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# Fatigue and cognitive symptoms in patients with diabetes: Relationship with disease phenotype and insulin treatment

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**Summary** Neurobehavioral symptoms are frequently reported in patients with diabetes. Nevertheless, the characterization of the specific symptom dimensions that develop in diabetic patients with respect to disease phenotype and treatment status remains obscure. This study comparatively assessed fatigue symptoms and cognitive performance using a dimensional approach in 21 patients with insulin-treated type 1 diabetes, 24 type 2 diabetic patients either insulin-free or undergoing insulin treatment for at least six months, and 15 healthy subjects. Specific dimensions of fatigue were assessed using the Multidimensional-Fatigue-Inventory (MFI). Cognitive performance on tests of choice reaction time, pattern recognition memory and spatial planning was evaluated using the Cambridge-Neuropsychological-Automated-Battery (CANTAB). Body mass index (BMI) and glycated-hemoglobin (HbA1C) concentrations were collected, as well as information on diabetes complications and disease duration. Patients with type 2 diabetes, regardless of insulin treatment status, exhibited higher scores of fatigue, primarily in the dimensions of general and physical fatigue as well as reduced activity. Cognitive alterations, in the form of longer reaction times and impaired spatial planning, were also detected in type 2 diabetic patients treated with insulin. These alterations were overall unrelated to glucose control, as reflected in HbA1C levels, and were not explained by complications and duration of diabetes. No specific alteration was measured in type 1 diabetic patients who exhibited fatigue scores and cognitive performance comparable to healthy participants. While associated with fatigue, increased BMI did not significantly account for the relationship of type 2 diabetes with general fatigue and physical fatigue. BMI, however, modulated the association of type 2 diabetes with reduced activity and the association of insulin-treated type

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2 diabetes with psychomotor slowing. These findings reveal specific fatigue and cognitive symptoms in patients with type 2 diabetes and suggest the involvement of differential pathophysiological processes.


## 1. Introduction

Based on recent estimates from the World Health Organization, more than 300 million people worldwide have diabetes (World Health Organization, 2011). This chronic disease is associated not only with an increased risk of cardiovascular diseases, strokes, kidney failure and related pathologies, but also with a higher incidence of neuropsychiatric symptoms, including fatigue and cognitive dysfunction. Most often documented in patients with type 2 diabetes, these symptoms significantly reduce the patient's quality of life and compliance to treatment and increase the risk of disease complications (Weijman et al., 2003, 2005; Chasens and Olshansky, 2008; Feil et al., 2009).

In a study conducted in 1137 newly diagnosed subjects with type 2 diabetes, the prevalence of fatigue was found to reach 61% (Drivsholm et al., 2005). Despite this elevated frequency and the impact of fatigue on the patient's wellness and treatment efficacy, only few studies have systematically explored this symptom dimension in diabetic patients and many of them were limited to nonspecific symptoms of fatigue (Fritschi and Quinn, 2010). In addition, there is little indication regarding the potential differential expression of fatigue in patients with type 1 *versus* type 2 diabetes. With respect to cognitive function, significant impairment, especially in tests involving attention/memory, executive function and information-processing speed, has been documented in type 2 diabetic patients (Manschot et al., 2006; Yeung et al., 2009; Van den Berg et al., 2010). These alterations were associated with abnormalities in brain magnetic resonance imaging, including deep white matter lesions, cortical/subcortical atrophy, and infarcts (Manschot et al., 2006). Although type 2 diabetes has been more frequently associated with neuropsychological disturbances, cognitive alterations have been also described in patients with type 1 diabetes, especially in conditions of long disease duration and/or microvascular complications (Brands et al., 2005; Brismar et al., 2007).

The mechanisms involved in neuropsychiatric comorbidity in diabetes remain unknown. This limitation may arise from the paucity of semiological characterizations regarding the specific symptom dimensions that develop in diabetic patients, in function of disease phenotype and insulin treatment status. Type 1 and type 2 diabetes are characterized by distinct pathophysiology and metabolic processes that may differentially influence the expression of fatigue symptoms and cognitive alterations. For instance, in comparison to type 1 diabetes, type 2 diabetes was found to be associated with increased adiposity and higher levels of inflammatory markers (Alexandraki et al., 2008), that were found, elsewhere, to be involved in the development of fatigue and cognitive alterations in medically ill patients (Capuron et al., 2001, 2002; Capuron and Miller, 2004; Bower et al., 2009). Thus, it may be likely that these processes, which are distinctly expressed in type 1 *versus* type 2 diabetes, lead to differential neuropsychiatric symptom phenomenology and profiles in the two populations of diabetic patients. Moreover, treatment options may also contribute to distinct manifestation of neuropsychiatric symptoms in the two types of diabetes. Insulin is used to treat type 1 diabetes and it is also prescribed in some refractory cases of type 2 diabetes. The initiation of insulin treatment in type 2 diabetic patients is frequently associated with weight gain (Rigalleau et al., 1999; Russell-Jones and Khan, 2007; Mavridis et al., 2008; Gin et al., 2010), a process that may influence the development of neuropsychiatric alterations through activation of metabolic and inflammatory pathways. Moreover, insulin *per se* has potent central actions, including effects on synaptic plasticity, notably by acting on glutamatergic and GABAergic transmission in a time dependent manner (Wan et al., 1997; Skeberdis et al., 2001; Williams, 2008). Insulin can also modulate the catecholamine reuptake (Figlewicz et al., 1993, 1994). Consistent with these data, insulin was found to modulate brain functions, including cognition (Park, 2001). At the clinical level, intravenous infusion or long-term intranasal administration of insulin was found to improve declarative memory and performance on the Stroop test in healthy subjects (Kern et al., 2001; Benedict et al., 2007). In diabetic patients, however, the influence of insulin treatment on cognitive function is unclear and studies have also reported detrimental effects. In support of this notion, one study performed in Japanese elderly subjects with type 2 diabetes found that patients treated with insulin exhibited poorer cognitive function (lower scores in Mini-Mental State Examination and Digit Symbol Test) than non-insulin-treated diabetic patients and non-diabetic subjects (Mogi et al., 2004). Based on these data, it is possible that insulin treatment, in conjunction with disease phenotype, influences the expression of neuropsychiatric symptom dimensions that develop in patients with diabetes.

The objective of this study was to provide a fine description of fatigue and cognitive alterations that develop in diabetic patients with respect to disease phenotype (type 1 *versus* type 2) and insulin treatment status, in comparison to a group of healthy individuals, and to assess the relationship of diabetes-related features (*e.g.*, adiposity, glucose control, complications) with these symptom dimensions.

## 2. Methods

### 2.1. Participants

#### 2.1.1. Patients

Twenty-four patients with type 2 diabetes and 21 patients with type 1 diabetes were recruited from the service of Diabetology at the Haut-Lévêque hospital in Pessac, France. Patients with type 2 diabetes had a personal history of overweight. 13 of them were on insulin therapy for at least 6 months after failure of oral antidiabetic treatment and the remaining were either on oral antidiabetic drugs ($N = 8$) or