Relationship between Neuropsychological Functioning, Behavioral Inhibition, and Glycemic Control in Type 2 Diabetes: Findings from Task-switching Study

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INTRODUCTION

Type 2 diabetes (T2D) is one of the fastest growing medical conditions associated with cognitive dysfunctions. Less attention is paid to the effects of diabetes on task switching (TS). Switching between tasks is a higher-order cognitive function which is executed through prefrontal cortex. Given that there are brain structural abnormalities (i.e., atrophy in cortical/subcortical gray matter volume and hyperintensities in cerebral white matter), reduced connectivity between hippocampus and adjacent brain regions (frontal and temporal gyri), and certain indirect mechanisms (amyloid-β deposition, hyperphosphorylation of tau protein, and insulin resistance, cortical deregulation) which causes frontotemporal dementia and neural degeneration in patients with T2D, it is expected that TS might be adversely affected.[1] We hypothesized that patients with T2D would show impaired TS and neuropsychological performance. TS performance would be correlated with behavioral inhibition, neuropsychological functioning, and glycemic control. Behavioral inhibition, neuropsychological functioning, and glycemic control would be significant predictors of TS performance in patients with T2D.

METHODS

The study received ethical approval. The research protocol followed the Declaration of Helsinki. Each participant gave written informed consent. Participants included forty patients diagnosed with T2D as per criteria defined by the American Diabetes Association[2] and forty matched healthy controls [Table 1]. Patients were recruited from Bahawal Victoria and Indus Hospital. Healthy control group was recruited from the local community if they had no history/present symptomology of diabetes. Participants in either group were not included if they had history/present symptoms of dementia as examined through mini-mental status examination score <24, psychological/neuropsychiatric disorder as assessed through mini-international neuropsychiatric interview, major medical conditions cancer, thyroid function, stroke, head trauma, coronary heart disease, and visual/hearing impairment as assessed by clinical examination. Blood samples were obtained. Montreal cognitive assessment (MoCA)[3] was administered to assess cognitive dysfunctions. MoCA has high test-retest reliability ($r = 0.92$), internal consistency ($\alpha = 0.83$), and criterion validity (0.72). A score equal to or above 26 out of 30 is considered normal. Following, clock-drawing test[4] was used to assess executive function (EF) and working memory (WM). Participants were asked to draw a clock which is scored from 0 to 8; lower score represents impaired performance. Test has good test-retest reliability ($r = 0.87$) and concurrent validity ($r = 0.59$). Upon completion, participants completed TS experiment. The experiment included 16 images as stimuli. For food
Table 1: Characteristics of sample of the study

| Characteristics                  | Control (n = 40) | Patients with T2D (n = 40) | t       | P       |
|----------------------------------|-----------------|----------------------------|---------|---------|
| Gender (male/female)             | 20/20           | 20/20                      |         |         |
| Age (years)                      | 62.12 (4.98)    | 59.47 (4.42)               | t(39) = 2.61 | 0.013 |
| Education (years)                | 12 (2.55)       | 12.15 (2.15)               | t(39) = 0.89 | 0.374 |
| Duration of diabetes (years)     | 8.00 (1.24)     | NA                         | –       | –       |
| Age at diagnosis (years)         | 54.0            | NA                         | –       | –       |
| SBP (mmHg)                       | 127 (1.29)      | 126 (1.25)                 | t(39) = 1.36 | 0.179 |
| DBP (mmHg)                       | 82 (1.47)       | 81.45 (1.45)               | t(39) = 1.74 | 0.088 |
| Total cholesterol (mmol/L)       | 5.00 (0.70)     | 4.20 (0.81)                | t(39) = 1.06 | 0.291 |
| HbA1c (%)                        | 7.30 (0.75)     | 5.50 (0.80)                | t(39) = 10.66 | 0.000 |
| HbA1c (mmol/mol)                 | 56              | 37                         | –       | –       |
| BMI (kg/m²)                      | 24.27 (0.75)    | 23.50 (3.55)               | t(39) = 1.36 | 0.181 |

Medication
- Oral hypoglycemic agents: 10
- Metformin: 20
- Insulin-secretagogue agents: 10

MMSE: 27.25 (0.86); MoCA: 21.42 (0.93); Working memory: 1.90 (0.59); Executive function: 1.80 (0.46); BAS: 7.57 (1.29)

Data are reported as mean (SD). T2D: Type 2 diabetes; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; BMI: Body mass index; MMSE: Mini-mental status examination; MoCA: Montreal cognitive assessment; BIS: Behavioral inhibition system; BAS: Behavioral activation system; SD: Standard deviation.

categorization task, food must be categorized as high fat versus palatable sweet. The picture of object served as a distractor. For object categorization task, objects are categorized as clothes versus furniture (food picture served as distractor in this condition). Tasks were presented in an alternating order FOFOFO... (counterbalanced across participants) and were cued by different colored backgrounds. The experiment had total 225 trials. Then, participants were asked to complete behavioral inhibition system/behavioral activation system (BIS/BAS) scale.[3] BIS refers to inhibition and withdrawal of behavior whereas BAS indicates approach behavior. Underactivation or hyperactivation of these systems has been presumed to explain physiological disorders. Internal consistency of the scale is high: BIS (r = 0.75) and BAS (r = 0.81). It is a valid tool as BIS positively correlates with neuroticism (r = 0.75) and depression (r = 0.48) whereas BAS negatively correlates with neuroticism (r = −0.06) and depression (r = −0.19).

Statistical analyses
Data were analyzed using Statistical Package for Social Sciences version 20.0 (IBM, Chicago, IL, USA). The data for the first trial were discarded. Mean reaction times (RTs) were averaged for 56 switch and 56 repeat trials for each task. Switch costs (SC) were calculated by subtracting mean RTs on switch from mean RTs on repeat trials. Analysis of variance (ANOVA) with repeated measures was used to examine TS data with factors as task (food vs. object categorization) x trial (switch vs. repeat) as within participants whereas group (patients vs. controls) as between participants. Bivariate correlation analysis was conducted to assess the relationship between SC, glycosylated hemoglobin (HbA1c), BIS, WM, EF, and MoCA. Linear regression analysis was computed to examine significant predictors of SCs.

Results
Clinical characteristics are shown in Table 1. TS data showed significant main effects of trial [F(1, 78) = 1458.17, P = 0.000, η² = 0.94], switch versus repeat (M = 1309 vs. 730 ms); task [F(1, 78) = 27.99, P = 0.000, η² = 0.26], food versus object categorization (M = 990 vs. 1050 ms); and group [F(1, 78) = 231.59, P = 0.000, η² = 0.74], patients versus controls (M = 1187 vs. 852 ms). The interaction between trial x group was significant [F(1, 78) = 108.79, P = 0.000, η² = 0.58]. Patients had greater SC than controls (M = 737 vs. 420 ms), t(39) = 10.67, P = 0.000. The interactions between task x group [F(1, 78) = 45.92, P = 0.000, η² = 0.37] and trial x task [F(1, 78) = 46.18, P = 0.000, η² = 0.37] were also significant. The higher-order interaction between trial x task x group was significant [F(1, 78) = 64.62, P = 0.000, η² = 0.45]. This interaction was further analyzed through ANOVA with factors as trial (switch vs. repeat) and task (food vs. object categorization) separately for patient and control data. The interaction between trial x task was significant for patient data [F(1, 39) = 58.03, P = 0.000, η² = 0.59]. Patients showed larger SC for object than food categorization, t(39) = 7.61, P = 0.000, M = 831 versus 642 ms. In healthy individuals, there was a significant
interaction between trial x task \([F(1, 39) = 7.42, P = 0.01, \eta^2_p = 0.16]\). In contrast to patient group, controls showed larger SC for food than object categorization, \(t(39) = 2.72, P = 0.000, M = 428\) versus 412 ms. SCs were correlated with BIS \((r = -0.90, P = 0.000)\), HbA1c \((r = 0.93, P = 0.000)\), MoCA \((r = -0.88, P = 0.000)\), and EF \((r = -0.81, P = 0.000)\). HbA1c \((\beta = 0.48, t = 5.61, P = 0.000)\), and BIS \((\beta = -0.22, t = 2.05, P = 0.044)\) were significant predictors of SC, \(R^2 = 0.90, F = (5,79) = 141.53, P = 0.000\). EF \((\beta = -0.55, t = 0.77, P = 0.442)\) and MoCA \((\beta = -0.09, t = 1.04, P = 0.300)\) failed to reach the level of significance.

**Discussion**

The results showed that patients with T2D demonstrated impaired neuropsychological and TS (larger SC) performance in contrast to healthy non-T2D individuals. This showed weaker modulation of WM and inhibitory control in patients with T2D as compared to healthy individuals. Participants have to recall task cue in order to perform accordingly while overcoming the interference between tasks. SC interacted with task in both groups. Patients with T2D showed larger SC for object categorization task when food-related cues were used as distractor. This result is indicative of deficient cognitive control on interference aroused by food stimuli. Patients with T2D paid more attention toward high-fat and palatable sweet food; therefore, object categorization suffered (larger SC). On contrary, healthy non-T2D individuals showed lesser SC for object than food categorization. This result indicated their top-down control to overcome the interference generated by food stimuli. Healthy individuals were efficient at BIS and suppressed urges reinforced by BAS. Our results supported association between neuropsychological functioning, SC, HbA1c, and BIS. Higher levels of HbA1c were associated with higher SC, decreased neuropsychological functioning, and behavioral inhibition. Glycemic control and BIS were significant predictors of TS performance. As a practical significance, the present study suggests that detection of BIS and glycemic control could identify individuals with T2D who are at risk of TS impairment in future. Additional prospective and controlled studies could reveal whether individuals with good inhibitory control are better at disease management.

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**Conflicts of interest**

There are no conflicts of interest.

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