst unaffected/unrelated individuals scored the highest. For the digit span backward, individuals with type 2 diabetes and their first-degree relatives had the lowest scores, followed by their second- to sixth-degree relatives, and unaffected/unrelated individuals scored the highest. For PFMT and PFMT Delayed Test, individuals with type 2 diabetes had the lowest scores, unaffected/ unrelated individuals had the highest scores, and those related to an individual with type 2 diabetes had intermediate scores.

No evidence for pleiotropy between BMI or waist circumference and neurocognition

Bivariate genetic analyses of BMI and waist circumference on cognitive functioning are shown in the electronic supplementary material (ESM) Table 1 and Table 2, respectively. Phenotypic, environmental and genetic correlations did not reach significance for any neurocognitive measure after correction for multiple testing, except for the phenotypic correlation between CPT d' and waist circumference ($\rho_p = -0.084$; ESM Table 2).

Deleterious effects of illness duration on neurocognition are confounded by age

Demographic characteristics of the unmatched and matched samples grouped by duration of type 2 diabetes (unaffected, duration <10 years, duration 10 years) are shown in ESM Table 3. ESM Fig. 1 shows age distributions for the age-matched groups. In the unmatched sample, the groups separated by type 2 diabetes duration differed significantly by age ($p<0.001$); in the matched sample, there was no statistically significant difference in age ($p=0.714$; ESM Table 3).

Analysis of illness duration group status on neurocognitive functioning are shown in Fig. 3 and ESM Table 4. When adjusting for sex, the duration <10 years group had lower cognitive scores than the unaffected individuals for 13 out of the 19 cognitive measures, while the duration 10 years group showed lower scores than the unaffected individuals for 16 out of the 19 measures (ESM Table 4). Moreover, the duration 10 years group showed lower scores than the duration <10 years group for digit symbol substitution ($\beta = -0.24$, $p=0.017$), Trail-Making A ($\beta = -0.36$, $p=0.001$), digit span forward ($\beta = -0.32$, $p=0.003$), Trail-Making B ($\beta = -0.24$, $p=0.041$), CVLT recall ($\beta = -0.26$, $p=0.018$) and emotion recognition ($\beta=-0.28$, $p=0.013$). Matching the groups by age attenuated most of these group differences, with the duration <10 years group performing worse than the unaffected individuals for CPT d' ($\beta = -0.30$, $p=0.006$), PFMT ($\beta = -0.27$, $p=0.015$) and PFMT Delayed Test ($\beta = -0.27$, $p=0.014$), the duration 10 years group performing worse than the unaffected individuals for CPT d' ($\beta = -0.26$, $p=0.026$), digit span forward ($\beta = -0.23$ $p=0.047$), CVLT recall ($\beta = -0.23$, $p=0.049$) and PFMT Delayed Test ($\beta = -0.23$, $p=0.049$), and the duration 10 years group performing worse than the duration <10 years group for digit span forward ($\beta = -0.34$, $p=0.010$). Adjusting additionally for age further attenuated these group differences, with the duration <10 years group performing worse than the unaffected individuals for PFMT ($\beta = -0.18$, $p=0.042$) and PFMT Delayed Test ($\beta = -0.22$, $p=0.009$), the duration 10 years group

performing worse than the unaffected individuals for CVLT recall ($\beta = -0.20$, $p=0.011$), and no statistically significant differences between the duration 10 years and duration <10 years groups.

Analyses of illness duration on cognitive functioning, with illness duration years as linear and quadratic functions, are shown in ESM Table 5 and ESM Table 6, respectively. Results were similar to above, with a significant effect of duration (linear function) on digit symbol substitution ($\beta = -0.019$, $p=0.001$), Trail-Making A ($\beta = -0.023$, $p=0.002$), digit span forward ($\beta = -0.016$, $p=0.021$), digit span backward ($\beta = -0.013$, $p=0.046$), letter number sequencing ($\beta = -0.014$, $p=0.021$), Trail-Making B ($\beta = -0.021$, $p=0.006$), CVLT learning ($\beta = -0.014$, $p=0.023$), CVLT recall ($\beta = -0.014$, $p=0.031$) and emotion recognition ($\beta = -0.015$, $p=0.021$) (ESM Table 5 and ESM Fig. 2). A significant effect of duration as a quadratic function, was also seen on digit symbol substitution ($\beta = -0.0006$, $p=0.001$), Trail-Making A ($\beta = -0.0007$, $p=0.014$), digit span forward ($\beta = -0.0005$, $p=0.034$), letter number sequencing ($\beta = -0.0005$, $p=0.011$), Trail-Making B ($\beta = -0.0007$, $p=0.011$), CVLT learning ($\beta = -0.0005$, $p=0.014$), and emotion recognition ($\beta = -0.0005$, $p=0.043$) (ESM Table 6 and ESM Fig. 3). No statistically significant effect of illness duration was seen when groups were matched for age, except for digit span forward ($\beta = -0.019$, $p=0.009$ for effect of duration as a linear function [ESM Table 5]; $\beta = -0.0005$, $p=0.032$ for effect of duration as a quadratic function [ESM Table 6]). There were no statistically significant effects of illness duration after further adjustment for age.

Discussion

Using a large sample of Mexican-American individuals from extended pedigrees, we established evidence for pleiotropy between cognitive impairment and type 2 diabetes. Significant genetic correlations were observed between type 2 diabetes and measures of attention, working memory and face memory, suggesting genetic overlap between type 2 diabetes and these cognitive domains. Moreover, significant genetic correlations were not observed between either BMI or waist circumference and cognitive performance, suggesting that the genetic overlap between type 2 diabetes and cognitive functioning is specific to the illness and not seen with general obesity factors. Finally, although there was an effect of duration of type 2 diabetes on magnitude of cognitive impairment, with individuals with a longer duration of illness showing larger impairments than individuals with a shorter duration of illness, these group differences were confounded by age. Our findings add to current knowledge about the pathophysiology of type 2 diabetes in several important ways.

First, the finding of pleiotropy between cognitive functioning and type 2 diabetes may be an important step forward in delineating the genetic underpinnings of type 2 diabetes, which affects an exponentially increasing number of individuals worldwide. While there has been progress in delineating the genetic architecture of type 2 diabetes [8], some argue that the illness remains 'a geneticist's nightmare' [9]. One strategy for identifying risk genes for type 2 diabetes is the application of endophenotypes [11, 36], i.e. traits that are genetically related to the illness. However, while there is strong evidence to suggest that individuals with type 2 diabetes show cognitive impairments, few studies have sought to establish whether these impairments are genetically correlated with the illness. Our finding of genetic overlap

between type 2 diabetes and measures of memory, working memory and attention is in line with evidence that the most consistent impairments in individuals with type 2 diabetes are in the domains of memory and executive function [18–20]. Moreover, this finding provides evidence for one of the principle criteria of endophenotypes: that the same genes that convey risk for the illness also influence the endophenotype [36]. Similarly, analyses of data from the UK Biobank and 24 international genome-wide association studies (GWAS) consortia showed that higher polygenic risk for type 2 diabetes was associated with decreased likelihood of obtaining a college degree [37]. However, a higher polygenic risk score (PRS) for type 2 diabetes was not associated with verbal reasoning, reaction time or memory in this sample [37], and no significant genetic correlations were reported between type 2 diabetes and any of the cognitive or education phenotypes when using linkage disequilibrium score regression (LDSC) [37]. Moreover, Mendelian randomisation (MR) analyses in the same sample provided no evidence for a causal association between type 2 diabetes and cognitive ability or educational attainment [38]. However, the methods used in the UK Biobank (PRS, LDSC and MR) primarily capture common genetic variance, while the genetic correlations observed in our study may be driven, at least in part, by rare genetic variants. In an ageing cohort, genetic risk of type 2 diabetes was positively associated with fluid intelligence, but no association was detected between type 2 diabetes PRS and verbal intelligence, memory or processing speed [39]. Thus, while our findings suggest that cognitive impairment may be a useful endophenotype of type 2 diabetes, future studies are needed to disentangle the genetic overlap between these traits at different ages, as well as across different cognitive domains. It is also worth noting that there are multiple possible interpretations of genetic correlations. While the same genetic variants may contribute both to type 2 diabetes risk and cognitive functioning, genetic variants related to type 2 diabetes risk may also have indirect effects on cognition, and genetic variants related to cognition may even have indirect effects on type 2 diabetes [32]. Nevertheless, the mechanisms underlying the observed genetic correlations between type 2 diabetes and cognitive impairment do not deter from the potential utility of cognitive functioning as an endophenotype for type 2 diabetes.

Second, we did not find evidence for a genetic association between cognitive function and either BMI or waist circumference. Previous evidence from twin and molecular genetic models indicate inconsistent findings regarding the genetic association between BMI and cognitive functioning, with reports of medium [40], small [41] and null [42] genetic correlations between the two traits. Even at the phenotypic level, the association between BMI and cognitive functioning is unclear, with reports of no association [43], cognitive impairment [44, 45] and even improved cognitive performance [46, 47] with higher BMI. We found null to small phenotypic and genetic correlations between neurocognition and both BMI and waist circumference, and none of these reached statistical significance after correction for multiple testing. Thus, any association between obesity indices and cognitive impairment may be due to environmental, rather than genetic, risk factors. Alternatively, genetic risk factors may interact with environmental changes throughout the life course, such that obesity-related pathology leading to cognitive impairment and/or decline may develop gradually over the course of many years [48]. Future studies are needed to determine whether this potential association between obesity indices and cognitive performance is moderated by age.

Finally, we found greater cognitive impairment in individuals with a longer duration of type 2 diabetes, but also that this group difference was attenuated when adjusting for age. Since age increases with duration of type 2 diabetes, adjusting for age undoubtedly attenuates part of the effect of duration on cognitive functioning. Nevertheless, this finding is in line with evidence that the magnitude of cognitive impairment associated with type 2 diabetes remains relatively stable throughout the lifespan [25]. Similarly, cognitive impairments are already present in individuals with recent-onset type 2 diabetes [21] and even in adolescents who later develop diabetes [22]. Moreover, a negligible effect of illness duration on cognition aligns with the finding of genetic overlap between type 2 diabetes and cognitive impairment, as well as the notion of a bidirectional relationship between these traits [13]. However, there have also been reports of an association between duration of type 2 diabetes and magnitude of cognitive dysfunction [49, 50]. Future longitudinal studies, which include individuals throughout premorbid and post-onset stages of type 2 diabetes, as well as repeating cognitive assessments, are needed to fully disentangle the complex mechanisms underlying the relationship between type 2 diabetes and poor cognitive outcomes. Moreover, future studies that use additional measures, such as blood glucose level and family history of type 2 diabetes, to examine whether some portion of the cognitive impairment associated with type 2 diabetes arises as a consequence of the illness, may also help elucidate these mechanisms.

This study has some limitations. First, due to the cross-sectional nature of this study, it is not possible to draw inferences about timing. While we found evidence for pleiotropy between type 2 diabetes and cognitive impairment, it remains unclear how these overlapping genetic factors might interact with other genetic and environmental risk factors over the lifecourse. Future longitudinal studies will help elucidate the complex mechanisms underlying risk for both type 2 diabetes and cognitive impairment, as well as potential developmental periods for optimal intervention and prevention. Second, the aim of this study was to examine pleiotropy between type 2 diabetes and cognitive impairment, but other potential explanations for the association between type 2 diabetes and cognitive impairment warrant further examination. As outlined above, future studies that are able to examine whether some portion of the cognitive impairment associated with type 2 diabetes arises due to the illness, or even whether some portion of type 2 diabetes risk is consequential to poor cognitive functioning, may yield interesting results.

Using a large sample of Mexican-American individuals from extended pedigrees, we established evidence for pleiotropy between impairment on measures of attention, working memory and memory, and type 2 diabetes. Thus, cognitive impairment may be a useful endophenotype of type 2 diabetes and may help elucidate the pathophysiological underpinnings of this chronic illness, which affects an large number of individuals worldwide. Future longitudinal studies will help disentangle these pathophysiological mechanisms over the life course in order to inform treatment strategies and intervention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations

CPT d'	Continuous Performance Test
CVLT	California Verbal Learning Test
ERV	Endophenotype ranking values
GOBS	Genetics of Brain Structure and Function
LDSC	Linkage disequilibrium score regression
mERV	Mean-based endophenotype ranking values
MR	Mendelian randomisation
PFMT	Penn Face Memory Test
PRS	Polygenic risk score
SOLAR	Sequential Oligogenetic Linkage Analysis Routines

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Research in context

What is already known about this subject?

- Type 2 diabetes has been associated with cognitive impairments

- Evidence suggests that these impairments are not sequelae of the illness

- Common genetic factors may influence both type 2 diabetes risk and cognitive dysfunction

What is the key question?

- Do the same genetic factors that influence type 2 diabetes risk also influence poor cognition?

What are the new findings?

- Negative genetic correlations between type 2 diabetes and performance on measures of attention, working memory and face memory suggest genetic overlap

- Cognitive performance was lowest in individuals with type 2 diabetes, highest in unaffected/unrelated individuals and intermediate in those related to an individual with type 2 diabetes

How might this impact on clinical practice in the foreseeable future?

- Cognitive impairment may be a useful endophenotype of type 2 diabetes and could help elucidate the pathophysiological underpinnings of this disease, eventually leading to improved detection and treatment
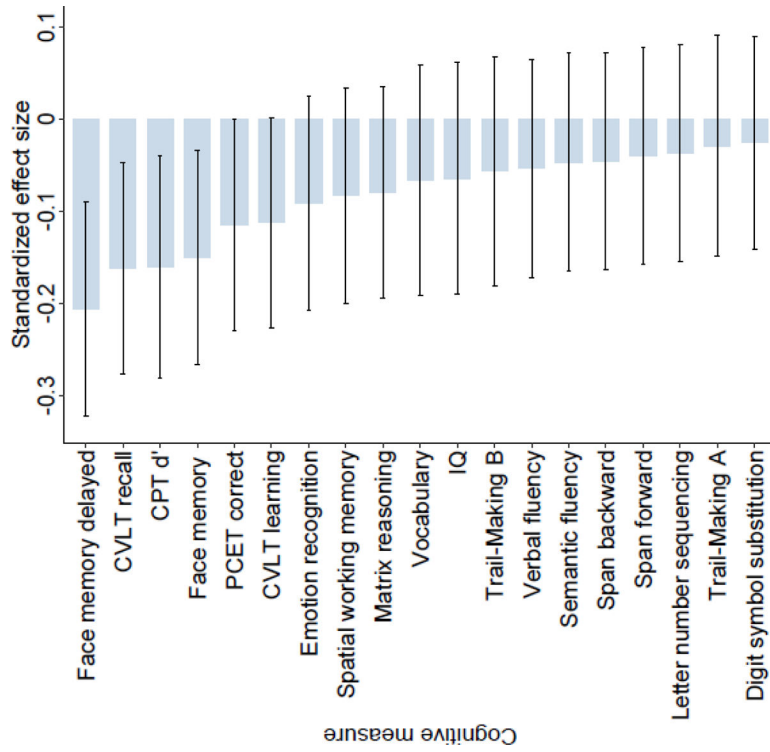
Fig. 1.
Standardised effect sizes and 95% CIs for all residualised cognitive measures comparing individuals with type 2 diabetes with individuals without (control data from unaffected individuals set at 0 for all measures). IQ, intelligence quotient; PCET, Penn Conditional Exclusion Test
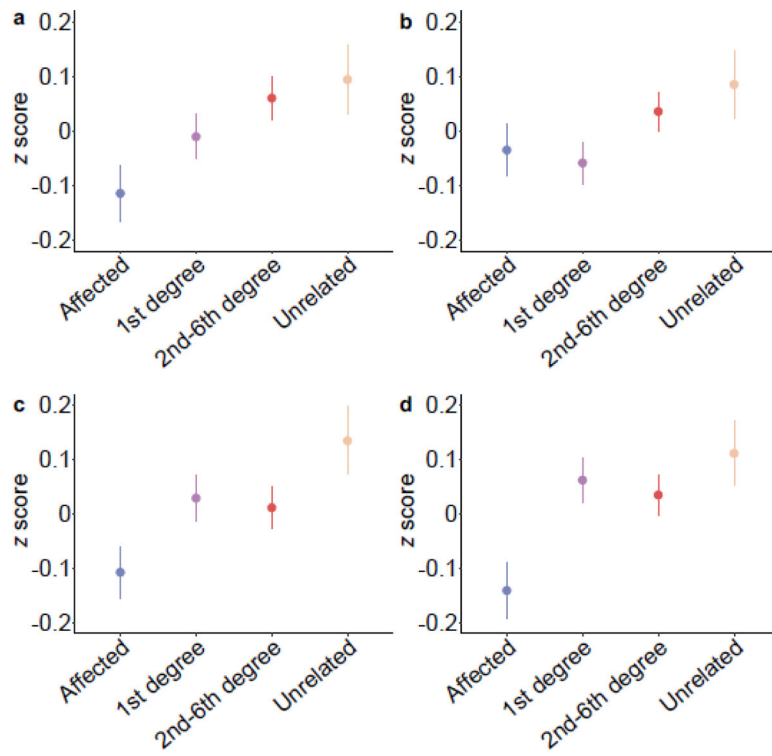
Fig. 2.
mERV analysis of cognitive measures with statistically significant genetic correlations, plotted by degree of relatedness. (**a**) CPT d': $\beta = -0.219$, $p=0.005$; (**b**) digit span backward: $\beta = -0.326$, $p=0.035$; (**c**) PFMT: $\beta = -0.171$, $p=0.023$; (**d**) PFMT Delayed Test: $\beta = -0.215$, $p=0.005$
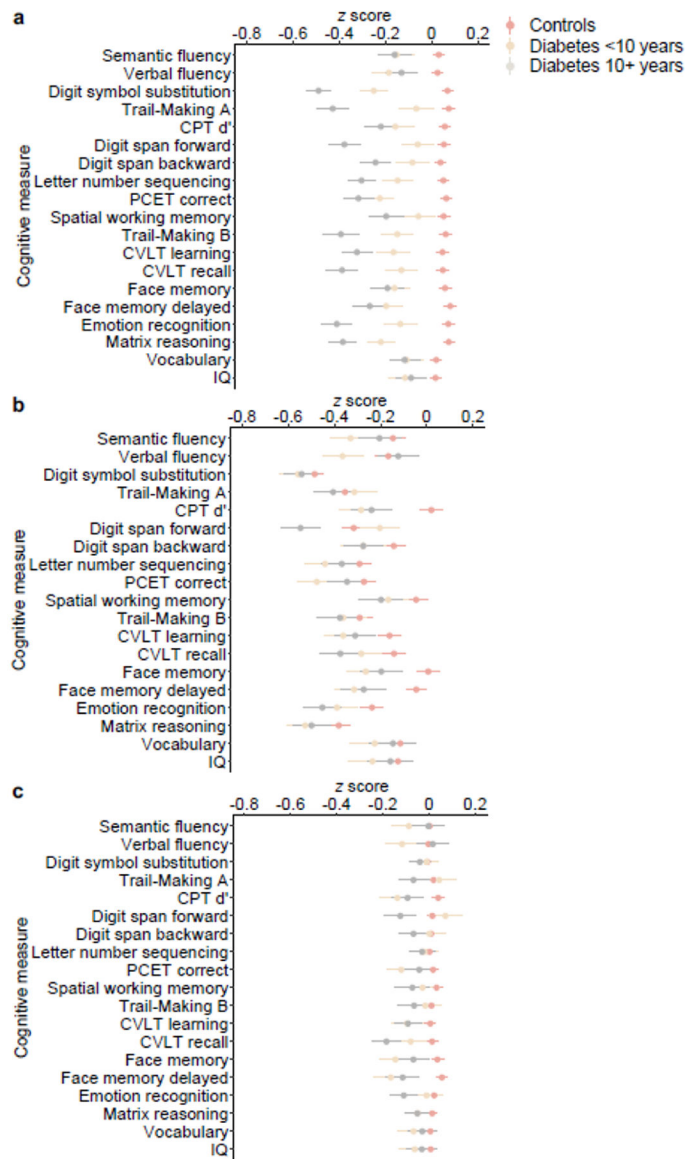
Fig. 3.
Means and SE of cognitive measures by illness duration, (**a**) adjusting for sex, (**b**) adjusting for sex and matched for age or (**c**) adjusting for sex, age, age^2, age×sex, age^2×sex. IQ, intelligence quotient; PCET, Penn Conditional Exclusion Test

Table 1

Basic demographics of the sample by degree of relatedness to an individual with type 2 diabetes

Degree of relatedness	n	Age, mean (SD)	Sex, % female
Affected	402	54.8 (12.6)	59.6
First degree	561	41.2 (13.4)	63.3
Second degree	337	34.3 (14.9)	57.0
Third degree	222	35.9 (12.7)	57.7
Fourth degree	105	29.4 (9.6)	61.0
Fifth degree	21	24.4 (8.3)	47.6
Sixth degree	1	19	100.0
Unrelated	243	45.5 (15.2)	63.0

Table 2

Results of genetic analyses of diabetes and cognitive measures

Cognitive Measure	Heritability		Phenotypic correlation		Environmental correlation		Genetic correlation		ERV
	h^2	p	ρ_p	p	ρ_e	p	ρ_g	p	
Semantic fluency	0.219	1×10^{-7}*	-0.043	0.277	0.022	0.821	-0.153	0.310	0.141
Verbal fluency	0.390	1×10^{-15}*	-0.045	0.254	0.056	0.609	-0.152	0.219	0.187
Digit symbol substitution	0.320	5×10^{-13}*	-0.018	0.668	-0.144	0.167	0.127	0.333	0.158
Trail-Making A	0.167	2×10^{-5}*	0.023	0.561	0027	0.778	0.024	0.888	0.048
CPT d'	0.380	1×10^{-17}*	-0.143	0.001*	0.087	0.402	-0.401	0.001*	0.296
Digit span forward	0.424	2×10^{-22}*	-0.055	0.170	0.007	0.949	-0.115	0.327	0.171
Digit span backward	0.307	1×10^{-13}*	-0.044	0.275	0.223	0.029	-0.380	0.005*	0.262
Letter number sequencing	0.272	8×10^{-12}*	-0.045	0.259	0.066	0.496	-0.203	0.133	0.180
PCET correct	0.241	4×10^{-10}*	-0.0,	0.047	-0.072	0.447	-0.095	0.501	0.117
Spatial working memory	0.272	2×10^{-12}*	-0.059	0.122	0.027	0.773	-0.186	0.167	0.172
Trail-Making B	0.305	2×10^{-11}*	0.052	0.195	0.030	0.765	0.085	0.530	0.124
CVLT learning	0.373	6×10^{-16}*	-0.086	0.027	0.043	0.678	-0.229	0.070	0.224
CVLT recall	0.355	1×10^{-16}*	-0.111	0.004*	-0.062	0.529	-0.173	0.160	0.191
PFMT	0.337	3×10^{-18}*	-0.127	0.002*	0.159	0.108	-0.476	2×10^{-4}*	0.305
PFMT Delayed Test	0.354	2×10^{-16}*	-0.148	2×10^{-4}*	0.034	0.742	-0.376	0.005*	0.270
Emotion recognition	0.212	1×10^{-7}*	-0.058	0.130	0.103	0.271	-0.341	0.029	0.202
Matrix reasoning	0.334	1×10^{-17}*	-0.058	0.142	-0.031	0.751	-0.095	0.448	0.137
Vocabulary	0.585	8×10^{-34}*	-0.053	0.187	0.064	0.605	-0.137	0.209	0.216
IQ	0.576	5×10^{-35}*	-0.049	0.228	0.030	0.810	-0.106	0.327	0.189

*
Significant after correction for multiple testing (FDR=0.05)

IQ, intelligence quotient; PCET, Penn Conditional Exclusion Test