

DIMINISHED PERFORMANCE ON RESPONSE-SELECTION TASKS IN TYPE 2 DIABETES¹

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Summary.—Comparisons of visual perception, response-selection, and response-execution performance were made between Type 2 diabetes mellitus patients and a matched nondiabetic control group. 10 well-controlled male patients with Type 2 diabetes without diabetic complications (*M* age 58 yr.) and an age and IQ-matched nondiabetic control group consisting of 13 male healthy volunteers (*M* age 57 yr.) were included. Significant differences were found only between the two groups on response-selection performance, which concerns the selection and preparation of an appropriate motor action.

Although the various angiopathic and neuropathic complications associated with Type 2 diabetes are well recognised, alterations in central nervous system functions have not been evaluated thoroughly. However, there is some evidence that diabetes mellitus may result in a variety of subtle cerebral disorders. Besides changes at a neurochemical, electrophysiological, and structural level, neurobehavioral disorders have been found (Biessels, Kapelle, Bravenboer, Erkelens, & Gispen, 1994). Over the last 20 years, a number of studies has examined cognitive functioning in patients with Type 2 diabetes with varying results (for a review see Strachan, Deary, Ewing, & Frier, 1997). Although some studies report no difference in cognitive performance between patients with Type 2 diabetes and nondiabetic control persons (Cerizza, Minciotti, Meregalli, Garosi, Crosti, & Frattola, 1990; Soininen, Puranen, Helkala, Laakso, & Riekkinen, 1992; Gradman, Laws, Thompson, & Reaven, 1993; Atica, Moses, & Sinclair, 1995), the majority of studies demonstrate that diabetic patients perform more poorly in at least one aspect of cognitive function (Perlmutter, Hakami, Hodgson Harrington, Ginsberg, Katz, Singer, & Nathan, 1984; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Reaven, Thompson, Nahum, & Haskins, 1990; Jagusch, Cramon, Renner, & Hepp, 1992; Worrall, Moulton, & Briffett, 1993; Croxson & Jagger, 1995; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Zaslavsky, Gross, Chaves, & Machado, 1995; Cosway, Strachan, Dougall, Frier, & Deary, 2001; Grodstein, Chen, Wilson, & Manson, 2001; Hiltunen, Keinanen-Kiukaanniemi, & Laara, 2001). The most commonly af-

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affected cognitive ability reported in these studies was verbal memory. Frontal lobe function, attention/concentration, and psychomotor ability tended to be less commonly affected (Strachan, *et al.*, 1997). However, these results must be interpreted with some caution since methodology and kinds of psychological tests used varied widely among the various studies.

To assess the types of cognitive abilities potentially affected by the disorder, it is useful to frame the question in terms of the stages assumed to compromise these abilities. Models of human information processing typically distinguish among at least three basic stages. These stages are referred to by a variety of names, e.g., stimulus identification, response selection, and response execution or perception, decision, and action. Despite the differences in terminology, the first stage generally involves perceptual processes concerned with encoding the stimuli, the second stage with selecting the correct response, and the third with executing the response (Wickens & Hollands, 2000). At present, no single study has investigated the effects of diabetic mellitus on these three basic stages. Therefore, the aim of the present study was to investigate whether there is a difference in stimulus identification, response selection, and response execution performance between patients with Type 2 diabetes and nondiabetic control persons. Further clinical relevance of this study lies in the possibility that tasks as herein used could possibly serve as a method for the early detection of neurological complications.

METHOD

Participants

Ten male patients with Type 2 diabetes and 13 male nondiabetic control persons ranging in age from 50–65 years volunteered for the study. They were recruited in collaboration with the Department of Internal Medicine and Endocrinology of the University Hospital Maastricht and the Department of Internal Medicine of the St. Anna Hospital, Geldrop. The patients with Type 2 diabetes were diagnosed by standard criteria (IDF, 1999). Exclusion criteria for the entire group were (1) history of cerebrovascular accident, (2) history of drug abuse or alcoholism, (3) structural disorders in hand, eye, or hearing functions, (4) clinical hypertension. Patients with diabetic complications (neuropathy, impaired renal function, retinopathy) were excluded, and none of them had evidence of cardiovascular disease as tested by ECG and blood-pressure monitoring during a bicycle ergometer ride to exhaustion. In addition, persons with diabetes in first degree relatives were excluded from the control group. Of the diabetes patients, four were taking sulfonylureas in combination with biguanids, one was taking an α -glucosidase inhibitor and sulfonylureas, and five were taking sulfonylureas only. Table 1 shows subjects' characteristics of participants in the Type 2 diabetes

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group and the nondiabetic control group. Except for glucose levels before and after testing, there were no significant differences between the two groups.

TABLE 1
CHARACTERISTICS OF VOLUNTEERS

Characteristic	Controls ($n = 13$)		Type 2 Diabetes ($n = 10$)	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
Age, yr.	56.8	4.8	57.7	4.4
Height, m	1.74	0.7	1.74	0.4
Weight, kg	80.5	9.9	85.1	13.9
Body Mass Index	26.4	1.9	27.9	3.9
IQ	116.1	9.7	116.4	12.9
Sum Beck Depression score	4.6	3.8	4.2	3.1
Glucose before testing, mmol/l	6.3	0.8	9.3	2.9
HbA1c, %			7.7	1.1

Cognitive Function Tasks

Stimulus perception was assessed using two tasks, an Identification task (e.g., Adam & Wilberg, 1992) and a Localisation task (e.g., Adam, Huys, van Loon, Kingma, & Paas, 2000). On the Identification task, four different and randomly chosen consonants were shown during a brief period of 100 msec. and were followed by a masking stimulus (a string of seven + signs). The volunteers were asked to identify the presented letters as accurately as possible. This procedure was repeated for a total of five practice and 20 test trials. Mean percentages of correctly identified letters were calculated. The Localisation task measured how accurately the location of a single stimulus could be perceived. Volunteers were asked to perceive and report the location of a single target stimulus (* sign) presented on a horizontal line as accurately as possible. Three different conditions of stimulus duration were randomly employed (43, 114, and 300 msec.). Ten practice trials and 50 test trials for each stimulus-duration condition were performed, and mean absolute spatial error (distance between target and response) was calculated.

Response selection was assessed on two tasks, a Choice Reaction Time task (e.g., Wallace, 1971) and a Precuing task (e.g., Miller, 1982; Adam, Paas, Teeken, van Loon, van Boxtel, Houx, & Jolles, 1998). On the Choice Reaction Time task, Compatible and Incompatible conditions were applied. In the Compatible condition the target stimulus (consisting of a plus sign [+]), and the response were mapped onto each other in a spatially compatible manner such that a stimulus appearing to the left of a central fixation point had to be responded to with a key press by the left index finger and a stimulus appearing to the right of a central fixation point had to be responded to with a key press of the right index finger. In the Incompatible con-

dition the target stimulus and the response were not mapped onto each other in a spatially compatible manner. A stimulus appearing in the left position had to be responded to with a key press by the right index finger and a stimulus appearing in the right position had to be responded to with a key press by the left index finger. Volunteers were asked to respond as quickly as possible and to minimise the number of errors. Twenty practice attempts and 100 test trials were performed in the Compatible and Incompatible conditions, and mean reaction time (RT) and percentage errors were calculated. The order of the conditions was counterbalanced. The Precuing task was a four-choice reaction task on which the participant had to respond to compatible spatial location stimuli with discrete key presses by the index and middle fingers of both hands. The display consisted of three horizontal rows representing warning, precue, and target stimuli, respectively. The warning stimulus consisted of 4 plus (+) signs indicating the four possible locations of the stimulus. The precue consisted of two plus signs indicating two possible locations of the stimulus, and the target stimulus consisted of one plus sign indicating location of the target stimulus. The temporal order of these three rows was that first the warning stimulus was presented, then after a constant delay the precue, and then after a variable delay (the "Preparation interval") the target stimulus location. Two basic precue conditions were distinguished, namely, the Cued and the Uncued condition. In the Cued condition, the cue contained two plus signs in two possible stimulus locations, thereby allowing selective preparation of two stimulus-response alternatives. In the Uncued condition, the cue contained plus signs in all four possible locations and thus provides no advance information. The Hick-Hyman law (Hick, 1952; Hyman, 1953) states that a two-choice reaction time task gives shorter reaction times than a four-choice task. Cue effectiveness was inferred from a significant reaction-time advantage for the Cued condition over the control (Uncued) condition. In the test, three preparation intervals were randomly employed, namely, 100, 1,000, and 2,000 msec. The volunteers were asked to respond as quickly as possible and to minimise the number of errors to the position in which the target signal occurred by pressing the appropriate response. Twenty practice trials and 80 test trials of each interval were given. Mean reaction time and number of errors for the several preparation intervals and different precue conditions were calculated.

Response execution was based on Discrete and Reciprocal tapping tests (e.g., Schmidt & Lee, 1999) during which the volunteers stood facing a table on which the tapping apparatus was placed. Two circular targets of equal size (24 mm) were separated by a distance of 320 mm. On the Discrete Tapping task the volunteers were asked to move the right index finger as quickly and accurately as possible from the right to the left target. They were instructed to start moving after an auditory signal. One practical trial and 10

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test trials were performed. Movement time, reaction time, and number of errors (misses) were calculated. In the Reciprocal Tapping test, the volunteers were asked to move the right index finger repetitively between the two circular targets for 15 sec. The instructions emphasised accuracy and speed. One practice trial and two test trials were performed. Movement time and number of errors were calculated as the average of the movements to both left and right targets.

Procedure

After giving the volunteers information about testing procedures, a blood sample from a prewarmed finger tip was taken for assessment of the blood glucose level before testing (Glucometer, Bayer Diagnostics). The set of tests was then administered on an IBM compatible computer. After completing the test, a blood sample from the finger was taken to measure the blood glucose level after testing. Then, after a pause of about 15 min., an intelligence test ("Short General Intelligence Test") was performed to estimate IQ scores in both control and the group with Type 2 diabetes. Finally, all volunteers answered the Beck Depression Inventory to assess severity of depression (Lustman, Clouse, Griffith, Carney, & Freedland, 1997). There is evidence that depression interferes with neurological function and can mimic organic dysfunction. A score of less than 14 on the inventory suggests minimal or no depression (Beck, 1961). Therefore, volunteers ($n=1$) with a score of more than 14 were excluded.

Statistical analyses were performed using the Statistical Packages for the Social Sciences (SPSS). Depending on the tasks involved, independent t tests were conducted or split-plot analyses of variance. Differences were considered significant when $p \leq .05$.

RESULTS

Stimulus Perception

Results for stimulus identification are presented in Table 2. Unpaired t -test analyses on the identification and localisation task data demonstrated no significant differences between the two groups on either measure of perceptual performance.

Response Selection

Results of response selection performance are presented in Table 3. Choice reaction times were analysed with split-plot analyses of variance with Group as between-subjects factor (control versus diabetic patients) and Compatibility as within-subjects factor. Analysis showed a significant main effect for Group ($F_{1,21}=6.11, p<.05$), for Compatibility ($F_{1,21}=421.7, p<.001$), and a significant interaction for Group by Compatibility ($F_{1,21}=4.96, p<.05$). The significant main effect for Group indicates a poorer performance in patients

TABLE 2
STIMULUS PERCEPTION PERFORMANCE, RESPONSE-EXECUTION PERFORMANCE, AND BLOOD GLUCOSE
LEVEL BEFORE AND AFTER TESTING IN TYPE 2 DIABETES AND CONTROL PERSONS

	Control		Type 2 Diabetes	
	M	SD	M	SD
Identification task: % correctly identified letters	47.1	11.2	40.2	13.1
Localisation task: M error, mm	3.8	1.5	5.3	3.6
Reciprocal Tapping test: Movement Time, msec.	250.0	45.0	300.8	98.0
Discrete Tapping test: Movement Time, msec.	294.0	35.0	331.0	74.0
Blood Glucose				
Before testing, mM	6.3	0.7	11.4	3.7
After testing, mM	6.3	0.9	9.4	2.9*

*Significant difference from "Before testing" ($p \leq .01$).

with Type 2 diabetes than in the control group, and the main effect for Compatibility indicated longer RTs in the Incompatible than the Compatible condition. The significant interaction indicated that differences between the two groups were only evident in the Incompatible condition and not in the Compatible condition.

TABLE 3
RESULTS OF RESPONSE-SELECTION PERFORMANCE IN TYPE 2 DIABETES AND CONTROL PERSONS

	Control		Type 2 Diabetes	
	M	SD	M	SD
Choice Reaction Time Test				
Reaction time, msec.				
Compatible trial	369	42	399	39
Incompatible trial	543	67	615	60
Precueing Test				
Reaction time, msec.				
Uncued 2000	601	121	687	103
1000	572	104	670	113
100	568	70	685	110
Cued 2000	536	111	683	123
1000	525	104	657	127
100	552	71	674	131

Split-plot analyses of variance were performed on precueing data with Group as between-subjects factor and Precue condition and Preparation interval as within-subjects factors. In accordance with choice reaction time results, a significant main effect was found for Group ($F_{1,21}=7.11$, $p < .01$), indicating longer RTs in the group with Type 2 diabetes than in the control group. The main effect for Precue condition ($F_{1,21}=10.39$, $p < .01$) indicated shorter RTs in the Cued condition than in the Uncued condition. The significant interaction between Group and Precue condition ($F_{1,21}=4.35$, $p < .01$) indicated that the difference between the two groups was only significant in the Cued condition.

.05) indicated that the effect of Precue condition was only significant for the control group, with the diabetic patients showing similar RTs in the Cued and Uncued conditions. In other words, only the nondiabetic volunteers showed a significant precuing benefit. The significant three-way interaction involving Group \times Precue Condition \times Preparation Interval ($F_{2,42} = 4.04$, $p < .05$) indicated that the precuing benefit for the control group increased with longer preparation intervals.

Response Execution

Response execution means and SDs are shown in Table 2. Means were subjected to split-plot analyses of variance with Group as between-subjects factor (control versus patients with Type 2 diabetes and Tapping condition as within-subjects factor. A main effect for Movement Time was found for Tapping condition ($p < .01$) which indicates that both groups had longer movement times on the Discrete than on the Reciprocal tapping task. No significant main effect for Group and no significant interaction was found. Errors on Reciprocal and Discrete tapping tasks were less than 3% and 1%, respectively, making further analysis of these errors futile.

Table 2 presents mean blood glucose level before and after testing in the group with Type 2 diabetes and the control group. Paired t tests in both groups indicated that there was a significant decrease in blood glucose level in the group with Type 2 diabetes but no changes in blood glucose level in the control group.

DISCUSSION

Results of the present study support the conclusion of several prior studies cited in the introduction that Type 2 diabetes is associated with impaired cognitive function. We used a noninvasive test battery consisting of computerised tasks. These included perceptual tasks, response-selection tasks, and tapping tasks. In contrast with most other studies we used stringent exclusion criteria based on depression, clinical hypertension, history of cerebrovascular accident, alcoholism, or drug abuse, and functional disorders (hand/eye/hearing function) and provided careful matching between the two groups on IQ score. Omission of such stringent exclusion and matching criteria could easily result in false-positive effects (Tun, Nathan, & Perlmutter, 1990; Asimakopoulou, Hampson, & Morrish, 2002).

Patients with Type 2 diabetes showed impaired performance on the cognitive aspect of response selection when tasks became increasingly complex. This was illustrated by the finding that no significant differences between the two groups were found on the simple Compatible 2-choice reaction test. On the more difficult Incompatible 2-choice reaction test, however, a significant difference between the group with Type 2 diabetes and the control group was found. This effect was supported by the results of the rel-

actively complex four choice 'precuing' reaction-time test. That is, in contrast to nondiabetic volunteers, the mean reaction time of the group with Type 2 diabetes did not improve with precuing. The finding that diabetes-related differences are more evident on complex cognitive tests is consistent with earlier studies (Perlmutter, *et al.*, 1984; Tun, *et al.*, 1990; Worrall, *et al.*, 1993). We did not find significant differences on stimulus perception and response-execution performance.

A possible pathogenic mechanism in the development of cerebral disorders in diabetes mellitus is thickening of capillary basement membranes, the hallmark of diabetic microangiopathy, which has been demonstrated in the brains of diabetic humans and animals (Johnson, Brendel, & Meezan, 1982; Jakobsen, Sidenius, Gundersen, & Osterby, 1987). In addition to morphological changes in the cerebral vasculature, decreased cerebral blood flow has been reported in both acutely and chronically hyperglycaemic animals (Duckrow, Beard, & Brennan, 1987; Harik & LaManna, 1988). Odawara, Tada, and Yamashita (1995) performed computed tomography studies of the brain in diabetes patients and found decreased blood perfusion in bilateral frontal and lateral lobes. They suggested that central blood perfusion may be focally decreased, which may result in cognitive deficits. Response-selection processes are typically located in the (pre)frontal lobe area (Gazzaniga, Ivry, & Mangun, 1998). The present study therefore suggests that this area may be especially vulnerable to diabetes-induced central neuropathy. Obviously, more mechanistic or neuroimaging studies are needed to investigate these findings.

A remarkable finding in the present study was the significant decrease in blood glucose level during testing for the group with Type 2 diabetes with no changes in blood glucose level in the control group. Analyses showed a decrement of approximately 17% in plasma glucose level in the group with Type 2 diabetes over 1.5 hr. There is evidence that decrements of less than 20% of postabsorptive plasma glucose concentration are sufficient to impair brain oxidative metabolism and to produce cortical brain dysfunction in normal men (Atiea, *et al.*, 1995). Most studies that measured cognitive function during acute hypoglycaemia suggest that mental activities which are relatively undemanding are often unaffected at all levels of experimental hypoglycaemia while the performance of more complex tasks deteriorates at glucose concentrations of around 3 mmol/l (Heller & Macdonald, 1996). In the present study it appears that the decreased glucose level had little influence on cognitive performance as blood glucose level in the group with Type 2 diabetes remained well above hypoglycaemic values. Also, if a gradual decline in blood glucose level in the patients with Type 2 diabetes should explain the impaired test performance in the present study, it would be expected that these patients performed poorly in the latter part but not in the

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beginning of the test battery. However, no such temporal effect on performance was found.

In conclusion, the present findings indicated that in patients with Type 2 diabetes without apparent complications, cognitive function is nevertheless impaired. Using a rigorous methodological approach to cognitive testing, we found an impaired performance in patients with Type 2 diabetes on response-selection performance. In contrast, performance differences on the perception and motor tasks seemed unaffected.

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