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PSYCHOSOCIAL ASPECTS (KK HOOD, SECTION EDITOR)

Assessing Premorbid Cognitive Ability in Adults With Type 2 Diabetes Mellitus—a Review With Implications for Future Intervention Studies

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Abstract Associations between type 2 diabetes mellitus (T2DM) and accelerated cognitive decline are well established. However, the sensitivity of neuropsychological tests to detect early deficits in cognitively normal adults with T2DM is unknown. This review examined cognitive domains and specific neuropsychological tests that are impaired in T2DM, based on clinically significant differences (effect sizes >0.5) between T2DM and groups without T2DM. Nine cross-sectional studies were identified which reported means and standard deviations for individual tests. Tests of executive function, working memory and psychomotor and attentional functions were found to be impaired in T2DM. Impairments of executive function and choice reaction time may have consequences for everyday functioning, in particular the risk of falls in older adults. More research on cognitive deficits in dual-task situations and how they impact everyday functioning is needed; the Trail Making Task, Symbol Digit Modalities Test, Verbal Fluency Task and tests of reaction time and processing speed could be included as core components of test batteries in future intervention studies. They could also be assessed in newly diagnosed T2DM and used to monitor progressive deterioration of cognitive function and the efficacy of therapeutic interventions on cognitive function.

Keywords Type 2 diabetes mellitus · Neuropsychological tests · Cognitive decline · Executive function

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Introduction

Cognitive impairment is one complication of type 2 diabetes mellitus (T2DM) that has gained considerable recognition in the last decade [1]. Pooled estimates from prospective studies of people with T2DM reveal a 60 % increased risk of future dementia [1], which is an independent risk factor for Alzheimer's disease (AD) [2•]. Not all cognitive domains may be equally or coincidentally affected by T2DM. The course of the disease, type, duration and timing of treatment, complications and comorbidity vary between individuals. Therefore, the aetiology of diabetes-induced cognitive decline is multifactorial and the precise underlying mechanisms remain unresolved [3], so the lack of a clear cognitive phenotype for T2DM is not surprising [4].

Nonetheless, the burden of T2DM-related cognitive impairment has significant clinical and lifestyle implications, particularly for dementia-free older adults who are living independently. The decline of cognitive function may jeopardize self-management behaviours or the use of appropriate health services such as foot/eye checks or mental health services for depression [5]. In fact, findings from a population-based study have shown that cognitive impairment in older adults with T2DM is associated with worsening of diet and physical activity adherence, which are the two important domains of diabetes self-care for achieving glycemic control [6]. Therefore, additional follow-up care such as repeated

neuropsychological testing may be necessary for older adults with T2DM. The question is which cognitive testing tool should be used.

In this review, we compared, from published cross-sectional studies, the cognitive domains in which adults with T2DM showed poorer performance than their counterparts without T2DM. We identified neuropsychological tests in which adults with T2DM were likely to perform at least half a standard deviation below those without T2DM. More importantly, we discussed the implications of these deficits for everyday functioning. Cognitive deficits in various domains could have implications for the clinical presentation of T2DM, for example, attentional deficits leading to problems of concentration and focus, memory impairment compromising adherence to medication and executive problems being associated with deficits in engaging in more complex behaviours. We recommend that these tests be included in future clinical study protocols aimed at examining and/or treating cognitive deficits in T2DM.

Potential Issues With Assessing Cognitive Function in Type 2 Diabetes Mellitus

Current prospective studies on diabetes-induced cognitive decline typically take the onset of dementia or mild cognitive impairment (MCI) as their primary endpoint [1]. The Mini Mental State Examination (MMSE)—a 12-item pencil-and-paper-based instrument—is the most widely used test to assess participants' cognitive status or to prospectively track changes in cognition [7••, 8]. However, there are many limitations of using the MMSE to determine cognitive status in research. For example, the MMSE assesses cognitive domains such as attention/working memory, verbal recall, expressive language and visual construction but not verbal fluency and abstract reasoning or judgment. It is known that memory impairment is an early characteristic of AD, whereas poor performance in verbal fluency is typical in the initial stages of vascular dementia, which is more likely to be related to diabetes [9]. In addition to its ceiling effects, the MMSE is relatively insensitive for detecting subtle cognitive changes in pre-MCI (intermediate stage between normal and MCI) stage [10], particularly in educated and high-functioning adults with T2DM [11]. There is also no single set of criteria for diagnosing MCI, as MCI can be divided into amnestic or non-amnestic and with or without impairment in other cognitive domains [12]. Hence, the MMSE has limited value in separating MCI from adults without T2DM, as well as identifying AD amongst those with MCI [8]. The typical clinical presentations of MCI may include subjective cognitive complaints and/or noticeable functional deficits or performing 1.0–1.5 standard deviation (SD) units below age- and education-matched controls in memory tests and/or in tests of other cognitive domains [13]. While cognitive deficits in early stages of disease onset rarely meet these MCI criteria [14], everyday cognitive skills may be implicated in sub-efficient cognitive function [15].

Psychometric tests are indeed more sensitive in detecting subtle cognitive changes and cognitive decline than the MMSE and are thus more suitable for testing high-functioning adults in a mild disease state [10]. It has been reported that a medium effect size, i.e. a difference of at least half a standard deviation (Cohen's *d*), in cognitive performance between target and reference groups is considered clinically or practically important for everyday functioning and independence [16], regardless of whether statistical significance is reached. However, most studies report only statistically significant differences in psychometric tests between diabetics and healthy control groups [17–25]. Moreover, without a standardized index or scale to compare between psychometric tests, it is difficult to gauge the extent of cognitive impairment in different studies.

A potential implication of these methodological issues is a lack of early strategies to attenuate/prevent diabetes-related cognitive decline in adults with T2DM. This may apply particularly to individuals who have premorbid cognitive impairments that do not differ statistically from their counterparts without T2DM. Hence, to prevent or attenuate diabetes-induced cognitive decline in adults with T2DM, it is necessary to firstly identify the cognitive domains and more specifically the neuropsychological tests which are most sensitive to early cognitive deficits. That is the aim of this review.

Methods

Identification of Studies and Inclusion/Exclusion Criteria

A systematic search for published papers of original cross-sectional studies written in English describing assessments of cognitive function in adults with diabetes was performed using the Scopus database, which is the largest worldwide database covering peer-reviewed literature in interdisciplinary fields in science, medicine, social sciences, arts and humanities. The search terms 'diabetes mellitus' and 'type 2 diabetes' were combined with terms related to 'cognition', 'neuropsychological test', 'memory' and 'cognitive test'. Titles and abstracts published between October 1993 and October 2013 were scanned, and potentially eligible articles were collected in full-text versions.

Studies were included if they met the following criteria: used a non-diabetic control group as the reference, included T2DM adults without serious comorbidities such as heart or kidney failure or neurological disorders and utilized a neuropsychological test battery comprising at least two cognitive tests. Evaluating multiple cognitive tests in a battery allowed

us to explore differential cognitive deficits and to look for consistency in the area of impairment. Articles were excluded if they were prospective studies, systematic reviews or meta-analyses, if no full text was available, if a pre-diabetic population was used or if the mean and SD/standard error of the mean was not reported for individual cognitive tests. Pooled SDs were also excluded unless the sample sizes for T2DM and healthy control groups were similar.

Grouping of Neuropsychological Tests Into Cognitive Systems

Neuropsychological tests used in the articles that met the inclusion criteria were grouped into cognitive domains, based on the compendium of neuropsychological tests [26].

Determining Effect Sizes

Effect sizes were determined by calculating the difference between means of each cognitive test for the T2DM group and the control group and dividing by the pooled SD or SD of the control group [27]. An effect size of ≥0.5 was taken as the minimum criterion for a clinically significant difference in cognitive performance between T2DM and control groups [16]. Cohen [28] considers 0.50 to be a medium effect size. For the purposes of this review, all effect sizes were converted to positive values and represent impairment in T2DM groups unless stated otherwise.

Results of the Search

Using the search terms as described above, 60 articles were identified, nine of which met the criteria for inclusion (Fig. 1).

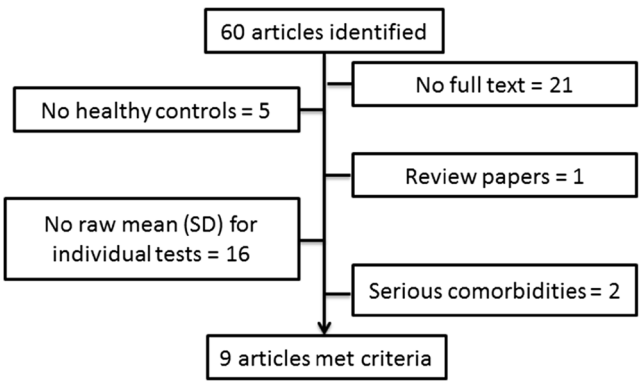

Fig. 1 A flow diagram of the systematic search for original cross-sectional investigations into the neuropsychological profiles of T2DM adults

Results and Discussion

Study Population

Demographic details of study populations and methods of determining whether they have T2DM in the nine studies are detailed in Table 1. Most studies recruited their diabetic population through diabetes education centres, self-reporting of the condition or medication use and identified through medical records in diabetes management centres. The mean age of participants in each of the included studies exceeded 50 years, and all had their T2DM diagnosis at least 1 year prior to cognitive assessment. All but three studies [19, 21, 24] reported participants' HbA1C levels (a marker of elevated blood glucose for the previous 4–6 weeks). The control groups were matched for age, gender and education/IQ level in all studies except [19]. All but three of the included studies excluded patients with dementia or suspected dementia through screening with the MMSE. One study [23] excluded patients with self-reported dementia status, while three studies [20, 22, 25] did not assess for dementia status in their studies. Those studies that screened for dementia did not find any statistical difference in scores between the T2DM and control groups.

Differences in Cognitive Performance Between Adults With and Without T2DM

This review of nine cross-sectional studies in adults with and without T2DM identifies the cognitive domains and neuropsychological tests that demonstrate impairment in T2DM. Deficits were evident in all domains and were particularly evident in executive function and attentional function. Primarily mediated by the frontal lobes [29], executive function governs high-level cognitive functioning, which is crucial for independent living in older adults. Impairments in executive function are manifest in everyday behaviours such as poor understanding of risk and a compromised ability to change strategy/behave flexibly where needed. There can also be a social dimension as poor executive function has been linked to social disinhibition. Such impairments are evident in early stages of amnestic and non-amnestic MCI [30] and strongly predicted the conversion from MCI to AD within 3 years [31]. However, a longitudinal study found that executive dysfunction persisted in patients with T2DM with no evidence of accelerated decline [32•] during a 4-year follow-up; thus, executive function could be a potentially reliable marker for monitoring the efficacy of interventions targeting early diabetes-related cognitive decline. Clearly, it is important to determine whether the choice of cognitive tests used constitutes a clinically or functionally important indicator of cognitive decline.

Table 2 details the effect size of differences in neuropsychological tests between T2DM and their controls in the nine

Table 1 Population characteristics of the nine studies included for review

Reference	No. of patients with T2DM	No. of controls	Gender of patients with T2DM (M/F)	Mean age of patients with T2DM	Mean age ofcontrols	Assessment of T2DM	Assessment of fasting glucose for controls	Mean duration of T2DM (years (SD))	HbA1C (%), T2DM	HbA1C (%), controls	Assessment of dementia	Matched for education level/IQ
van Harten et al. 2007 [21]	92	44	40/52	73.2	72.9	ND	Yes	13.8 (10.8)	7.7	5.7	ND	Yes
Brands et al. 2007 [20]	119	55	62/57	65.9	65.2	Identified	Yes	9 (6)	6.9	5.5	ND	Yes
Ryan and Geckle 2000 [23]	50	50	15/35	50.8	50.5	Self-reported	ND	8.1 (5.9)	10.2	6.7	ND	Yes
Zihl et al. 2010 [18]	12	19	ND	Good GC, 34.2 Poor GC, 50.7	36.8	ND	ND	Good GC, 7.3 (5.5) Poor GC, 5.3 (1.8)	Good GC, 7.1 Poor GC, 9.7	ND	ND	Yes
Christman et al. 2010 [17]	28	150	14/14	66.4	63.43	Self-reported and identified	Self-reported	ND	ND	ND	MMSE (through medical records)	No
Asimakopoulou et al. 2002 [22]	33	33	19/14	62.4	62.40	Identified	ND	9 (5.91)	ND	ND	MMSE	Yes
Yeung et al. 2009 [19]	41	424	19/22	69.6	70.0	Self-reported	ND	8.3 (7.9)	ND	ND	MMSE	Yes
Mehrabian et al. 2012 [15]	37	22	17/20	56	56	Identified	ND	7 (3.5)	6.7	5.7	MMSE	Yes
Takeuchi et al. 2012 [16]	42	32	26/16	62.4	63.8	Identified	Yes	11.5 (9.7)	9.5	5.5	MMSE	Yes

Good GC good glycemic control defined as HbA1c (%) ≤7.5 %, *Poor GC* poor glycemic control defined as HbA1c (%) 7.6–12.5 %, *ND* not defined, *Identified* identified through medical records and diabetes education centres

cross-sectional studies meeting criteria for inclusion in this review. Statistically significant differences are also indicated by asterisks ($P<.05$). The T2DM groups showed diminished performance in most tests except the number of correct responses in Digit Span Forward and Backward [24], Logical Memory II (Wechsler Memory Scale—Revised) [19], Digit Symbol Test [18] and two-back TAP response [20], where T2DM groups performed better than groups without T2DM. The Trail Making Task, Symbol Digit Modalities Test, d2 cancellation task and the Verbal Fluency Task appeared to have sufficient sensitivity to detect performance deficits in psychometric tests in otherwise cognitively intact adults with T2DM. A description of these tests and how they might impact daily functioning are discussed below.

Executive Function

Executive function, typically assessed using measures of time sharing, sequencing, response inhibition, set shifting and perseveration [32•], was assessed in most included studies. Executive control, measured via performance of the Verbal Fluency (letter) test and the subcomponents of the Trail Making Task (Part B and interference score) were both statistically and clinically significantly poorer in the T2DM group in six studies reviewed. The effect sizes were also greater than 0.50.

Trail Making Task

The Trail Making Task, Part A, measures the ability to scan and to connect 25 numbers/letters consecutively that are placed randomly on a page (i.e. 1-2-3-4… or A-B-C-D…). This process requires both working memory and processing speed, which is found to be less efficient in T2DM. Part B of the task assesses cognitive flexibility and processing speed, a process generally referred to as executive control, while alternating between connecting a number and letters in sequence with speed and accuracy (e.g. 1-A-2-B-3-C…) [33]. Time taken to complete Parts B and A forms an interference ratio score (B:A) which is also an indicator of executive control function [34]. We found impaired performances in Part B of the Trail Making Task in four out of six studies reviewed [17–19, 22]. Two studies [23, 25] that reported their interference scores also found poorer performance in T2DM.

Verbal Fluency Task

The Verbal Fluency Task (semantic or phonemic) requires participants to generate a list of words or items associated with a particular category (e.g. words beginning with letter 'p' or animals) in a given period of time. Successful performance of this task requires the use of executive function such as initiating a non-routine cognitive search for related words/concepts in the given category and listing as many items as

Table 2 Effect size differences of the neuropsychological tests in the nine studies reviewed

Cognitive domains	Cognitive tests	Mehrabian et al. 2012 [15]	Takeuchi et al. 2011 [16]	Christman et al. 2010 [17]	Zihl et al. 2010 [18] (good GC)	Zihl et al. 2010 [18] (poor GC)	Yeung et al. 2009 [19]	Brand et al. 2007 [20]	Van Harten et al. 2007 [21]	Asimakopoulou et al 2002 [22]	Ryan & Geckle 2000 [23]
Executive function											
	Verbal fluency (letter)	2.38*	0.59*	0.50*				0.50*	0.65*		
	Verbal fluency (animal)	0.23						0.23	0.52		
	Verbal fluency (category-naming)		0.77*	0.32*	0.47	0.38			0.65*		
	Verbal fluency (design)			0.72*							
	Trial making task Part B	3.49*	1.02*	0.72*				0.79*		0.12	0.32
	Trail making test (interference)								0.50		0.65
	Wisconsin Card Sorting Test (category)		0.56*	0.36							
	Wisconsin Card Sorting Test (Perseveration)		1.00*	0.38							
	Verbal fluency (opposites)						0.15				
	Verbal fluency (Figures of speech)						0.15				
	Verbal fluency (Similarities)						0.18				
	Hayling sentence completion test						0.56*				
	Brixton spatial anticipation test						0.32	0.44*			
	Stroop test (interference)						0.36	0.21	0.21		0.75*
	Colour trails 2						0.52*				
Attentional Function											
	Symbol of digit modalities test	0.95*		0.69*	1.71	1.41		0.30			
	d2 cancellation (accuracy)				3.47*	2.67*					
	d2 cancellation (speed)				1.65	1.86					
	Digit Vigilance test										0.55*
Processing Speed											
	Digit symbol coding (subtest of the WAIS-R) Correct responses within a fixed time		0.17*				0.39*			0.14	0.44
	Salthouse perceptual comparison			0.49							
	Lexical decision (ms)						0.47*				
	Stroop word reading							0.52*	0.41*		
	Stroop colour naming							0.32	0.55		

Table 2 (continued)

Cognitive domains	Cognitive tests	Mehrabian et al. 2012 [15]	Takeuchi et al. 2011 [16]	Christman et al. 2010 [17]	Zihl et al. 2010 [18] (good GC)	Zihl et al. 2010 [18] (poor GC)	Yeung et al. 2009 [19]	Brand et al. 2007 [20]	Van Harten et al. 2007 [21]	Asimakopoulou et al 2002 [22]	Ryan & Geckle 2000 [23]
Working Memory											
	Digit span forward		0.37	0.41*				0.08		0.02†	
	Digit span backward		0.64*	0.49*				0.31*		0.03†	
	Corsi block tapping design - forward							0.08			
	Corsi block tapping design - backward							0.19			
	TAP (one-back) response time				0.91	0.69					
	TAP (one-back) no. of correct response				0.00	0.25					
	TAP (two-back) response time				1.71*	2.13*					
	TAP (two-back) no. of correct response				2.10†	1.15*†					
	Brief test of attention (Letters)			0.39							
	Brief test of attention (Numbers)			0.52*							
	Serial Subtraction 7's									0.54*	
	Trail making task Part A	2.44*	0.88*	0.44*				0.90*	0.50*	0.02	
Secondary Memory											
	Auditory/Verbal memory										
	RAVLT (total trials 1-5)		0.53*					0.30	0.35		
	RAVLT (delayed)		0.34				0.07	0.29	0.39		
	RAVLT (recognition)		0.13				0.14	0.50*	0.35		
	Logical Memory A		0.54*	0.46†						1.20*	
	Logical Memory B		0.64*	0.53†						0.06	
	Rivermead Behavioural Memory test (immediate recall)								0.47		
	Rivermead Behavioural Memory test (delayed recall)								0.45*		
	Buschke Free and Cued Selective Reminding Test (FCST) Free recall	0.77*									
	FCSRT Cued recall	0.34									
	Hopkins verbal learning test (total trails 1-3)			0.26							
	Hopkins verbal learning test (delayed recall)			0.16							
	Word list recall						0.38				
	Verbal paired-associate learning test (immediate)										0.44
	Verbal paired-associate learning										0.25
	test (delayed)										
	Symbol-digit paired association learning test (immediate)										0.11
	Symbol-digit paired association learning test (delayed)										0.20
	Story memory test						0.38				0.36

Table 2 (continued)

Cognitive domains	Cognitive tests	Mehrabian et al. 2012 [15]	Takeuchi et al. 2011 [16]	Christman et al. 2010 [17]	Zihl et al. 2010 [18] (good GC)	Zihl et al. 2010 [18] (poor GC)	Yeung et al. 2009 [19]	Brand et al. 2007 [20]	Van Harten et al. 2007 [21]	Asimakopoulou et al 2002 [22]	Ryan & Geckle 2000 [23]
	Visuospatial memory:										
	Rey Osterrieth Complex Figure test (copy trial)		0.47	0.53				0.24			
	Rey Osterrieth Complex Figure test (delayed recall)		0.27					0.39*			
	Brief visuospatial Memory test (learning trials total 1-3)			0.39							
	Brief visuospatial Memory test (delayed recall)			0.31							
	Wechsler Memory Scale (visual production 1)			0.43							0.41
	Wechsler Memory Scale (visual production 2)			0.43							
	Embedded figures test										0.36
	Semantic Memory										
	Sentence verification (ms)						0.52*				
	Sentence verification (% error)						0.39*				
	Fact recall (40-item test of general information)						0.08				
Intelligence/ general cognitive function											
	Raven's progressive Matrices (no. of correct items)				1.8*†	1.1*†		0.17			
	Raven's progressive Matrices (verbal)				2.46*	1.64*					
	Raven's progressive Matrices (visual)				1.07*	1.36*					
	National adult reading test			0.70							
	Wechsler adult intelligence scale (information)			0.58							
	Wechsler adult intelligence scale (similarities)			0.63							
	Wechsler adult intelligence scale (Block design)			0.60							
	Wechsler adult intelligence scale (Picture completion)			0.24							
	Benton Facial Recognition Test			0.37							
Language function											
	Boston naming test	1.52*									
	Vocabulary test						0.11				
Psychomotor function											
	Grooved Pegboard test (dominant)								0.88*		1.24*
	Grooved Pegboard test (non-dominant)								0.56*		1.24*
	Binary choice								0.49		

Empty cells indicate that the test was not used in that study

GC glycemic control

[a]Having an effect size of ±0.5

[b]Statistically significant impairment in the T2DM group compared with the control groups

[c]T2DM group performing better than the control groups

quickly as possible, while inhibiting words/items that do not belong to the category [35]. Semantic processing capability relates to everyday tasks, for example, finding the right words to use in a conversation [36] or recognizing the ingredients of a particular food item (i.e. individual ingredients to make a hamburger) [37]. Assessment of verbal fluency is not assessed in the MMSE [9], further suggesting that the MMSE may not be the most suitable test of global cognition for adults with T2DM. The modified mini-mental state test (3MS), Cognitive Abilities Screening Instrument (CASI) or the Short and Sweet Screening Instrument for Cognitive Impairment (SASSI) are alternate global cognition test batteries that include Verbal Fluency Task [9]. Verbal Fluency Task performance is relatively preserved with increasing age as word-based knowledge is well maintained throughout adulthood [38]. However, there is a clear effect of education attainment on performance [39]. While semantic memory (listing items/words relating to the category) has been shown to be unaffected, neurocognitive speed (number of words/items listed in 60s or 90s) appeared deficient in early T2DM-related cognitive decline [40]. Most studies included in this review reported the Verbal Fluency Composite Score rather than the raw scores of its subcomponents, yet task performance was both statistically and clinically significantly poorer in adults with T2DM. Nonetheless, future studies should examine processing speed in the Verbal Fluency Task as a separate parameter, as this may be a potentially useful clinical marker to monitor change/improvement.

Implications of Executive Function Deficits for Daily Functioning

Moderate decrements in performance in the abovementioned tasks may reflect inefficiency in everyday functioning abilities which could undermine quality of life in the latter years. For instance, having the cognitive flexibility to switch between conditions in the Trail Making Task relates to activities of daily living such as the ability to return to a task after being interrupted or to do two things simultaneously [36]. In the context of diabetes self-management, this could have implications for recording incorrect values during blood glucose monitoring or memory lapses if interrupted, e.g. forgetting that one's medication has not been taken. For older adults with T2DM and cognitive impairments, poor performance on the Trail Making Task has implications for balance and gait including gait speed and accuracy of foot placement, thereby increasing the risk of falls [32•]. In other words, one misplaced step resulting from choosing the incorrect motor response in an unfamiliar or novel environment could result in a trip or fall [41]. This risk is likely to be further heightened in T2DM sufferers with peripheral neuropathy or vascular disease. Poor gait performance is also linked to poor cognitive and everyday physical function such as shopping, travelling to health care facilities and meal preparation [7••].

Gait deviations may seem trivial for cognitively normal T2DM adults; however, executive dysfunction may pose a challenge when placed in complex dual-task situations [32•] (i.e. looking for a seat in a crowded food court while holding a tray of food and drinks). The psychomotor deficits in T2DM are likely mediated by altered neural activity in the cerebellum [42•]. While the increased resting neural activity in the cerebellum of T2DM patients may be suggestive of a compensatory mechanism for diminished activity in other brain areas [42•], insulin resistance associated with T2DM may have impacted on the optimal glucose uptake in the cerebellum (a structure densely populated with insulin-sensitive glucose transporters) during motor task [43]. The relationship between psychomotor deficits and glucose metabolism in the cerebellum of T2DM adults warrants future investigation. Nonetheless, dual-task performance involving motor task and cognitive task can be assessed clinically. Dual-task activities more closely mimic everyday function than single tasks; therefore, it seems plausible to include dual-task activities in the test battery to challenge high-functioning and cognitively normal T2DM adults. Types of dual-task assessments may include performance in a 6-min walk test (total distance covered in 6 min), serial subtractions (counting backwards in 3s, 7s or 11s) or reciting the alternate letters of the alphabet simultaneously. Outcome measures are the distance covered in 6 min or the number of correct calculations or correct letters [32•].

Attention

Tests including performance of the Symbol Digit Modalities Test, d2 cancellation task and digit vigilance test also tended to be diminished in T2DM, although not all of these tests were found to be statistically significant in individual studies. Although the Digit Symbol Coding test was found to be significantly different in two studies [18, 21], the effect size differences were less than 0.5.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test is a common measure of attentional function, but it also requires complex visual scanning, perceptual motor speed and working memory. Participants are asked to pair as many specific numbers with given geometric figures (symbols) in 90 s. Responses can be in written and/or oral forms, with moderate to strong correlations with raw scores on the Digit Symbol Test (subset of the Wechsler Adult Intelligence Scale) and test-retest reliability (r=.74) [44]. Although the Digit Symbol Test (writing down the symbol that corresponds to the digit-symbol pair) is similar to the Symbol Digit Modalities Test (substituting symbols for digits), the Digit Symbol Test is a measure of cognitive

processing speed. Hence, these tests are not interchangeable as the individual's performance on the Symbol Digit Modalities Test tends to yield lower performance relative to the normative population scores for the Digit Symbol Test [45]. Three studies reviewed [17, 19, 20] reported greater magnitude of impairment in T2DM with the Symbol Digit Modalities Test.

D2 Cancellation Test

Another test of attentional function worth including in future test batteries is the d2 cancellation test where Zihl and colleagues [20] reported large effect size differences between T2DM and healthy controls in accuracy and speed. This test requires participants to scan across each line consisting of the letters 'd' and 'p' with one to four dashes. The task involves identifying and crossing out each 'd' with two dashes. Performance is scored based on the number of correct responses and the time taken to complete one page of the d2 test form (14 lines of 47 characters) [46]. Like the Trail Making Task and Symbol Digit Modalities Test [47], performance on the d2 cancellation task is age, gender and IQ dependent [46].

Memory

Under the domain of memory, test performance of working memory (retrieval memory)—Part A of the Trail Making Task—the two-back TAP test and serial subtraction 7s elicited a greater difference between groups with and without T2DM compared with secondary or declarative memory (auditory/visual, visuospatial memory). The two-back TAP test consists of single words or numbers shown on the computer screen consecutively, and the task is to answer for each word/number whether it is the same as the word/number shown two items back by pressing 'yes' or 'no' on the keypad. The serial subtractions task requires the participant to count backward in intervals of either 3, 7 or 11 from a given number. The digit forward and backward span tests (subsets of the Wechsler Adult Intelligence Scale where one recites a string of words, numbers or letters in the same order as it is given or in the reverse order [26]) were assessed in four of the nine studies reviewed. While three studies found significant deficits in the T2DM groups, only one study reported an effect size difference of more than 0.50 [18].

Implications of Attentional and Working Memory Deficits for Daily Functioning

It is important to understand that deficits in cognitive domains rarely occur in isolation. Therefore, it is difficult to comment on the specific implications of declining attention and working memory performance for daily functioning. However, a community-wide population study has shown that cognitive impairment (i.e. a combination of poor working memory, executive function and informational processing speed) is associated with poor adherence to diet and physical activity recommendations in older adults with T2DM [6]. Considering the complexity of diet plans and exercise regimes, it may be challenging for the individual to remember the exercises or types of food that are beneficial for them. This may have a negative impact on self-care health behaviours, thus leading to worsening of the disease condition. Currently, very little is known about attentional function and working memory on health behaviours relating to T2DM self-management. Nonetheless, clinicians may wish to monitor attention and working memory performance regularly to screen those at risk.

Intelligence

Two studies in this review [19, 20] assessed general intelligence using Raven's Progressive Matrices and the Wechsler Adult Intelligence Scale. These studies reported poorer performance in patients with T2DM. However, only the Raven's Progressive Matrices task was found to be both statistically and clinically impaired in T2DM [20]. This nonverbal task requires the participant to identify the missing element that completes a pattern presented in the form of a 4×4, 3×3 or 2×2 matrix and varying in difficulty.

Language and Psychomotor Function

Similarly, only two studies [23, 25] assessed language, using the Boston Naming Test and psychomotor function (Grooved Pegboard Test and Binary Choice); in both cases, there was considerable impairment in adults with T2DM.

Implications of Psychomotor Function Deficits for Daily Functioning

While it is difficult to draw meaningful conclusions from our analysis of two cross-sectional studies, psychomotor function and dexterity are critical for occupational performance as well as everyday living, yet their importance has been underrecognized in characterizing cognitive deficits in T2DM. Two studies included in this review [23, 25] assessed psychomotor function using the Grooved Pegboard Test and Binary Choice Reaction Time Test; in both cases, there were large differences between T2DM and reference groups. Attention and concentration and information processing speed are also involved in both tests. The Grooved Pegboard Test is a test of fine motor dexterity where participants rotate and insert the pegs into 25 randomly positioned slots. The speed of peg removal is also assessed [48]. However, the Grooved Pegboard task may not be suitable for the older T2DM adults suffering from arthritis of the hand or deteriorating vision. The Binary Choice Reaction Time Test may be better suited for

most individuals. For this task, the participant pushes one of two buttons on the keypad that corresponds to the position of the coloured block on the computer screen. The next stimulus is presented immediately after a key is pushed; hence, errors are greater if reaction times are quick, implying poor decision-making. Psychomotor slowing may have implications for daily activities such as operating a motor vehicle or machinery. It is believed that peripheral neuropathy, a diabetes-related complication, which leads to reduction of nerve conduction velocity [49] and vision changes due to chronic hyperglycaemia may be implicated in poor psychomotor performance. However, longer reaction times in response to a computer-based stimulation of traffic light changes in adults with T2DM compared with non-diabetics have been shown to be independent of disease duration, age or fasting glucose levels [50]. The extent to which poor psychomotor response time may impact on everyday functioning is unknown. More research targeting dual-task decision-making and reaction time is warranted in drivers with premorbid T2DM.

Implications for Future Intervention Studies

Diabetes-related cognitive decline is known to be heterogeneous, as seen in the studies in this review. This is in part attributable to methodological differences and the aetiology of the disease. So far, no studies have examined diabetes-related cognitive decline in untreated or uncomplicated T2DM (without comorbidities such as hypertension); hence, the causal link between T2DM and cognitive impairment is unknown. This relationship must be addressed in the context of vascular risk factors, medication use, age, gender and cognitive status [3]. There is a need for consensus on a core battery of neuropsychological tests to be employed in future studies of cognitive impairments in T2DM and an agreed standard of screening assessments to be employed prior to enrolment into the study. For instance, not all studies in this review excluded or screened their participants for suspected dementia or obtained biomarkers of diabetes prior to neuropsychological testing. Thus, it was likely that some participants in the control group might have had undiagnosed T2DM.

Adults with T2DM, being a chronic disease, are also likely to suffer other comorbidities such as hypertension or hypercholesterolaemia. Anti-hypertensive treatments may confer some degree of neuroprotection which is independent of blood pressure changes [51], while the use of statins has been shown to lower dementia risk by up to threefold [52], potentially explaining the heterogeneity in cognitive test outcomes. However, the effects of anti-diabetic medications on cognitive function have been somewhat controversial. A recent study found that within the T2DM cohort, those on metformin therapy had poorer cognitive performance and the decline was partially mediated by the effect of metformin on declining vitamin B_{12} levels [53]. Similarly, longitudinal population-based studies have found that, amongst T2DM patients, those on insulin therapy are at greater risk of dementia as they tend to have more severe diabetes or longer exposure to diabetes-related risk factors [54, 55]. In contrast, regular treatment with anti-diabetic medication has led to improved glycemic control in elderly T2DM adults, which is associated with better scores for the Trail Making Task and Grooved Pegboard [56]. To minimize the influence of confounding variables, adjustment must be made in the analysis for the presence of vascular risk factors and treatment modalities. In addition, other medical conditions known to impact on cognitive function such as depression [57] should be excluded or matched closely with the control group.

Subjective cognitive deficit complaints, either self-reported or reported by close family members, can be captured relatively quickly and easily from T2DM participants. A recent prospective study showed that older adults with subjective memory impairment, without cognitive deficits as assessed by neuropsychological tests, were three times at risk of conversion to any dementia within 1.5 years [58]. While current evidence of subjective complaints of cognitive decline in T2DM is lacking, subjective complaints are typical presentations in MCI [13] and, therefore, collecting such information may contribute to clinical and individual decisions about interventions to lower the risk of cognitive impairment.

None of the studies reviewed controlled for dietary intake or standardized feeding prior to neuropsychological testing. The timing and effect of food and type of beverage consumption (i.e. caffeinated drinks) may also impact on mood and/or cognitive performance [59, 60]. However, a fasting protocol would run the risk of hypoglycaemia during testing. Only one of nine studies in this review [19] monitored plasma glucose levels prior to testing to rule out hypoglycaemia. Acute hypoglycaemia has been shown to transiently impair cognitive function [60, 61], with the risk of hypoglycaemia greater in those on insulin treatment. Future study design could control for the intake of food or assess plasma glucose levels before and during testing. In addition, the duration of the neuropsychological test battery should be kept brief and limited to core tests that are sensitive enough to detect clinically and functionally important declines in otherwise healthy adults with T2DM. The test battery should include tests of executive and attentional function including Verbal Fluency, the Symbol Digit Modalities Test, the Trail Making Task and tests of psychomotor function, preferably presented in dual-task situations. Ideally, neuropsychological test administrators should also be blinded to patients' conditions to reduce tester bias.

Conclusion

It is clear that some aspects of cognitive functioning including executive and attentional functions are impaired in adults with

T2DM. Particularly for older adults with T2DM, these cognitive deficits may impact on their everyday functioning and T2DM self-management behaviours. Assessments in the management of T2DM should include a standardized neuropsychological battery consisting of tests of executive, attentional and psychomotor functions (if possible) that are relevant to everyday functioning, such as dual-tasking assessments for sufferers who are dementia free. This standard battery may be part of the baseline assessment for newly diagnosed T2DM and should be repeated periodically to monitor deterioration in cognitive domains. It should also be used to assess benefit in clinical intervention trials. Assessment of global cognition or determination of dementia status should be measured using 3MS, CASI or SASSI rather than the MMSE test battery. In addition, use of this test battery for selection or control of participants enrolled in future studies would minimize the influence of confounding variables and variability in the assessment of cognitive outcomes. As well as negatively affecting everyday functional capacity as outlined in this review, compromised cognitive abilities in these domains have clinical ramifications for those with T2DM. These include issues of compliance with medication/lifestyle regimes and adherence to glucose monitoring. Furthermore, future studies in this area should include focused assessment of the impact of treatment regimens on the cognitive domains differentially impaired in T2DM.

Compliance with Ethics Guidelines

Conflict of Interest Rachel Heloise Xiwen Wong, Andrew Scholey and Peter Ranald Charles Howe declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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