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Executive functions in patients with Alzheimer's disease, type 2 diabetes mellitus patients and cognitively healthy older adults☆

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ABSTRACT

Objectives: The present study investigated whether the performance on executive function tasks of patients with type 2 diabetes mellitus (T2DM) is as impaired as that of Alzheimer's disease (AD) patients and to compare their performance with that of a group of cognitively healthy older adults. We also investigated whether glycosylated hemoglobin levels (HbA1c, a measure of glucose regulation) are related to performance on executive control tasks.
Methods: Three groups of participants (AD, T2DM, and healthy older adults) completed medical and psychological evaluations and performed a series of computerized tasks, including processing speed (simple and choice reaction time) tasks, verbal and visuospatial working memory (WM) updating (*n*-back) tasks, and the Wisconsin Card Sorting Test (WCST), to assess processing speed and executive functioning.
Results: As expected, the results showed that AD patients performed significantly worse than the healthy older adult group in all tasks. Executive functions deteriorated in the two groups of patients but more in the AD group. The T2DM group differed from healthy older controls but not from AD patients in the percentage of perseverations and the percentage of perseverative errors (WCST).
Conclusions: These findings revealed working memory (updating and maintenance) and executive control declines in the T2DM compared to healthy older controls but smaller than that suffered by the AD patients. The impairment of executive processing of T2DM patients despite the glycosylated hemoglobin control suggests that these patients are at risk of developing AD.

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1. Introduction

The rapid growth in the percentage of older adults in our society is accompanied by an exponential increase in the number of elderly people who will suffer cognitive impairment and dementia in the coming decades. Moreover, the incidence of Alzheimer's disease (AD), the most common dementia, is expected to double or triple in the next few decades (Brookmeyer et al., 2011). Nowadays, the incidence of both AD and type 2 diabetes mellitus (T2DM) has become a major public health concern in many developed countries (Takeda et al., 2011), and they are considered to be among the greatest age-related risk factors for cognitive dysfunction in older adults (Craft, 2005; Stolk et al., 1997). Epidemiological studies suggest that T2DM patients are at higher risk of developing AD (Maher & Schubert, 2009). The main question addressed in the present study is whether diabetic patients with good glycemic control (HbA1c) would show similar decrements in performance on executive control tasks as those exhibited by AD patients or whether they would show a pattern closer to that of healthy older adults.

Cross-sectional and longitudinal studies have associated normal aging with decrements in performance in a number of cognitive and perceptual domains, including peripheral vision and dynamic visual acuity (Muiños & Ballesteros, 2014, 2015), processing speed (Salthouse et al., 1996), working memory and executive functions (Hoyer & Verhaeghen, 2006; Salat et al., 2002; Salthouse et al., 1996), and episodic memory (Park & Gutchess, 2005). These cognitive decrements are associated with brain changes occurring with age. Structural brain imaging studies suggest substantial age-related gray and white matter shrinkage in the lateral prefrontal cortex, the hippocampus, and the basal ganglia (Raz et al., 2005). AD patients have less total and gray matter volume in the PFC than cognitively healthy older adults matched for age (Salat et al., 2001; Salat et al., 2002). The frontal, temporal and parietal neocortical areas are affected early in the course of the disease (Brun & Englund, 1981; deToledo-Morrell et al., 1997). These patients show impaired WM in the early stages of the disease (Huntley & Howard, 2010; Lim et al., 2008), deficits in attention (Perry & Hodges,

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1999), especially the inhibitory mechanisms (Amieva et al., 2004), executive processes (Ballesteros et al., 2013; Binetti et al., 1996; Waltz et al., 2004), perseverations (Baddeley et al., 2001), and long-term episodic memory (Ballesteros & Reales, 2004; Fleischman, 2007; Fleischman & Gabrieli, 1998; Huberman et al., 1994).

A wealth of studies has shown that diabetes exacerbates age-related impairments in several cognitive functions, including attention, processing speed, episodic memory and visuospatial abilities (McCrimmon et al., 2012; Van den Berg et al., 2009). However, other investigators have reported impaired semantic memory in these patients but not deficits in other cognitive domains (Arvanitakis et al., 2010). Brain imaging studies have shown that T2DM is associated with cortical and subcortical brain atrophy and an increase in small-vessel disease. This might contribute to a series of abnormalities in functional and structural connectivity occurring in the diabetic brain that could cause the cognitive dysfunction observed in these patients (Biessels & Reijmer, 2014). A meta-analytic study (Monette et al., 2014) showed that patients with type 2 diabetes performed significantly worse than healthy controls without diabetes ($p < 0.05$) in all the evaluated cognitive abilities, including verbal recall, attention, reasoning, verbal fluency, motor speed and verbal learning, with moderately significant effect sizes ranging from −0.14 to −0.37. Investigators have attributed the neural dysfunction and the impairments in cognition from T2DM-related disease to several mechanisms such as metabolic, inflammatory, vascular and oxidative changes, which are common comorbidities of diabetes, rather than to diabetes itself (Hassing et al., 2004; Messier, 2005). A growing body of literature links the metabolic and vascular changes occurring in the brain of the diabetic patient to those occurring in AD (Craft, 2005; Kuljis & Salkovic-Petrisic, 2011; Liu et al., 2009).

There is a well-known negative association between poor glycemic control (measured by the glycosylated hemoglobin level, HbA1c) and cognitive functioning (Cukierman-Yaffe et al., 2009; Gagnon et al., 2011; Nilsson & Whalin, 2009), although one study reported a positive relationship between elevated levels of HbA1c and cognitive functioning in very old (75+ years of age) cognitively intact men (Huang et al., 2012). This might result from a protected survivor effect, whereby a few individuals are protected against risk factors.

There is a large body of literature concerning the biological neurodegenerative processes occurring in both AD and T2DM (Bosco et al., 2011; Fei et al., 2014; Han & Li, 2010; Kuljis & Salkovic-Petrisic, 2011; Liu et al., 2009; Luchsinger, 2012; Luchsinger & Gustafson, 2009; Matsuzaki et al., 2010; Takeda et al., 2011; Winkler et al., 2014). In fact, most investigations describing the mechanisms common to the two diseases have found that one of the neuronal glucose transporters (GLUT3) and tau Nuclear protein O-linked β-*N*-acetylglucosamine glycation (O-GlcNAcylation) are decreased in the T2DM brain, as in AD patients, whereas phosphorylation of tau is increased, which could be one of the mechanisms increasing the risk of AD in T2DM (Correia et al., 2012; Liu et al., 2009). Hyperinsulinemia, hyperglycemia and insulin resistance are accepted risk factors for developing AD (Matsuzaki et al., 2010). It is therefore not surprising that researchers have highlighted the role of two typical T2DM injuries, 'impaired brain insulin signaling' and 'vascular damage', in the pathogenesis of AD (Kuljis & Salkovic-Petrisic, 2011; Takeda et al., 2011). Higher glucose levels may be a risk factor for dementia even in individuals without diabetes (Crane et al., 2013). For this reason, in the current study, we investigated whether older adults with T2DM and good glycemic control suffer similar impairments in speed of processing and executive control functions as AD patients. We compared their performance with that of cognitively healthy older adults. In sum, the main question addressed in the present study was whether executive control and speed of processing functions in AD and T2DM patients are similarly impaired despite good glycemic control. We hypothesized that both AD and T2DM patients would show a slowing-down in processing speed and an executive control impairment compared to healthy older adults.

2. Methods

2.1. Participants

One hundred and forty-five participants were recruited from several hospitals and primary health care centers in the Valencian Community (Spain). After reviewing the participants´ medical records (with their consent) to obtain information about their educational level, personal history of diabetes, hypertension, cardiovascular disorders, and the possible intake of benzodiazepines or hypnotic drugs, they underwent a complete medical examination, involving cardiopulmonary and carotid-artery auscultation, palpation of foot pulses or, if none were detected, calculation of the ankle to brachial index, measurement of blood pressure, blood and urine analyses and magnetic resonance imaging (MRI).

After screening, 22 AD patients (mean age 78 years; range 68–85, 6 female), 20 older patients with diabetes mellitus –T2DM (mean age 71; range 64–79, 8 female), and 23 cognitively healthy older adults (mean age 72 years; range 65–78, 12 female) participated in the study. Participants who presented anomalous results in the medical examination or in the magnetic resonance imaging (MRI) scan were excluded. The T2DM group was matched for age with the control group. The same participants took part in another experimental session to investigate their performance in implicit and explicit memory tasks (Redondo et al., 2015). The two sessions were carried out within a week.

Exclusion criteria were a history of major neurological or psychiatric disorder, hypertension, cardio-vascular disease, a history of alcohol or drug abuse, Mini Mental State Examination (MMSE) (Folstein et al., 1975) values under 24 (out of a maximum of 30) except in the AD group, HbA1c values higher than 6.1% for non-T2DM participants, and brain lesions (except for the AD group). Participants had between 6 and 10 years of formal education (educational level was curtailed for many seniors in Spain today due to the Spanish civil war) and normal or corrected-to-normal vision or hearing.

The AD patients were referred from the neurology outpatients department of two hospitals in the Valencian Community (Spain). They met the NINCDS-ADDRA criteria for the diagnosis of probable AD (McKhann et al., 1984). The evaluation included medical, neurological, and psychological examinations, laboratory testing and MRI. All the AD patients had a history of progressive cognitive impairment. None of them had a history of psychiatric disorder, or used anxiolytic, antidepressant, or sedative drugs.

T2DM patients were recruited through general practitioners in the city of Elche (Valencian Community). They had been diagnosed with type 2 diabetes at least one year before their participation in the study, following the classification of the American Diabetes Association (2011). They were functionally independent and were all Spanish speakers. As it is unusual to find diabetic patients without vascular risk factors, their mean blood pressure values at the time of the evaluation were 143 mm/Hg (systolic) and 75 mm/Hg (diastolic). They did not suffer from hypertension or other cardiovascular risks and had a well-controlled glycosylated hemoglobin level [mean 7.16%]. Eighteen patients were taking T2DM oral medication (metformin) and only two were insulin-dependent.

Participants in the control group were volunteers recruited from several community centers for older adults in the same city. All were healthy individuals living an independent life with full access to national health care.

Before the study started, all the participants signed an informed consent form for participation in this study, which was approved by the Ethical Review Board of the *Generalitat Valenciana* and by the Ethical Committee of the UNED. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki as revised in October 2008. The participants were community-dwelling native Spanish speakers. None of them had prior experience of the experimental tasks included in this study. Table 1 shows the demographic

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