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Genetics

Alzheimer's genetic risk intensifies neurocognitive slowing associated with diabetes in nondemented older adults

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Abstract

Introduction: We examine interactive and intensification effects of type 2 diabetes (T2D) with *APOE* and an Alzheimer's disease genetic risk score (GRS) on neurocognitive speed performance and change in nondemented older adults.

Methods: In an accelerated longitudinal design, we used latent growth modeling to test moderators of level and change in a neurocognitive speed latent variable for 628 adults (baseline median age = 69.0) followed over 9 years. The GRS was compiled using the cumulative risk of *APOE, CLU*, *CR1*, and *PICALM*.

Results: First, T2D predicted slower speed performance at centering age (75). Second, no predictive effects were associated with *APOE* or GRS. Third, a significant interaction showed that high risk from both T2D and GRS was selectively associated with steeper longitudinal slowing than all comparison cross-domain risk groups.

Discussion: Higher AD-related genetic risk intensified deleterious effects of diabetes on neurocognitive slowing in nondemented aging beyond the independent influence of *APOE*.

Keywords: Alzheimer's disease genetic risk score; *APOE*; Type 2 diabetes; Neurocognitive speed; Victoria longitudinal study

1. Introduction

Risk factors associated with Alzheimer's disease (AD) can be identified several years before the onset of the disease (e.g., obesity [1]). Prominent clusters of risk factors for AD also influence patterns of nondemented cognitive aging. These include biological (genetic polymorphisms), medical (type 2 diabetes [T2D]), lifestyle, and environmental factors. T2D is a potentially modifiable risk factor that has been linked to increased risk of AD [2,3] and to changes in the non-AD brain (e.g., exacerbated insulin dysregulation, disrupted Aβ clearance). These changes are associated with decrements in neurocognitive performance in cross-sectional and longitudinal studies [4–9]. The effects of T2D on nondemented cognitive aging may be modified or intensified by other risk factors including genetic risk [10–12].

Although *APOE* is the gene most consistently linked to AD risk, genome-wide association studies have identified several additional genotypes associated with AD [13–15]. These include *clusterin* (*CLU*), *complement component (3b/4b) receptor 1* (*CR1*), and *phosphatidylinositol-binding clathrin assembly protein* (*PICALM*). *APOE* has been associated with AD, mild cognitive impairment [16,17], and nondemented cognitive decline [18–20]. Specifically, ε4 carriers are at higher, and ε2 carriers at lower, risk for cognitive deficits, including neurocognitive speed [18,20,21]. *CLU, CR1,* and *PICALM* all contribute to AD

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risk, but the effects on cognitive outcomes show mixed results. The *CLU* risk allele (i.e., C) has been linked to faster rates of memory decline in individuals who eventually convert to mild cognitive impairment or AD [22]. The *CR1* risk allele (i.e., A) has been associated with faster decline in a five-domain global cognition measure [23]. For the *PICALM* risk allele (i.e., T), no significant associations with memory [24] or executive function [25] performance have been reported. This prompted us to test the minor allele (C) as a risk factor for cognitive decrements in nondemented aging. Independently, these genes present relatively low penetrance and consequently low effect sizes, but together they may account for substantial AD risk [13,14,26,27], especially within the context of other risk factors [28,29]. A joint or multilocus approach in the form of a genetic risk score (GRS) may be informative in representing combined AD genetic risk [26,28,30]. Although identification of multiple genetic risk factors via genome-wide association studies is very important, the in-depth examination of selected individual risk variants, both separately and in combination, provides novel understanding of the pathways leading to cognitive decline and AD [28,31]. Specifically for the present study, we examine *APOE* (rs429358, rs7412), *CLU* (rs11136000), *CR1* (rs6656401), and *PICALM* (rs541458).

Neurocognitive speed is considered a basic cognitive ability influencing decline on multiple complex cognitive processes with aging [32,33]. Speed may be an early indicator of normal or preclinical cognitive decline, possibly shaping the change profiles of more complex processes such as episodic memory or executive function. Speed has been reported to predict individual differences in global cognition and episodic memory [32,33], mild cognitive impairment [34,35], and risk of AD [36]. Important for the present study, T2D has been associated with typical speed deficits in older adults [7]. The present study uses a combinatorial candidate gene approach to identify an AD-related GRS. T2D status, *APOE,* and a GRS (i.e., *APOE, CLU, CR1, PICALM*) were analyzed independently and interactively (i.e., GRS × T2D status) using speed, modeled as a latent variable, as the outcome.

After first determining the best latent growth model representing the functional form of speed performance and change, we examined two research goals. Research goal 1 was to determine if T2D status, *APOE*, or GRS independently predicted latent speed level or 9-year longitudinal change. We hypothesized that both T2D status and GRS, but not *APOE*, would independently predict speed level and change. Research goal 2 was to determine if T2D status and *APOE* or GRS interactively predicted level of speed performance at age 75 (intercept) and 9-year slowing (slope). We hypothesized an intensification effect in that higher-risk GRS would magnify the negative associations of T2D with speed level and change above that of other risk combinations (including *APOE* independently). For validation, we checked the effects of T2D-associated factors as covariates and an alternate GRS (i.e., without *APOE*).

2. Methods

2.1. Participants

Participants were community-dwelling volunteer adults (initially aged 53–91 years) from the Victoria longitudinal study (VLS). The VLS is a longitudinal sequential study examining neurocognitive aging and impairment in relation to biomedical, genetic, health, lifestyle, and other aspects [37]. The VLS and all present data collection procedures are in full and certified compliance with prevailing human research ethics guidelines and boards. Informed written consent was provided by all participants. Using standard procedures (e.g., [38,39]), we assembled longitudinal data consisting of three VLS samples, each with three available waves collected in the 2002–2012 period. The longitudinal period was 8.9 years, and the band of aging represented was about 40 years (53–95).

The eligible source sample consisted of 683 participants with genetic data (collected in 2009–2011). Several exclusionary criteria were then applied to this source sample as follows: (1) a diagnosis of AD or any other dementia, (2) a mini-mental status examination [40] score of less than 24, (3) a self-report of "severe" for potential comorbid conditions (e.g., epilepsy, head injury, depression), (4) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurologic conditions (e.g., stroke, Parkinson's disease), and (5) insufficient cognitive data. From the remaining participants, we applied the standard and strict VLS multilevel diagnostic regimen for classifying T2D [7,9]. Specifically, inclusion into the T2D group required the following conditions during any of the three data collection waves: (1) self-report of T2D diagnosis, (2) specified method of treatment (i.e., oral medication, insulin, diet and exercise, no control), (3) objective evidence of reported T2D medication, and (4) validation of T2D status (repeating the three previous steps) from the subsequent wave.

The final baseline sample for this study consisted of 628 nondemented adults; 422 were women and 206 were men (mean [M] age = 69.0 years, standard deviation [SD] = 7.57, range 53.2–91.0). See Table 1 for all background characteristics. The standard T2D diagnostic procedure resulted in 54 adults (8.6%) with T2D (at W1 M age = 70.0, SD = 7.57, range = 55.4–88.2 years; 29 women [53.7%]). Therefore, the W1 non-T2D group included 574 adults (M age = 68.9, SD = 7.57, range = 53.2–91.0 years; 393 women [68.5%]).

2.2. Neurocognitive speed measures

Three multitrial computer-based reaction time measures were used to assess neurocognitive speed: (1) choice reaction time, (2) lexical decision, and (3) sentence verification (see Supplementary Material for description of tasks). All tasks were presented on a computer that controlled the presentation rate of the stimulus [35]. Correction procedures