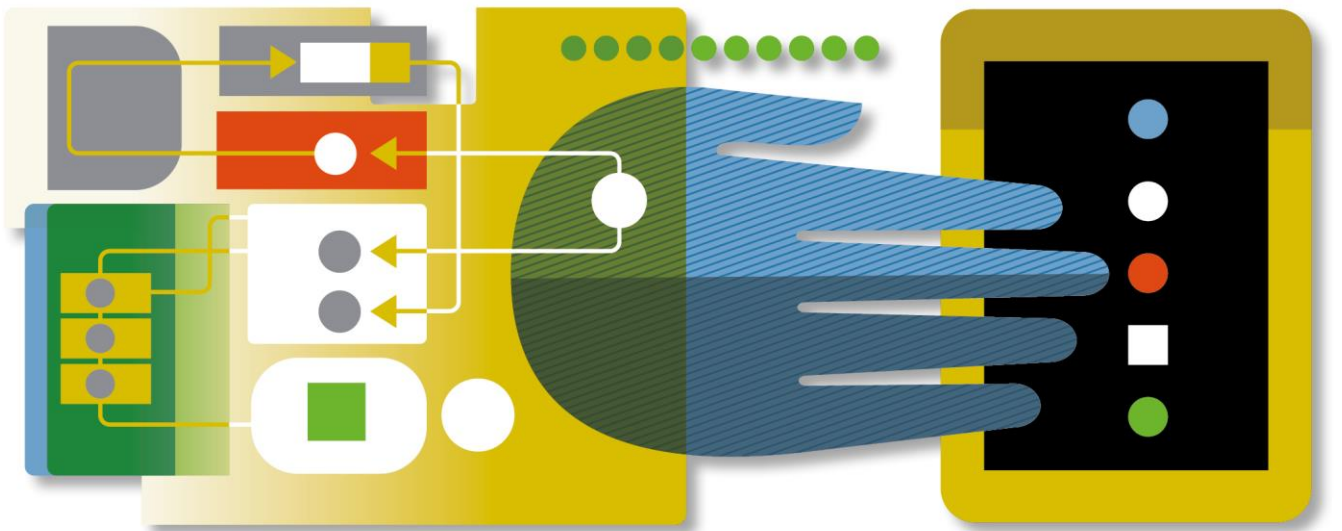


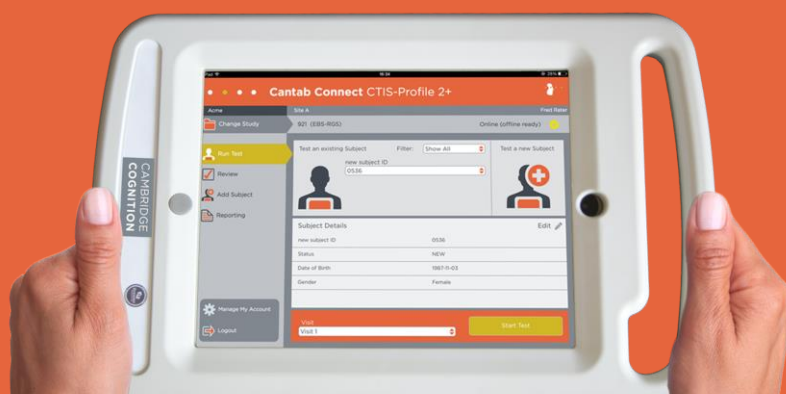
# Diabetes and Cognition

Disorder-specific impairments and treatment-induced effects on cognitive function



## Overview

- Individuals with diabetes mellitus experience cognitive impairments, particularly in domains of processing speed and executive function.
- Type 2 diabetes is associated with an increased risk of late-life cognitive deficits. Long-term, well-controlled diabetes may decrease the risk or severity of these late-life cognitive impairments.
- Treatments and medications for type 1 and type 2 diabetes can result in both positive and negative effects on cognition.
- Systematic, computerized assessment of the impact of treatment on cognitive function can minimize risk and differentiate a treatment from others.



## Cognitive deficits in diabetes

Diabetes mellitus is defined by high blood glucose concentrations and the body's inability to regulate these concentrations properly. Both type 1 and type 2 diabetes mellitus are characterised by hyperglycaemia, their epidemiology, pathophysiology, and associated comorbidities are, however, different. Type 1 (insulin dependent) diabetes accounts for 5–10% of patients with diabetes and typically develops in childhood or early adulthood; in most patients, the age of onset is younger than 30 years. The incidence of type 2 (non-insulin dependent) diabetes increases with age, from less than 0.1% in people younger than 30 years to 1% in people around the age of 70 years. The incidence and prevalence of diabetes vary across countries and are expected to increase during the coming decades owing to the influence of lifestyle and socioeconomic factors. The current prevalence of diabetes in Europe and the USA peaks at 10–20%, at around 70 years of age.

Diabetes is a complex disorder and several factors, either related to the disease itself or treatment thereof, can impact the brain and affect cognitive function. These factors include age of disease onset (Ferguson 2005), treatment regimen, and the number and time of occurrence of hypo- and hyperglycaemic episodes (Biessels, 2008). Depending on the nature of the insult, cognitive impairments can be transient or permanent (Desrocher 2004). Research has shown that cognitive impairment due to onset of diabetes may occur at particular periods of time during the lifespan: during structural neurodevelopment change in childhood; and during neurodegenerative change during late adulthood (Biessels, 2008). Cognitive decline outside of these time periods is primarily associated with long-term treatment and disease related comorbidities, such as cerebrovascular complications.

## Type 1 diabetes

There is compelling evidence that children with type 1 diabetes demonstrate pathology-related cognitive impairment and perform worse at school compared to age-matched healthy children; sizeable cognitive deficits in children with type 1 diabetes have been reported in measures of attention, processing speed, memory and executive functions (Biessels 2008; Desrocher 2004). However, the specificity and magnitude of these effects are considerably heterogeneous across studies, possibly due to methodological limitations such as small sample sizes, selection bias and the presence of confounding variables such as age of disease onset (Desrocher, 2004). Desrocher (2004) found that cognitive impairments are highly dependent on the neurodevelopmental stage children are at when the disease first manifests or fluctuations of blood glucose levels occur. For example, it is widely asserted that the hippocampus and the prefrontal cortex reach full development at different stages; broadly, frontal lobe neural development occurs later than temporal areas development. Figure 1 represents a hypothetical depiction of these relationships. The key variables that seem to be related to poor cognitive outcome are age of onset, hypoglycaemia, hyperglycaemia, puberty, and duration of the disease.

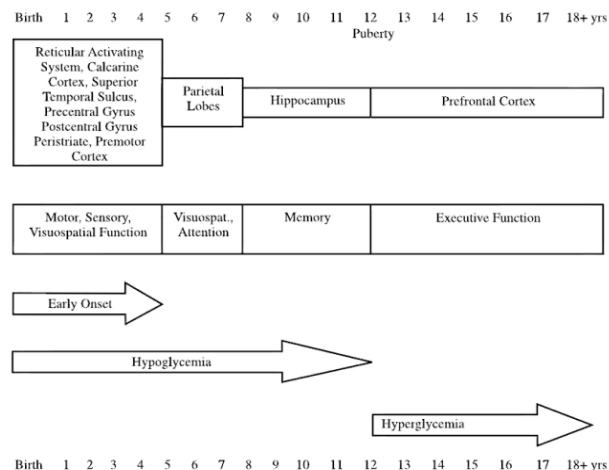


Figure 1. Model of the relationship between diabetes variables and neurocognitive development.

There are currently no treatments that are shown to ameliorate the observed cognitive impairments in patients with diabetes. Type 1 diabetes is primarily treated with insulin in an attempt to achieve normo-glycaemia and decrease the risk of comorbid complications. Insulin crosses the blood-brain barrier and affects the central nervous system, giving it the potential to modulate a range of cognitive functions (Ryan, 2006). Improving patients' glycaemic control has been associated with improved cognitive function (Ryan, 2006, see Figure 2); however intensive treatment with insulin (three or more injections daily) increases the risk of hypoglycaemic episodes (The Diabetes Control and Complications Study Group (DCCT), 1993; 2007). This increased risk of severe hypoglycaemia as a result of intensive treatment presents a key barrier to implementation of such treatment, as it causes concern of long-term negative effects on patient's thinking ability and performance at school or work (DCCT, 2007).

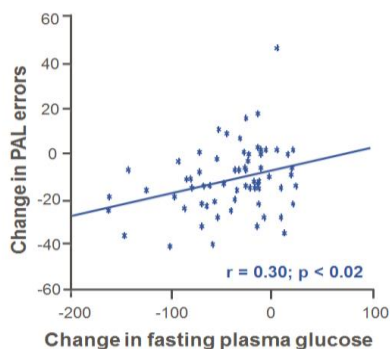


Figure 2. Improving glycaemic control with an insulin sensitizer reduces the number of errors made on an episodic memory task (Cantab Paired Associates Learning (PAL)).

The adverse effects of repeated and severe episodes of hypoglycaemia on the central nervous system might be an important mediator of the so-called “early-onset effect” of diabetes, although hypoglycaemic episodes can also affect intellectual development in older children and adolescents (Biessels, 2008). Jacobson (2010) reported that patients with a long history of type 1 diabetes who experienced chronic hyperglycaemia demonstrated slowed psychomotor speed, which may be associated with disruption of various brain regions and neural networks as a result of fluctuating glucose levels. The safety of treatments that alter glucose levels in the brain and affect these neural networks needs to be established as they may result in chronic cognitive deficits that persist into adulthood.

### **Type 2 diabetes**

Prevalence of type 2 diabetes is greater in older adult populations and is thus associated with late-life cognitive impairment. This tends to be manifested by a moderate increase in age-related decline, as well as an increased risk for vascular dementia, stroke and other dementia related diseases (Biessels, 2005; Biessels, 2006; Cukierman, 2005). Biessels identified a number of factors related to type 2 diabetes that are considered predictors of cognitive decline, dementia and cerebrovascular disease, such as hypertension and dyslipidaemia. Studies have reported that patients with diabetes demonstrate slower processing speed and impaired executive function compared to healthy individuals, which may be mediated through cerebrovascular pathology (Qui, 2013; Cukierman, 2005).

Similarly to type 1 diabetes, adverse effects of hyperglycaemic episodes and insulin resistance may also be factors associated with the cognitive dysfunction observed in individuals with type 2 diabetes. A review of observational studies reported that patients with impaired glucose tolerance experience a greater magnitude of cognitive decline than those without, supporting the link between hyperglycaemia and cognitive dysfunction (Cukierman, 2005). Measures of processing speed and executive function have demonstrated sensitivity to glycaemic changes in individuals with type 2 diabetes (Ryan, 2006; Saczynski, 2008). Ryan suggests that, following hyperglycaemic episodes, cognitive impairments are seen in domains associated with cortical systems that have high glucose metabolism requirements, such as the prefrontal cortex, hippocampus and basal ganglia. Ryan went on to report treatment-induced glycaemic changes after 24 weeks of insulin, which led to improvement on an executive function task, indicating that certain cognitive processes may be sensitive to blood insulin concentration changes. Whether these cognitive improvements would be maintained over an extended time period, or whether adults with a greater magnitude of cognitive impairment would show further improvement in performance with similar treatment, has yet to be verified.

Other treatment options for type 2 diabetes include changes in diet and exercise; decreased fat tissue and increased muscle mass lead to better glucose absorption. Maintaining long-term control of diabetes by monitoring these types of factors may decrease the risk of late-life cognitive impairments. Hypoglycaemic drugs are also prescribed to improve patients' glycaemic control either by increasing insulin production or reducing glucose output. Studies have indicated that glucose-lowering medication and level of glycaemic control may modulate the risk of cognitive impairment in older adults with type 2 diabetes (Ryan, 2006). Conversely, other research has not found an association between medication and cognitive function (Saczynski, 2008). The variance in the relationship between diabetes medication and cognition indicates the need for larger-scale, longitudinal studies to establish the relative safety and impact of treatments being developed for diabetes.

## Cantab and diabetes

Cantab tasks have been extensively validated in over 1,400 peer reviewed papers across a wide range of conditions, including type 1 and 2 diabetes (Ryan, 2006; Saczynski et al, 2008; Lasselin, 2012; Ba-Tin, Strike & Tabet, 2011; Kaufmann, 2012; Qui, 2014), and over 150 regulatory clinical trials for cognitive safety and efficacy. Cantab tasks assessing working memory, processing speed and executive function have shown sensitivity to cognitive dysfunction associated with diabetes.

### Sensitivity to treatment effects and risk factors

Several studies using Cantab have shown that some tasks are sensitive to the cognitive changes associated with glucose levels in the brain; Lasselin et al (2012) reported impairment of performance in insulin-treated type 2 diabetic patients on Cantab tasks of processing speed (Choice Reaction Time) and executive function and planning (One Touch Stockings of Cambridge) compared with those not treated with insulin, healthy individuals, and patients with type 1 diabetes on insulin (Figure 3).

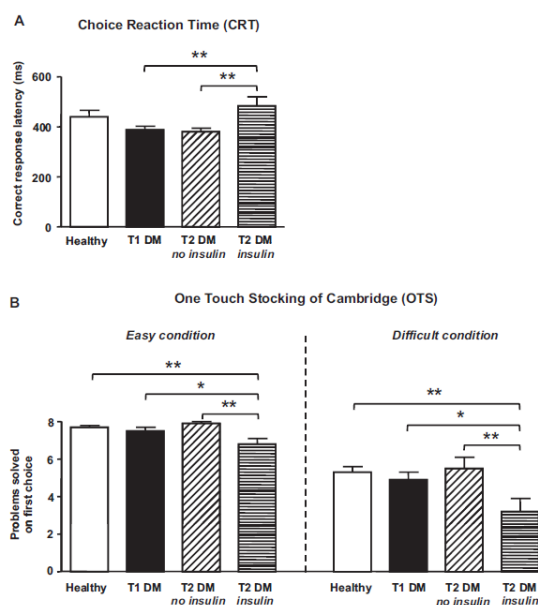


Figure 3. A: performance on Choice Reaction Time task; B: performance on One Touch Stockings of Cambridge task.

Furthermore, Kaufmann et al (2012) demonstrated that the Cantab Spatial Working Memory (SWM) task is sensitive to glycaemic change. Figure 4 shows that, after controlling for age and response speed, children with type 1 diabetes who have poor glycaemic control make more errors on the SWM task than healthy controls.

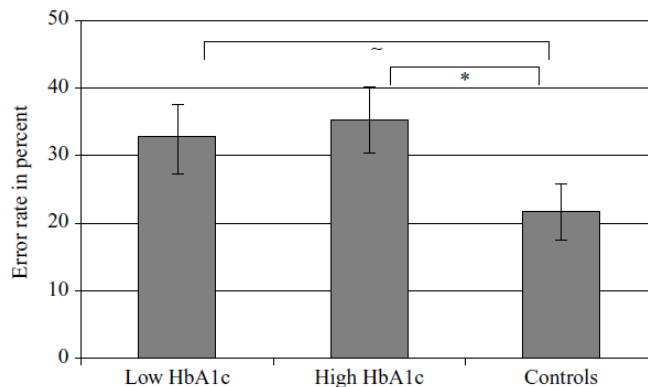


Figure 4. Performance on the Spatial Working Memory (SWM) task by children with type 1 diabetes compared to healthy controls (% errors). \* denotes significant group difference; ~ denotes approaching significance.

Treatment of patients who have type 2 diabetes is often directed at vascular risk factors and aims to reduce insulin resistance (e.g. via diet, exercise, or drug therapies) and increase endogenous insulin secretion. Cantab tasks have proven sensitivity to vascular risk factors such as obesity (Lasikiewicz, 2012), alcohol consumption (Manning et al, 2008) and diet. Furthermore, the tests are sensitive to the fluctuating blood sugar levels associated with diabetes, as illustrated by Ryan (2006). Other studies have also demonstrated that Cantab tests can detect changes in cognition that are related to vascular damage (Jailard, 2009; Bird & Cipolotti, 2007; Mavaddatt, 2000; Salmond, 2006) and age-related decline and mild cognitive impairment (MCI) (Summers, 2011) in domains of executive function, memory, processing speed and attention (Figure 5).

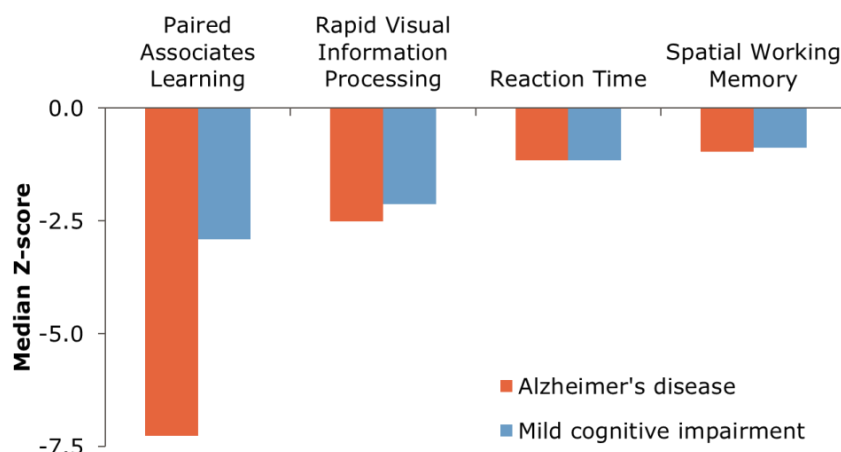


Figure 5. Profile of impairment in patients with Alzheimer's disease and mild cognitive impairment.

### Sensitive to cognitive changes over the lifespan

Selected Cantab tests carried out in normally developing children and healthy adults have been found to be sensitive to the aforementioned developmental neural substrates that may be affected by diabetes. Whilst tests of visual memory such as Pattern Recognition Memory (PRM) and Paired Associates Learning (PAL) are sensitive to changes in medial temporal functioning, executive function tasks such as Spatial Working Memory (SWM) and Stockings of Cambridge (SOC) are pre-frontal cortex dependent. As shown by the normative data illustrated below, the age of optimum performance differs between the visual memory tests (Figure 6) and the executive function tests (Figure 7). The patterns of performance match the differing rates of maturation of the brain regions in question – frontal and temporal lobes – and can be informative when measuring disease progression and developmental trajectories.

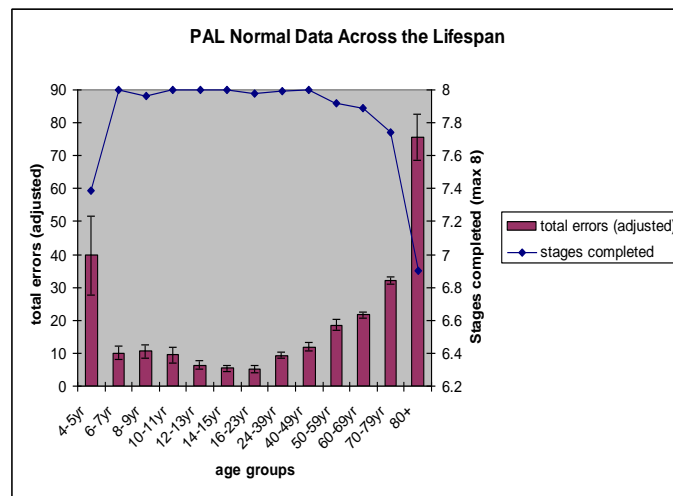


Figure 6. Graph showing PAL norm data over the lifespan. The number of total errors adjusted can be seen to drop significantly after the first 5 years of life. It then gradually increases from 24 years onwards. Stages completed follows a similar pattern.

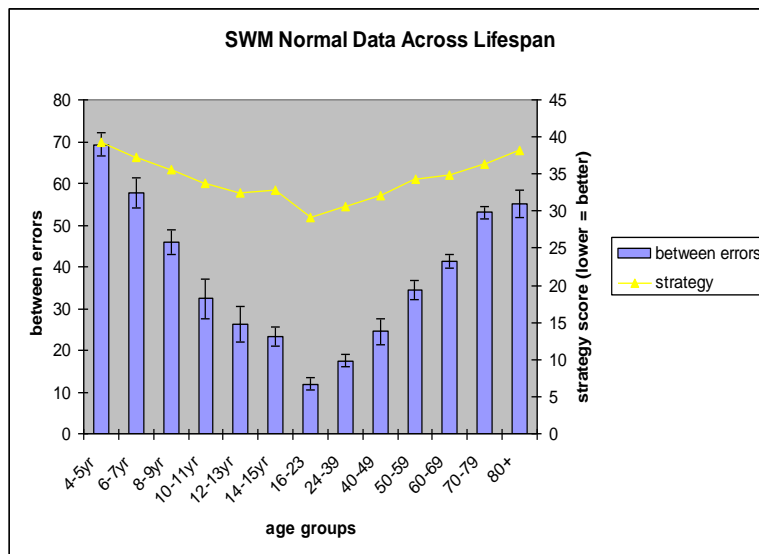


Figure 7: Graph showing SWM norm data over the lifespan. The number of between errors is at a clear minimum at 16-23 years. It decreases gradually over the first 16 years of life, and increases gradually after 23 years. The strategy score seems to follow a similar trend.

## Cantab cognitive safety assessment tool

### Clinical Trial Information Systems

Determining the safety of a compound can be complex and challenging, from both a scientific and an operational perspective. *CTIS-Profile* and *CTIS-Profile 2+* products are designed to support the assessment of compounds for cognitive safety throughout all phases of drug development.

The CTIS products are delivered on the Cantab Connect platform, combining leading cognitive neuroscience with innovative cloud technology enabling more reliable and sensitive cognitive testing.

CTIS-Profile and CTIS-Profile 2+ target key cognitive domains commonly affected by pharmacological manipulation, including psychomotor processing speed, visual episodic memory, working memory and executive function. The touchscreen assessment tools offer automated administration and scoring to reduce workloads and optimize productivity and are regulatory approved and designed for GCP compliant studies. Clean and reliable data is guaranteed with Cantab science and data management built into every CTIS product.

For more information visit [www.cambridgecognition.com/safety](http://www.cambridgecognition.com/safety)





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