

**Cognitive Performance in Adolescents With Type 2 Diabetes and Those Without:
Pilot Data from a Case-Control Study**

Irina Podinic

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School of Epidemiology and Public Health
Faculty of Medicine
University of Ottawa

PREFACE OF THE THESIS

I, Irina Podinic, declare that I am the sole author of this document. I have been responsible for participant recruitment and data collection for the Cognitive Performance in Adolescents with Type 2 Diabetes (CPAT2D) study, the source of data used in this thesis project. Along with my colleagues Caroline Dutil and Amelia Eaton, I marked data generated thus far by the CPAT2D study. I also prepared the data for, and performed myself, the statistical analyses reported in this thesis project. Aside from my responsibilities to the CPAT2D study, I have been involved in data collection for the larger Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) study at CHEO, the doctoral dissertation project of Caroline Dutil, which has provided comparator data for this thesis. In order to adequately perform data collection for the CPAT2D and SMART2D studies, I have had to familiarize myself with many new laboratory techniques, including electroencephalography cap application and blood sample centrifugation. The CPAT2D and SMART2D studies generally involve one and three full (7-to-8-hour) days of data collection, respectively, per participant; thus, throughout the duration of my graduate degree, I have had the opportunity to prepare and take part in approximately ninety of these sessions and run or assist with many intake visits. In turn, I have learned a great deal about conducting research with human participants. It is my intention to publish an article with colleagues based on this research once the recruitment target for the CPAT2D study is reached. The CPAT2D study is funded by the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada.

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ABSTRACT

Adolescent type 2 diabetes (T2D) diagnoses are on the rise. Consistent with the adult literature, preliminary evidence in adolescents suggests that T2D is associated with reduced brain volume and white matter microstructural integrity. As part of the Cognitive Performance in Adolescents with T2D (CPAT2D) study, this project aimed to test whether T2D diagnosis is associated with poorer cognitive performance in adolescents.

Five adolescents with obesity and T2D (60% female; body mass index [BMI] percentile 98.2 ± 2.0 ; age 16.7 ± 1.1 years) were recruited and matched to two control adolescents with obesity but without T2D (50% female; BMI percentile 99.9 ± 0.2 ; age 15.9 ± 1.3 years) on at least three of the following characteristics: age, sex, pubertal stage and habitual sleep duration. All participants wore a wrist actigraphy device for seven consecutive nights to measure sleep at home and then completed two neuromotor cognitive tasks at a laboratory testing session assessing motor preparation (simple reaction time task) and executive functioning (affective shifting task [AST]). Control data were available through the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) study. Premotor reaction time outcomes in either task and proportions of commission and omission error trials in the AST were subsequently analyzed.

Based on this preliminary participant sample, there is no evidence to suggest that adolescents with compared to without T2D perform differently on the neuromotor cognitive tasks. The results should be confirmed once the intended sample size is reached. In the meantime, clinicians should monitor for changes in cognitive function in adolescents with T2D, perhaps by asking about academic achievement. The majority of our sample exhibited sub-optimal movement behaviours; to preserve overall health, adolescents with obesity and/or T2D should strive to meet sleep, physical activity and screen time recommendations for their age group.

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
AST	Affective shifting task
CHAL	Centre for Healthy Active Living
CHEO	Children's Hospital of Eastern Ontario
CI	Confidence interval
CNS	Central nervous system
CPAT2D	Cognitive Performance in Adolescents with Type 2 Diabetes
Ctrl	Control tone task condition (simple reaction time task)
DTI	Diffusion tensor imaging
EC	Eyes closed task condition (simple reaction time task)
EO	Eyes open task condition (simple reaction time task)
EPIC	Electronic medical records software
ESS	Epworth Sleepiness Scale
F	Food block task condition (affective shifting task)
fMRI	Functional magnetic resonance imaging
HALO	Healthy Active Living and Obesity
IQR	Interquartile range
MRI	Magnetic resonance imaging
O	Object block task condition (affective shifting task)
PANAS	Positive and Negative Affect Scale
Peds-QL	23-Item Pediatric Quality of Life Inventory for 13-18 Year Olds
PHQ-A	Patient Health Questionnaire 9 Modified for Adolescents

RT	Reaction time
SAS	Startling acoustic stimulus
SES	Socioeconomic status
SMART2D	Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TFEQ	Revised 18-Item Three-Factor Eating Questionnaire
WHO	World Health Organization

Chapter 1: Introduction

Type 2 diabetes (T2D) used to be referred to as *adult-onset* diabetes, given its typical presentation in individuals above 35 years of age; however, it is now clear that T2D onset can occur as early as in childhood and adolescence. In fact, several reports from different countries, including Canada (Shazhan Amed, Islam, Sutherland, & Reimer, 2018), the United States (Divers et al., 2020), and the United Kingdom and Ireland (Candler et al., 2018), have highlighted significant upward trends in both the prevalence and incidence of pediatric T2D diagnoses over the past three decades (Magliano et al., 2020).

The leading risk factor for pediatric T2D before adulthood is obesity (Viner, White, & Christie, 2017); consequently, the present obesity crisis is thought to contribute at least in part to rising rates of T2D in this age group. Children and adolescents with T2D also often come from low socioeconomic status households (Copeland et al., 2011), belong to non-Caucasian minority (e.g., Indigenous, Black, Hispanic) populations (S. Amed et al., 2010; Copeland et al., 2011), and have a family history of the disease (Viner et al., 2017). Moreover, pediatric T2D cases typically occur beyond the age of 10 years, and in middle-to-late stages of pubertal development (Reineher, 2005).

Youth-onset compared to adult-onset T2D may impact health in a differential manner, though the reasons for this remain unclear. In middle-aged and older adults, after controlling for current age, earlier age at T2D diagnosis has been associated with greater all-cause and cardiovascular mortality risk (Huo et al., 2018). Furthermore, end-stage renal disease and mortality in middle age have been found to be significantly more common among Pima Indian people with onset of T2D before age 20 compared to between 20 and 54 years of age, but not after adjusting for disease duration (Pavkov et al., 2006). Onset of T2D in childhood, then, poses the threat of

longer burden of illness, and therein may be more detrimental to long-term health than later-onset T2D.

Still, others have posited that there are inherent differences in the pathophysiology of T2D in childhood as opposed to adulthood (Magliano et al., 2020). For instance, in both youth and adults, T2D is characterized by insulin resistance and some level of failure of insulin-releasing pancreatic beta cells; however, a randomized clinical trial of pharmacological interventions to preserve beta cell function in adults and youth with T2D found that beta cell function deteriorated at a faster annual rate in youth compared to adults (Edelstein, 2019). Findings such as this have propagated the idea that the pathogenesis of youth-onset T2D is more severe than that of adult-onset T2D.

Less explored is the possibility that the specific *timing* of disease onset could have an impact on the severity of youth-onset T2D. In adolescents with T2D, the body is burdened with disease-related physiological stresses as it progresses through growth and maturation; therefore, perhaps individuals with T2D onset even in their early twenties could benefit long term from better health during their earlier developmental years. Moreover, children with T2D have less control over their living situation and diet than adults, potentially influencing the extent of their influence over their own health. Finally, children living with T2D today as opposed to several decades ago could be facing added barriers to optimal health, like high amounts of screen time and sedentary behaviour as well as insufficient physical activity and sleep duration, which have become pervasive among today's youth (ParticipACTION, 2020; Tremblay et al., 2016).

Thus, for many reasons, T2D onset before adulthood within the current societal context is a serious issue, and it occurs most often in adolescence. Despite their age, adolescents with T2D do develop diabetes-related complications, such as kidney disease and peripheral and central nerve

damage (Ryder et al., 2020; TODAY Study Group, 2021); these well-known complications are prevalent in adults with T2D and are screened for and monitored regularly by pediatricians. However, knowledge about cognitive health in adolescents with T2D is scarce, despite many negative cognitive- and brain-related outcomes being associated with T2D in adulthood.

Specifically, adult-onset T2D is significantly associated with varying degrees of cognitive dysfunction, including early onset of dementia and Alzheimer's disease (Strachan, Reynolds, Marioni, & Price, 2011). Interestingly, dementia risk was recently found to be significantly increased in adults with earlier age at T2D diagnosis (Barbiellini Amidei et al., 2021). The exact mechanism underlying this association is not known; however, magnetic resonance imaging (MRI) studies in adults have found significant associations between T2D and structural brain differences that could influence cognition, including total or regional brain atrophy (Roy et al., 2020) and reduced microstructural integrity of white matter (Wang et al., 2020) affecting several cortical and subcortical brain regions.

Adults with T2D have also been shown to perform more poorly than adults without T2D on neuropsychological tests (Monette, Baird, & Jackson, 2014). Examples of cognitive task performance outcomes that have been associated with T2D in adults include a greater number of errors made on a Go/No-Go task (Ishizawa, Kumano, Sato, Sakura, & Iwamoto, 2010), slower performance on the Trail Making Test measuring executive function (Smith et al., 2014), and longer reaction time in both a working memory task (Gorniak, Ray, Lee, & Wang, 2020) and a simple reaction time task involving a visual stimulus (Sanchez-Marin & Padilla-Medina, 2010).

The few studies that have examined cognitive- and brain-related outcomes in adolescents with T2D have been instrumental in building this thesis project. Four cross-sectional MRI studies have reported reduced white matter microstructural integrity or cerebral or focal atrophy in

multiple brain areas in adolescents with compared to without T2D, independent of obesity (Bruehl, Sweat, Tirsi, Shah, & Convit, 2011; Rofey et al., 2015; Yau et al., 2010). In one of these studies that also administered a neuropsychological assessment, adolescents with T2D scored significantly lower on tests of general intellectual ability, verbal memory, psychomotor efficiency and executive function than their counterparts without T2D (Yau et al., 2010). Initial findings from these studies appear to be generally consistent with the adult literature, but more observational research is needed to confirm if T2D is reliably associated with worse cognitive performance in adolescents.

Healthy cognitive functioning is crucial for optimal well-being and quality of life in adolescents. Not surprisingly, cognitive ability in general is associated with academic achievement (Peng & Kievit, 2020), an important consideration for a school-age population. In fact, better reaction time performance on a cognitive task has been correlated with higher standard intelligence test scores in adolescents (Jensen & Munro, 1979). Furthermore, complex activities in which adolescents participate, such as sport and other extracurricular activities as well as learning to operate a motor vehicle, require extensive central cognitive and motor input.

Therefore, following preliminary reports of structural brain differences on MRI between adolescents with and without T2D, the purpose of this research was to investigate the association between diagnosis of T2D and cognitive performance in adolescents. The present thesis is part of a larger study entitled Cognitive Performance in Adolescents with T2D (CPAT2D). Findings are presented using pilot data from the CPAT2D study.

Chapter 2: Review of the Literature

2.1 Type 2 Diabetes

When levels of circulating blood glucose in the body are high, the hormone insulin acts on several tissues to promote glucose uptake and storage as glycogen, thereby maintaining blood glucose level within a normal range. Type 2 diabetes mellitus (T2D) is the condition that arises when the body is no longer able to maintain glucose homeostasis due to a pathological insensitivity to insulin (Galicia-Garcia et al., 2020). Insulin-releasing beta cells of the pancreas can function to compensate for insulin resistance by secreting greater amounts of the hormone; however, beta cell function may also eventually decline to such an extent that insufficient insulin is released to overcome insulin resistance. Therefore, in T2D, insulin resistance possibly accompanied by insufficient compensatory beta cell function contributes to a persistent state of hyperglycemia. With extended disease duration or poor glycemic control, chronic hyperglycemia can cause damage to blood vasculature in tissues throughout the body, driving the development of serious macrovascular (coronary and peripheral arterial disease and stroke) and microvascular (diabetic nephropathy, central and peripheral neuropathy, and retinopathy) complications that are typical of diabetes (Zheng, Ley, & Hu, 2018). Consequently, T2D is associated with increased risk of morbidity and mortality and can greatly affect quality of life. As the most common form of diabetes in adults, T2D poses a significant public health challenge.

2.2 Youth-Onset Type 2 Diabetes

2.2.1 Rising Prevalence and Incidence

T2D has historically been referred to as ‘adult-onset’ diabetes for its typical lack of onset before middle age. However, this condition is diagnosed in children and adolescents as well, and

there is evidence from several countries to suggest that the prevalence and incidence of pediatric cases of T2D are increasing. For example, the US SEARCH for Diabetes in Youth study, a multicentre, population-based registry study, recently reported a significant increase in incidence of T2D in children between 10-19 years of age from 2002 to 2015 (9.0 to 13.8 cases per 100 000), amounting to an annual percent increase in incidence of 4.8%, after accounting for age, sex, and race or ethnicity (Divers et al., 2020). In 2014, results from the same study demonstrated a 30.5% (95% confidence interval [CI], 17.3% - 45.1%) overall increase in prevalence of T2D in youth under 20 years of age between 2001 and 2009 (Dabelea et al., 2014). Prospective surveillance studies carried out in the United Kingdom and Republic of Ireland found that the incidence rate of T2D in youth under 17 years of age was approximately 35% higher in 2015 than in 2005 (Candler et al., 2018).

Similar trends have been reported in multiple provinces within Canada. Recently, T2D prevalence and incidence within a representative sample of British Columbia youth less than 20 years old were estimated to have significantly increased from 0.009% to 0.021% and from 3.45 to 5.16 cases per 100 000, respectively, between 2002-2003 and 2012-2013 (Shazhan Amed et al., 2018). An Annual Statistical Report published by the Nova Scotia Department of Health noted that while T2D was hardly reported in children under 19 years of age in the early 1990s, by 2007-2008, it composed approximately 10% of new diabetes cases (average of rates from the previous five years) in this age group (Nova Scotia Department of Health, 2008). Furthermore, in 2020, the Manitoba Centre for Health Policy reported increases in prevalence and incidence of T2D among children between 7 and 17 years of age living in Manitoba from 2009-2010 to 2017-2018 (Ruth et al., 2020). Importantly, the studies cited in this section have estimated prevalence or incidence of diagnosed youth-onset T2D, but the frequency of undiagnosed T2D among youth could affect

these estimates (Spurr et al., 2020). Also, Canadian data on pediatric T2D rates are limited as not all provinces have surveillance programs for tracking diabetes prevalence in children that differentiate T2D from type 1 diabetes (Shulman et al., 2019).

2.2.2 Risk Factors

Several important risk factors for youth-onset T2D have been identified. The leading risk factor for youth-onset T2D is obesity. The prevalence of obesity in youth with T2D is very high, often reported at over 80% or 90% (S. Amed et al., 2010; Candler et al., 2018). It is thought that the obesity crisis may be a contributing factor to observations of increased pediatric T2D diagnoses (Buttermore, Campanella, & Priefer, 2021). In 2012 and 2013, approximately 30% of Canadian children and adolescents were estimated to have overweight or obesity based on objectively-measured body mass index values (Rao, Kropac, Do, Roberts, & Jayaraman, 2016). As pediatric obesity rates in Canada over the past decade have generally remained constant (Rao et al., 2016), it is reasonable to expect a continuation of new cases of T2D in youth.

Most youth with T2D have a family history of T2D and come from low socioeconomic status households (Viner et al., 2017). Youth-onset T2D is also known to disproportionately affect non-Caucasian minority populations, including those of Indigenous (e.g., Canadian Aboriginal, American Indian, etc.), Black, Hispanic, or Asian and Pacific Islander descent (Viner et al., 2017). In Canada, there is concern about the rates of youth-onset T2D among First Nations children. A Canadian surveillance study from 2010 reported a minimum T2D incidence rate of 12.5 cases per 100,000 youth under 18 years of age per year in the province of Manitoba, noticeably higher than the national estimate of 1.54 cases per 100,000 (Shazhan Amed et al., 2010); indeed, most of the study's participants of Indigenous descent were Manitoba residents. Furthermore, the Manitoba

Centre for Health Policy recently reported that, in 2017-2018, 82.4% of Manitoba children with diagnosed T2D were registered First Nations people (Ruth et al., 2020). Recent evidence from Ontario suggests that the incidence of T2D (assumed) among First Nations children increased from 37 to 94 cases per 100 000 per year from 1995-1996 to 2014-2015 (Shulman et al., 2019).

Pediatric T2D is typically diagnosed after the age of ten years, and in middle-to-late stages of puberty (T. Reinehr, 2005). As a result, many investigations into the health impacts of youth-onset T2D have been performed in the adolescent population, which is also the population under study in this thesis project.

2.2.3 Health Impacts Compared with Those of Other Diabetes Forms

Youth-onset T2D may have a greater negative impact on long-term health than adult-onset T2D. In a large sample of middle-aged and older adult Australians with T2D ($n = 743\,709$), after controlling for current age, people with younger compared to older age at disease onset (i.e., longer disease duration) had increased all-cause and cardiovascular mortality risk (Huo et al., 2018). Similarly, end-stage renal disease and mortality by middle age (20-54 years) were significantly more common in a sample of Pima Indian people from Arizona, Texas ($n = 1856$) with onset of T2D before the age of 20 years compared to between 20 and 54 years of age; however, after controlling for disease duration, the opposite association was found (Pavkov et al., 2006), indicating that longer disease duration largely accounted for the association between age at onset and adverse outcomes in this sample. T2D onset in adolescence, then, could result in much longer disease duration by middle age and thereby increase the risk of negative long-term health outcomes relative to T2D onset in adulthood; however, more studies are needed to test this hypothesis.

Inherent differences in pathophysiology between youth-onset and adult-onset T2D may exist as well. Youth-onset T2D, similar to adult-onset T2D, is characterized by insulin resistance and some degree of beta cell failure, which impairs compensatory insulin release (D'Adamo & Caprio, 2011). However, youth-onset T2D may have different metabolic properties than adult-onset T2D that result in increased disease severity. For example, the annual rate of beta cell functional decline may be greater in adolescents compared to adults with T2D (Arslanian et al., 2013; Edelstein et al., 2018). This possibility was explored during the Restoring Insulin Secretion (RISE) Trial, which investigated the effect of two pharmacological interventions targeting beta cell function in youth (aged 10-19 years) and adults (aged 20-69 years) with impaired glucose tolerance or recently diagnosed T2D (Edelstein et al., 2018). In the trial, a hyperglycemic clamp was performed at baseline, 12 months after randomization to pharmacological treatment (12 months of metformin or 3 months of insulin glargine plus 9 months of metformin), and 3 months after the end of treatment to obtain insulin sensitivity and beta cell response measures over time; simultaneous changes in beta cell responses and insulin sensitivity between time points were subsequently assessed.

At baseline, youth exhibited significantly lower insulin sensitivity and higher beta cell responsiveness than adults in both treatment arms (Edelstein, 2019). In youth, regardless of treatment group, beta cell responses decreased from baseline to 12 months and from 12 months to 15 months, indicating a deterioration in beta cell function. Meanwhile, in adults after 12 months, beta cell response measures relative to baseline had either remained constant or significantly improved and insulin sensitivity was increased in the metformin group; three months after treatment was stopped, beta cell response measures combined with insulin sensitivity in adults did not differ from those recorded at baseline (Edelstein, 2019). The findings suggest that T2D in

youth compared to adults is marked by faster progression of beta cell functional decline, and that optimal pharmacological treatment for beta cell decline differs for youth and adults. Therefore, perhaps there are intrinsic differences in the properties of T2D in childhood compared to adulthood that could render the childhood disease more severe.

The timing of T2D onset may also have an impact on long-term health outcomes. A recent systematic review and meta-analysis of 26 studies assessing the impact of earlier age at diagnosis on macrovascular and microvascular diabetes complications found that, after adjusting for current age, a 1-year increase in age at T2D diagnosis was associated with 4%, 3% and 5% decreased risk of all-cause mortality, macrovascular complications and microvascular complications, respectively (Nanayakkara et al., 2021). The study also included a sensitivity analysis examining the effect of age at T2D diagnosis on outcomes after adjusting for T2D duration, which revealed that a 1-year increase in age at T2D diagnosis was significantly associated with 6%, 6% and 5% increased risk of all-cause mortality, macrovascular complication and microvascular complication, respectively (Nanayakkara et al., 2021).

While studies on the effect of age at T2D onset on health outcomes do exist, they have primarily been performed in middle-aged and older adult populations, and therefore do not consider the full range of ages at which T2D diagnosis can occur. The possibility that the specific *timing* of disease onset prior to adulthood could be associated with more severe health consequences remains unexplored. Certain combinations of risk factors preceding youth-onset T2D, such as rapid weight gain during development and entry into puberty, are unique to this age group and might interact differently with chronic disease than typical risk factors preceding adult-onset T2D. An adolescent with T2D is exposed to physiological stresses associated with a metabolic disease on top of typical growth and maturation processes, while a person diagnosed

with T2D later in adulthood may experience long-term health benefits due to increased health during their developmental years. As well, adolescents do not possess the same level of independence (i.e., financial, legal) as adults when diagnosed with T2D; consequently, they may have less control over their diet or other important targets for intervention in T2D treatment. On a broader scale, adolescents diagnosed with T2D and obesity today as opposed to several decades ago could face added barriers to optimal diabetes management, given contemporary behaviour patterns among youth that are harmful to overall health, such as increased use of screens, increased sedentary behaviour, decreased physical activity, and sub-optimal sleeping habits (ParticipACTION, 2020; Tremblay et al., 2016). Therefore, timing of disease diagnosis could function through age-related biological or environmental factors to exacerbate the negative impact of youth-onset T2D on health.

Among children and adolescents, the most prevalent form of diabetes is immune-mediated type 1 diabetes (T1D), which is caused by an autoimmune reaction to insulin-producing pancreatic beta cells. In response to recorded rises in pediatric diabetes cases attributed to T2D, some studies have compared the effects of T1D and T2D in young people. In a study of Canadian youth between 1 and 18 years of age from Manitoba ($n = 1018$), multivariate analysis revealed that children with T2D compared to T1D were found to have a 47% higher risk ($p = .04$) of any diabetes-related complication, independent of socioeconomic status, sex, and body mass index (Dart et al., 2014). Kaplan-Meier analyses were also conducted to examine event-free survival by group for select microvascular complications; these revealed significant differences ($p < .001$) in renal and neurologic complication rates between groups beginning approximately five years post diagnosis. Additionally, although major complications (i.e., dialysis, blindness, amputation) were rare in the

group with T1D at all time points during follow-up, they occurred in 26.0% of participants with T2D analyzed at 15 years ($n = 25$) and in 47.9% analyzed at 20 years ($n = 6$) after disease diagnosis.

A comparative clinic-based Australian study reported that, in adolescents under 18 years old with T2D ($n = 68$) compared to T1D ($n = 1433$), rates of peripheral and autonomic neuropathy were similar and rates of hypertension and microalbuminuria were higher, even though the adolescents with T2D had statistically significantly shorter mean disease duration, at 1.3 (0.6 – 3.1) years compared to 6.8 (4.7 – 9.6) years, statistically significantly lower glycosylated hemoglobin levels, and statistically similar social disadvantage risk score relative to adolescents without T2D ($p = .06$) (Eppens et al., 2006). However, the group of adolescents with T2D did, on average, score worse on the instrument assessing social disadvantage risk; given that low socioeconomic status is a risk factor for T2D, but not T1D, consideration of the impact of socioeconomic status on results should always be made when interpreting comparative studies of the effects of T2D and T1D on rates of diabetes-related complications or other health outcomes. Nonetheless, the results of studies such as these have prompted the idea that disease progression in T2D relative to T1D may be more aggressive in youth.

Overall, for many reasons, T2D onset before childhood is a serious condition that threatens long-term health. Adolescents with T2D, who make up most of the population of children diagnosed with T2D, do present at diagnosis with or prematurely develop chronic diabetes-related complications. These include but are not limited to hypertension and other vascular characteristics that could increase cardiovascular disease risk (e.g., increased vessel thickness or accelerated vascular aging), nephropathy, retinopathy, and central or peripheral neuropathy (O. Pinhas-Hamiel & Zeitler, 2007; Ryder et al., 2020). Recently, an observational follow-up study of adolescent participants from the TODAY Study described the incidence of different diabetes-related

complications in the sample when the adolescents had reached early adulthood ($n = 500$; age [mean $\pm$ SD] 26.4 ± 2.8 years; mean duration of disease 13.3 ± 1.8 years) (TODAY Study Group, 2021). Incidence rates were 54.8% for diabetic nephropathy (moderate-to-severe albuminuria), 32.4% for peripheral neuropathy, and 13.7% for retinopathy (TODAY Study Group, 2021). By the end of follow-up, 60.1% of participants had experienced at least one complication (TODAY Study Group, 2021).

Evidently, well-known complications of T2D in adults, such as kidney, peripheral nerve, and retinal disease, are also present in children and adolescents, and increase in prevalence by early adulthood. As a result, pediatricians are recommended to regularly screen for and monitor these complications in adolescents with T2D, according to Diabetes Canada Clinical Practice Guidelines (Panagiotopoulos, Hadjiyannakis, & Henderson, 2018). However, there is little knowledge in the literature, and therefore virtually no clinical guidance, regarding cognitive function in adolescents with T2D, despite evidence in middle-aged and older adults of a significant relationship between T2D and cognitive health.

2.3 Type 2 Diabetes and Cognitive and Brain Health

Neuropathy is a common microvascular complication of diabetes, including T2D, that affects the tissues of the nervous system. Diabetic peripheral sensorimotor neuropathy is the most prevalent of the diabetes-related neuropathies, and can contribute to both sensory problems, such as paresthesia or pain (Tesfaye & Selvarajah, 2012), and motor problems, such as postural instability (Horak, Dickstein, & Peterka, 2002; Toosizadeh, Mohler, Armstrong, Talal, & Najafi, 2015). However, diabetic neuropathy may also impact the central nervous system (CNS). Observations of motor impairments in individuals with diabetes who do *not* have peripheral

neuropathy, including poor balance in T2D patients (Centomo, Termoz, Savoie, Béliveau, & Prince, 2007), have prompted hypotheses regarding a putative role of diabetes-related CNS changes in contributing to sensorimotor impairments in patients with T2D (Ferris, Timothy Inglis, Madden, & Boyd, 2020). Below, we describe in more detail cognitive- and brain-related health outcomes that have been associated with T2D in adulthood.

2.3.1 Cognitive Dysfunction

In middle-aged and older adults, T2D is associated with varying degrees of cognitive dysfunction, including diabetes-associated cognitive decrement, mild cognitive impairment and accelerated onset of dementia and Alzheimer's disease (Biessels, Deary, & Ryan, 2008; Biessels & Despa, 2018; Cheng, Huang, Deng, & Wang, 2012). The magnitude of increased risk of dementia in adults with T2D has been estimated at 1.5-2.5 times that in adults without T2D (Strachan et al., 2011). In a nationwide population-based study from Taiwan ($n = 142\,744$; maximum of 11 years of follow-up), T2D in middle age was found to increase Alzheimer's disease risk by 57% (95% CI: 34% - 85%; $p < .001$) after controlling for age, sex, comorbidities, geographic area, urbanization status, and pharmacological diabetes treatment (Huang et al., 2014). The risk of negative cognitive outcomes in individuals with T2D may be positively associated with disease duration, as shown in a study assessing accelerated cognitive decline in an adult sample ($n = 5653$; median age 54.4 years) (Tuligenga et al., 2014). Moreover, a longitudinal cohort study of adults aged 35-55 years (median follow-up of 31.7 years) recently found that, in addition to dementia rates being higher in participants with compared to without T2D, younger age at T2D onset was significantly associated with a higher risk of dementia (Barbiellini Amidei et al., 2021).

Since mild-to-moderate cognitive function deficits have also been associated with T1D in adults and adolescents (Kirchhoff, Jundt, Doty, & Hershey, 2017), some studies have directly compared people with T2D versus T1D on cognitive function outcomes. In adults, there are very few studies of this type, the results of which are mixed; for example, one study reported that adults with T2D performed better than adults with T1D on tests of total cognition, language, executive function, psychomotor processing speed, and verbal episodic memory, but worse on visual episodic memory (Lacy et al., 2022), while another study reported no statistically significant differences in cognitive function between groups (Brands et al., 2007). In young adults and adolescents, one study compared age-corrected composite Fluid Cognition score in those with T2D compared to T1D, finding that an initially statistically significant association between T2D and worse score was attenuated after adjusting for differences in crystallized cognition, central adiposity and mental health (Shapiro et al., 2021).

2.3.2 Brain Structure

The mechanism underlying the significant association between T2D and cognitive dysfunction in older adulthood is not known (Strachan et al., 2011); however, imaging studies have provided information about anatomical brain changes associated with T2D in adulthood (Biessels & Reijmer, 2014) that could possibly contribute to deficits in cognitive function. A frequent finding on magnetic resonance imaging (MRI) is more pronounced total (De Bresser et al., 2010; Espeland et al., 2013) or localized brain atrophy in adults with T2D compared to adults without T2D. Localized brain atrophy has been reported in the amygdala and hippocampus (den Heijer et al., 2003; Moran et al., 2013), subcortical memory and emotional regulation centres of the brain; gray matter (Espeland et al., 2013; Moran et al., 2013), neuron-dense brain matter that typically

composes functional brain areas; and white matter (Moran et al., 2013), which has a crucial role in promoting crosstalk between different functional brain areas.

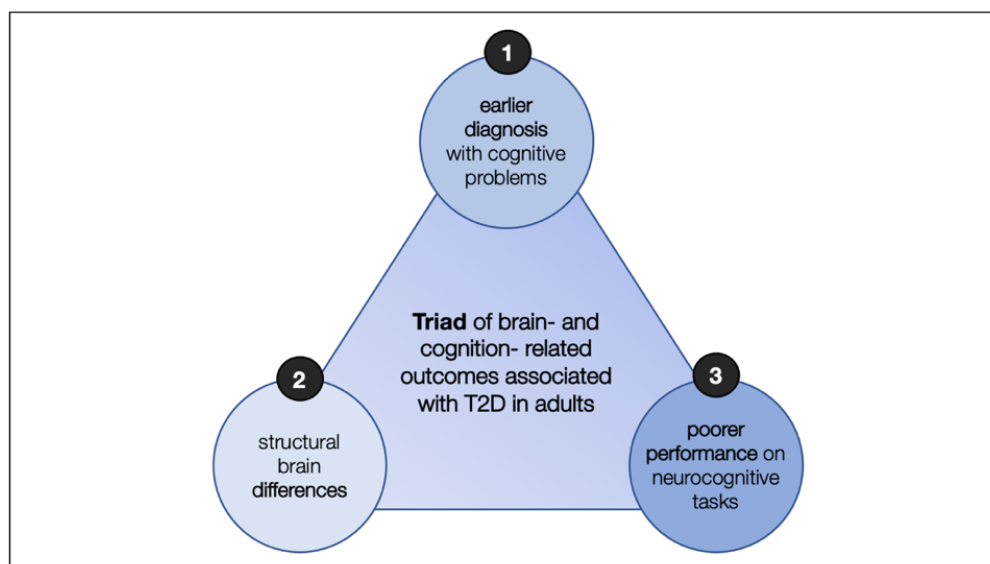
Some studies have attempted to identify brain imaging correlates of cognitive deficits in individuals with compared to without T2D. For instance, one study reported lower scores on tests of memory as well as reduced hippocampal volume on MRI in subjects between 45 and 70 years of age with T2D compared to control subjects matched on age, sex, and education (Gold et al., 2007). Another study compared brain volumes between T2D patients 70 years of age and older with ($n = 25$) and without ($n = 23$) mild cognitive impairment or early dementia; the study found that grey matter volume was significantly reduced in the group with cognitive impairment ($p = .042$), especially in the right temporal lobe and subcortical brain regions (Groeneveld et al., 2018). Further research is needed to confirm how cognitive deficits and brain structural findings are related in people with T2D. Moreover, it should be considered that T2D patient samples in these cross-sectional brain imaging studies vary in their mean hemoglobin A1c and blood glucose levels, which are indicators of glycemic control; therefore, results from these studies could have been partly affected by how well T2D in the case groups was managed. However, overall, middle-aged and older adults with T2D appear to be at heightened risk of accelerated cognitive decline, which may at least in part be explained by findings of T2D-associated brain changes.

2.3.3 Performance on Neurocognitive Tasks

Quite a few studies of performance of middle-aged and older adults with T2D on several different types of neurocognitive tasks have been performed; this research area is important to understanding what, if any, barriers to optimal cognitive functioning adults with T2D may face that in turn could increase their risk of injury or the ease with which they complete activities of

daily living. Overall, adults with compared to without T2D have been shown to perform more poorly on several different types of neurocognitive tasks. Cognitive task performance outcomes that have been associated with T2D in adults include a greater number of errors made on a Go/No-Go task (Ishizawa et al., 2010), slower performance on the Trail Making Test measuring executive function (Smith et al., 2014), longer reaction time in a working memory task (Gorniak et al., 2020), and longer reaction time in a simple reaction time task with a visual stimulus (Sanchez-Marin & Padilla-Medina, 2010). A literature search of studies of cognitive abilities using neuropsychological tests in people with T2D was conducted in 2014, which concluded that T2D is associated with mild-to-moderate deficits in all measured cognitive abilities, with the largest effect sizes being attributed to processing speed with motor task demands and divided attention or shifting (Monette et al., 2014). Therefore, in adults, it can be said that T2D is associated with a triad of adverse cognitive- or brain-related outcomes: accelerated diagnosis with cognitive problems; brain structural differences that could negatively impact cognition, and; poorer performance on neurocognitive tasks (**Figure 1**).

Figure 1. *Triad of brain- and cognition-related outcomes associated with T2D in adults.*



2.3.4 Evidence in Adolescents

Little is known about potential detrimental effects of T2D on the brain and cognition in youth. Early work has identified associations between T2D and several unfavourable structural brain changes in adolescents. Four studies have reported adolescents with T2D and obesity, compared with non-insulin-resistant control adolescents with obesity alone (Bruehl et al., 2011; Yau et al., 2010) or with a second non-insulin-resistant adolescent control group with healthy weight (Nouwen et al., 2017; Rofey et al., 2015), to have reduced white matter microstructural integrity or evidence of cerebral atrophy or focal atrophy involving many different areas of the brain. Affected brain regions include *cortical* structures such as the prefrontal lobe (Bruehl et al., 2011) and *subcortical* structures, such as the thalamus (Rofey et al., 2015), hippocampus (Bruehl et al., 2011), amygdala and basal ganglia (Nouwen et al., 2017; Rofey et al., 2015).

Cortical and subcortical brain regions subserve important cognitive functions. Executive functions (e.g., working memory, attention, response inhibition, decision-making, cognitive flexibility) rely heavily on the prefrontal cortex, with contributions from other cortical and subcortical brain areas (Robbins, Weinberger, Taylor, & Morris, 1996). Voluntary motor control mainly involves the primary and secondary motor cortices, with subcortical structures (e.g., putamen, thalamus) controlling certain aspects of movement (Bosch-Bouju, Hyland, & Parr-Brownlie, 2013). Thus, in adolescence, a period already marked by incomplete prefrontal lobe maturation (Arain et al., 2013), T2D could be associated with brain structural changes affecting cognitive functions that are important for self-management of T2D and overall well-being.

To date, only two cross-sectional studies have compared cognitive performance in adolescents with and without T2D. In 2010, Yau *et al.* reported that, relative to non-insulin-

resistant adolescents with obesity ($n = 18$), adolescents with T2D and obesity ($n = 18$) scored statistically significantly lower on tests of general intellectual ability ($p < .001$) (Wechsler Abbreviated Scale of Intelligence – Vocabulary and Matrix Reasoning Subscales), verbal memory ($p = .04$) (Wide Range Assessment of Memory and Learning) and psychomotor efficiency ($p = .05$) (Digit Symbol Substitution Task) (Yau et al., 2010). Adolescents with T2D also committed more perseverative errors than control adolescents ($p = .06$) on the Wisconsin Card Sorting Test, which measures executive function. The groups did not significantly differ with respect to age, education, socioeconomic status, or self-reported obstructive sleep apnea rating, and adolescents with sexual development Tanner stage less than 4 were excluded from the study.

In 2017, Brady *et al.* compared cognitive performance, behaviour, and executive function between adolescents with T2D and obesity ($n = 20$) and lean adolescents ($n = 20$). The study groups did not significantly differ on sex or socioeconomic status; however, the study groups significantly differed in age, race and, not surprisingly, on body mass index z-score. Ideally, in a study with adolescents, there should not be a significant difference in age between groups. However, the study found that the adolescents with T2D, who were older, on average, than the adolescents without T2D, scored significantly lower on cognitive tests of working and verbal memory ($p = .02$) (Wide Range Assessment of Memory and Learning), processing speed ($p = .02$) (Wechsler Intelligence Scale for Children/Wechsler Adult Intelligence Scale), and semantic and phonemic fluency ($p = .02$ and $p = .002$, respectively) (Controlled Oral-Word Association Task). Adolescents with T2D also performed worse on an assessment of internalizing and externalizing behaviours ($p < .001$ and $p = .01$, respectively) (Child Behaviour Checklist, $n = 18$ per group) (Brady et al., 2017). The study also found that longer diabetes duration was statistically significantly correlated with worse working memory and processing speed scores.

However, the internal validity of comparisons made by Yau *et al.* and Brady *et al.* may have potentially been compromised by uncontrolled confounding. For instance, comparisons made by Brady *et al.* between lean adolescents and adolescents with obesity and T2D may be confounded by obesity. As previously described, obesity is the most prominent risk factor for T2D in youth. Additionally, obesity has been associated with deficits in multiple areas of neurocognitive functioning, including executive function and motor and visuo-spatial skills (Liang, Matheson, Kaye, & Boutelle, 2014). Thus, studies of cognitive performance in adolescents with T2D should account for weight status.

Neither of the existing studies on cognitive performance in adolescents with T2D measured and controlled for sleep duration, where decreased sleep duration negatively impacts cognitive function and brain structures in adult and pediatric populations (de Bruin, van Run, Staaks, & Meijer, 2017; Dutil et al., 2018; Lo, Loh, Zheng, Sim, & Chee, 2014; Lo, Ong, Leong, Gooley, & Chee, 2016; Lowe, Safati, & Hall, 2017) and has been associated with at least one T2D biomarker in children and adolescents (Dutil & Chaput, 2017). Therefore, reported associations between T2D and cognitive performance deficits in adolescents could be confounded by sleep duration.

Finally, while Yau *et al.* excluded participants with sexual maturation stage less than 4 based on the Tanner stages of pubertal development (Marshall & Tanner, 1969, 1970), Brady *et al.* neither matched the adolescent participants in their studies nor restricted participation based on pubertal status. This is problematic as puberty could confound the relationship between T2D and cognitive performance. Progression through puberty is tied to cognitive development (Juraska & Willing, 2017). Furthermore, puberty is a risk factor for T2D (Orit Pinhas-Hamiel, Lerner-Geva, Copperman, & Jacobson, 2007; Thomas Reinehr, 2013) and has been shown to be associated with

decreased insulin sensitivity, independent of body fat percentage (Hannon, Janosky, & Arslanian, 2006). Therefore, future studies should consider controlling for this potential confounder.

With only two existing studies of cognitive performance in adolescents with T2D, additional studies on this topic are necessary. Observational studies are an appropriate choice to study cognitive performance as it relates to T2D in adolescents, as the condition in this age group is overall relatively rare. However, future studies of this relationship should aim to account for important potential confounding variables, such as obesity, sleep duration and pubertal stage.

2.4 Importance of Healthy Cognitive Functioning in Adolescents with T2D

Healthy cognitive functioning is imperative for all adolescents to achieve optimal well-being and quality of life. Not surprisingly, cognitive ability in general is associated with academic achievement (Peng & Kievit, 2020). In fact, better reaction time performance on a cognitive task has been correlated with higher standard intelligence test scores in adolescents (Jensen & Munro, 1979). Since adolescents are attending school, this is an important consideration. Furthermore, adolescents participate in a range of simple to complex activities of daily living, many of which require extensive central cognitive and motor input. These include playing sports, engaging in other extracurricular activities important to their personal and professional development, and learning how to drive. For adolescents with T2D, healthy cognitive function can also facilitate self-management of T2D on top of a busy life schedule. With a rise in T2D cases among young people, it is imperative to understand whether adolescents with T2D exhibit any early observable cognitive deficit, especially given their exposure to the disease during an important period of brain development. Below, we describe how existing studies of cognitive performance in adolescents

with T2D can be built upon using the objective measurement of cognitive functioning in domains such as executive functioning and motor preparation using custom neuropsychological tasks.

2.4.1 Measurement of Cognitive Performance

Experimental paradigms based in cognitive neuroscience provide a means to administer specific, objective neuropsychological assessments (Kessels, 2019). Neuropsychological tasks that employ an experimental paradigm vary in design but fundamentally adhere to a methodological framework specific to the paradigm, and often include cognitive and motor task components. For example, in a typical neuromotor task based on a go/no-go paradigm, participants initiate and execute a motor movement in response to a visual imperative ('go') stimulus, but must *inhibit* this movement in response to a distractor ('no-go') stimulus. The number of motor responses to distractor stimuli, or commission errors, made in this task has been proposed as an indicator of response inhibition (Meule, 2017), a component of executive function, and has been used, for example, to study response inhibition in middle-aged males with T2D (Ishizawa et al., 2010).

To expand upon previous studies of executive function in adolescents with T2D (Brady et al., 2017; Yau et al., 2010), executive functioning can be investigated in this population using a more complex go/no-go task called an affective shifting task (AST), in which the stimulus-response association *reverses* after every other block (Meule, 2017). AST performance relies on rapid visual processing of the stimulus, decision-making, and subsequent inhibition or initiation of a motor movement. In shift blocks, where the stimulus-response association has been *reversed* from that in the previous block, the complexity of cognitive processing necessitated by the task is greater as the participant must *recall* the imperative stimulus in the current block; therefore, multiple executive functions (e.g., working memory, mental flexibility, attention) are useful to

deal with shifting rules in the task (Meule, 2017). Executive function indicators in the AST consist of commission errors made in ‘no-go’ trials, a potential measure of response inhibition (Meule, 2017); omission errors made in ‘go’ trials (failure to produce a motor response to an imperative stimulus), possibly reflective of attention level and working memory in the task (Meule, 2017); and premotor RT in correct ‘go’ trials, an indicator of general executive functioning, as it measures the efficiency with which the brain processes a complex set of cognitive functions. AST outcomes are typically analyzed by difficulty level of the block or by stimulus type (i.e., food or object image) as these factors may impact performance (Meule, 2017).

Another cognitive function yet to be specifically investigated in adolescents with T2D is motor response preparation. Motor preparation has been described as an activation of neurons in key cortical brain regions to just below a threshold level required for initiation of a planned motor response, and is thought to decrease the reaction time (RT) needed to execute this response (Wickens, Hyland, & Anson, 1994). This component of healthy motor function allows for efficient performance of calculated motor movements, such as in sport, in activities of daily living, and while operating a motor vehicle. Multiple studies have associated T2D in adolescence with neuronal atrophy indicators in subcortical and cortical brain areas, including possibly those areas involved in motor preparation, such as the primary motor cortex (Deecke, 1987). Thus, adolescents with T2D may exhibit reduced motor preparation ability relative to adolescents without T2D, potentially creating a barrier to physical activity, an integral component of T2D treatment.

Motor preparation can be measured using a simple RT task with a startling acoustic stimulus (SAS). In this kind of task, a participant is instructed to release a *prepared* motor movement in response to an auditory stimulus, where premotor RT needed to initiate the motor response provides an index of motor preparation (Maslovat, Drummond, Carter, & Carlsen, 2015).

This method involves the occasional replacement of the imperative stimulus with a loud auditory stimulus, which induces a reflexive startle response in a participant, triggering involuntary release of a prepared motor movement at a very short latency (Maslovat et al., 2015). This SAS is thought to circumvent motor response initiation and facilitate direct execution of a prepared motor movement through a subcortical pathway activation mechanism in what has been termed the StartReact effect (Carlsen, Maslovat, & Franks, 2012). The use of a SAS in a simple RT task is important to be able to assess if motor preparation is being measured throughout the task.

Multi-tasking is common in many activities of daily living that involve motor preparation. Since adolescents with T2D are susceptible to T2D complications that could affect balance, such as diabetic peripheral neuropathy, they may, relative to their counterparts without T2D, need to allocate more cognitive resources towards subcortical control of an action as simple as standing posture or balance at the expense of concurrent motor preparation performance. Studies of balance deficits in clinical populations have been previously performed using dual-tasks, in which two task components are performed concurrently by the participant (Gorniak, Lu, Lee, Massman, & Wang, 2019; Gorniak et al., 2020; Mohammadi-Rad et al., 2016; Paul, Ellis, Leese, McFadyen, & McMurray, 2009). One of these studies has shown that prioritization of balance control by the brain over another cognitive task may be more pronounced in the absence of visual input, as the difficulty of a standing balance task has been shown to be increased when eyes are closed under dual-task conditions (Mohammadi-Rad et al., 2016).

2.5 Purpose, Objectives and Hypotheses of the Research

If unfavourable brain structural changes are associated with T2D in adolescence and if they are significant enough to impact cognitive function, it would be reasonable to expect adolescents

with T2D to perform more poorly on cognitive tasks than adolescents without T2D. Therefore, the purpose of this research project was to compare performance on two neuromotor cognitive tasks between adolescents with obesity and T2D and adolescents with obesity presenting with risk factors for T2D, matched on age, pubertal status, sex, and sleep duration. This study aimed to address the following questions:

1. In adolescents with obesity, is T2D associated with motor preparation deficit?

Objective: We compared, using a simple RT task with a SAS, mean premotor RT between adolescents with obesity and T2D and adolescents with obesity who were at risk of T2D.

Hypothesis: We hypothesized that, overall, adolescents with obesity and T2D would exhibit decreased motor preparation ability, as indicated by a longer mean premotor RT, compared to adolescents with obesity who were at risk of T2D.

2. In adolescents with obesity, is T2D associated with executive function deficit?

Objective: We compared, using an AST, (a) mean premotor RT in ‘go’ trials, (b) the mean proportion of ‘go’ trials in which omission errors were made, and (c) the mean proportion of ‘no-go’ trials in which commission errors were made, between adolescents with obesity and T2D and adolescents with obesity who were at risk of T2D.

Hypothesis: We hypothesized that, overall, adolescents with obesity and T2D would exhibit decreased executive functioning ability, as indicated by longer mean premotor RT in ‘go’ trials as well as higher mean proportions of ‘go’ and ‘no-go’ trials with omission and commission errors, respectively, compared to adolescents with obesity who were at risk of T2D.

Chapter 3: Methodology

3.1 Ethics Approvals

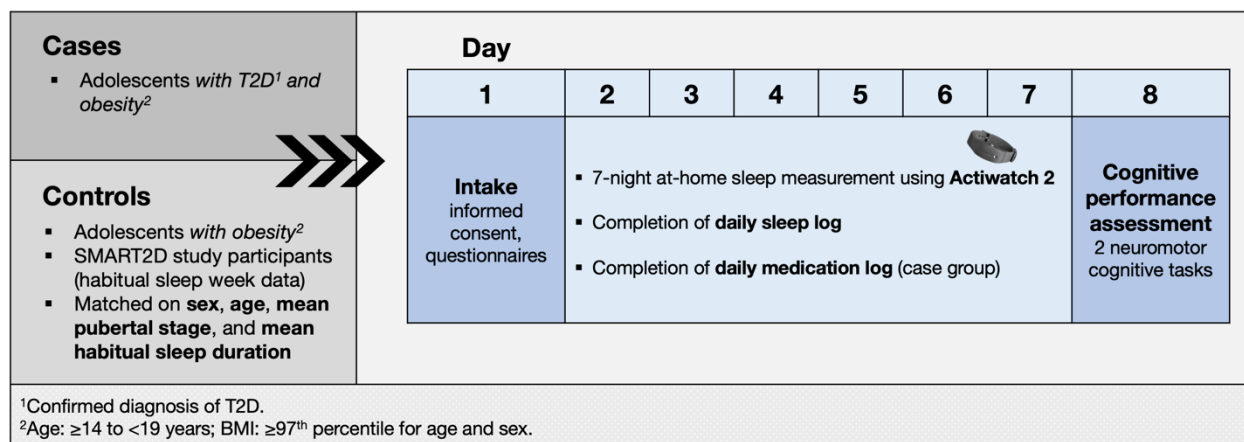
Ethical approval to conduct this research was granted by the Research Ethics Board at the Children's Hospital of Eastern Ontario (CHEO) and the University of Ottawa (approval letters available in **Appendix A** and **Appendix B**, respectively). All participants provided informed consent before participation. At the end of study involvement, each participant received \$25 and ten volunteering hours.

3.2 Study Design

This study is part of a larger project entitled Cognitive Performance in Adolescents with Type 2 Diabetes (CPAT2D). For the present investigation, we employed a 2:1 (control:case) matched case-control study design to compare cognitive performance outcomes between adolescents with obesity and T2D (cases) and adolescents with obesity but without T2D (controls). Matching characteristics consisted of age, sex, pubertal stage, and mean habitual sleep duration.

The study necessitated a time commitment of 8 days. Informed consent and intake questionnaires to confirm eligibility were completed at the intake visit (Day 1 of the study). For cases, objectively-measured habitual sleep duration at home over one week (Days 1-8 of the study) and performance data on two neuromotor cognitive tasks during a subsequent assessment visit in the Healthy Active Living and Obesity (HALO) research laboratory at the CHEO Research Institute (Day 8 of the study) were collected. Comparator data were obtained for controls through their participation in the Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes (SMART2D) study at CHEO. The study timeline and design are depicted in **Figure 2**.

Figure 2. CPAT2D study timeline and design.



Note. The CPAT2D study compared adolescents with a confirmed diagnosis of T2D and obesity (BMI ≥ 97th percentile for age and sex) to adolescents with obesity and without T2D (SMART2D study participants with complete comparator data), matched on sex, age, mean pubertal stage, and mean habitual sleep duration, on their performance on two neuromotor cognitive tasks. Sleep duration was objectively measured at home in the seven-night period preceding the cognitive performance assessment using wrist actigraphy. All participants completed a daily sleep log at home to gather descriptive data and to supplement the objective sleep measurement. Participants with T2D additionally completed a daily medication log so that average percent adherence in the case group to T2D medication during the study could be calculated.

Abbreviations: BMI, body mass index; CPAT2D, Cognitive Performance in Adolescents with Type 2 Diabetes; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

3.2.1 Participants

Eligible case participants (1) were aged ≥14 to <19 years and were attending secondary school; (2) had obesity, defined by the World Health Organization (WHO) as BMI ≥ 97th percentile based on age and sex (de Onis et al., 2007), (3) had a diagnosis of T2D by a CHEO pediatric endocrinologist registered in the hospital's electronic health record system (EPIC) and (4) had prescribed therapy for T2D for at least three months. The age range was chosen based on the mean age of the pool of potential control (i.e., SMART2D study) participants. Eligible control participants met participation criteria for the SMART2D study of BMI ≥ 97th percentile based on age and sex and at least one of the following diagnoses: dyslipidemia (high-density lipoprotein and/or total cholesterol), polycystic ovarian syndrome, or non-alcoholic fatty liver disease. Exclusion criteria for the study included: (1) use of sleep-modifying or certain stimulant

medications (e.g., methylphenidate), (2) a history of diagnosed sleep and/or psychiatric disorders, and (3) significant physical disability that could interfere with neuromotor task completion (e.g., deafness, blindness, missing limb).

3.2.2 Sample Size

An *a priori* sample size calculation determined that a *total* sample size of 14 was required to detect a significant difference between cases and controls in commission error count (a main outcome of this study), given a desired power of 0.80, a type 1 error of 0.05 and expected effect size of 0.80 based on findings in adults with T2D using a go/no-go task (Ishizawa et al., 2010). Through expert consultation with pediatric endocrinologist Dr. Stasia Hadjiyannakis, it was estimated that 80 adolescents are currently undergoing treatment for T2D in the Ottawa, Ontario area. The SMART2D study, which has a similar study population to the CPAT2D study and first began recruiting study participants in 2019, has a demonstrated recruitment success rate of approximately 75%. Based on this information, the recruitment target for the case group of the CPAT2D study was $n=20$. However, due to the COVID-19 pandemic and the lack of vaccination in this at-risk population during the data collection period (November 2020 to March 2021) we are reporting findings made based on a preliminary sample of five case participants in this thesis.

3.2.3 Adherence Strategies

Participants with T2D only were asked to adhere to their prescribed T2D treatment regimen throughout the duration of the study. To encourage and track adherence, participants were instructed to log medication doses taken during the study week using a daily medication log in which they also entered prescription medicine dosage information. On Day 8 of the study, study

staff reviewed the contents of the medication log with participants to confirm log completion. Daily SMS reminders were sent to participants to remind them to complete study logs and, for case participants only, to take T2D-related medication as prescribed. Percent adherence to medication in the case group was calculated by scoring, for each case participant, medication adherence per day (1 = medication taken, 0 = medication not taken) on each of the 7 days preceding the assessment visit. Mean scores across the week were averaged and the resultant values converted to a percentage to provide the average percent adherence to medication in the case group.

3.2.4 Matching

Individual matching of case and control participants was performed manually after data collection. SMART2D participants with incomplete comparator data were excluded from the matching process. Intended matching variables consisted of age at intake, biological sex, mean pubertal stage score, and mean sleep duration over the sleep measurement period. In the first step of the matching process, each SMART2D study participant was designated as being similar to each case participant on age at intake (± 1 year), mean pubertal stage (± 1 numeric value), sex, and mean habitual sleep duration (± 30 minutes) or not. Based on the results of these comparisons, two matches were identified for each case participant on at least *three* of the four intended matching characteristics. There were over 40 potential control (i.e., SMART2D study) participants, which provided sufficient numbers for 2 (control) : 1 (case) matching on at least three of the intended matching characteristics. Where a case participant had more than two acceptable matches, preference was lent to matches on four as opposed to three matching characteristics and to matches with more recent SMART2D study participation.

3.3 Recruitment

Recruitment of case participants was conducted through the CHEO C10 Endocrinology Clinic between November 2020 and March 2021. Chart screening of patients with upcoming C10 appointments was performed by research staff using EPIC and a list of potentially eligible adolescents was shared with overseeing physician Dr. Stasia Hadjiyannakis. A second eligibility screen was conducted during C10 appointments by Dr. Hadjiyannakis, who obtained consent to be contacted by research from youth aged ≥ 14 to < 19 years with obesity and a diagnosis of T2D, deemed medically fit by the physician to participate in a research study. Control participants (SMART2D study participants) were recruited from referral and discharge lists of the CHEO Center for Healthy Active Living (CHAL); a CHAL volunteer screened for potential participants and obtained consent to be contacted by research personnel. Adolescents who expressed interest in joining the study upon being contacted by the research team were invited to an intake appointment to confirm study eligibility and provide informed consent. Control participants included in the present analytic sample were recruited to the SMART2D study between September 2019 and May 2021.

3.4 Measurements

The CPAT2D study was developed to be an extension of the SMART2D study. Unless otherwise specified, all of the measurements and protocols described in this section were taken from SMART2D study protocols developed by Caroline Dutil.

3.4.1 Descriptive Measurements

Body mass index. At the intake visit, height was measured twice with the head in the horizontal Frankfort plane using a Seca 213 portable stadiometer (Seca 213, Seca Corporation, Germany). Weight was measured twice using a digital scale (Seca 634, Seca Corporation, Germany). If measurements differed by more than 0.5 cm for height and 0.1 kg for weight, a third measurement was taken. Mean height and weight values were obtained from the two closest values and were used to compute body mass index (BMI) values. BMI percentiles for age and sex were calculated using WHO BMI-for-age reference values for girls and boys (de Onis et al., 2007).

Screening questionnaire. At the intake visit, participants completed a screening questionnaire to confirm study eligibility and obtain demographic and other descriptive characteristics. Age at intake was obtained by calculating the difference, in years, between the date of a participant's intake and their date of birth (verified using EPIC). Self-reported biological sex was collected using the question "What sex were you assigned at birth, such as on an original birth certificate?", with the following possible responses: Male; Female. Self-reported gender was collected using the question "How do you describe yourself?", with the following possible responses: Male; Female; Trans Male/Trans Man; Trans Female/Trans Woman; Genderqueer/Gender Non-Conforming; Other Identity (Specify). Self-reported race or ethnicity was collected using the question "What is your race or ethnicity (select all that apply)?", with the following possible responses: White or Caucasian; Hispanic, Latino, or Spanish; Black, African descent, or Caribbean descent; Asian or Asian Indian; Middle Eastern or North African; Aboriginal (First Nations, Inuit, and Métis peoples); Pacific Islander; Other Race/Ethnicity (Specify). Due to small sample size and the need to maintain anonymity, responses to the question about race and ethnicity were recoded under one of the following categories: Caucasian (response of White or

Caucasian) or non-Caucasian (all other responses). A proxy measure of socioeconomic status was collected by asking participants to report the highest level of education attained by their parents or legal guardians; coding of responses was done in accordance with a previous study in which the highest reported level of education was assigned to one of three categories: very low to low (did not complete high school); low to medium (completed high school or some college); and medium to medium-high (completed a bachelor's or postgraduate degree) (Chaput et al., 2018). Self-reported history of T2D among immediate family members (mother, father and siblings) was collected using the open-ended question "Is anybody in your family being treated for type 2 diabetes?" Self-reported alcohol consumption was obtained using the question "How much (if any) alcohol do you drink on average?", with the following possible responses: Drinks per day (specify amount); Drinks per week (specify amount); Drinks per month (specify amount); I never drink alcohol. Self-reported tobacco use was assessed using the question "Are you a current smoker?", with the following possible responses: Yes (indicate how many cigarettes you smoke per day); No. Self-reported recreational drug use was assessed with the question "On how many occasions (if any) have you used recreational drugs?" To respond, participants selected the number of occasions (0; 1-2; 3-5; 6-9; 10-19; 20-39; 40 or more) on which they used recreational drugs in their lifetime, during the last year, and during the last 30 days. Self-reported daily physical activity level was collected using the question "How many minutes each day do you engage in physical activities that make your heart beat faster and make you breathe faster, like walking fast or running?", with the following possible responses: less than 10 minutes; 10 minutes; 20 minutes; 30 minutes; and 60 minutes. To assess study eligibility, participants were asked to answer an open-ended question about their medical history; for participants with T2D, the question was phrased "Do you have any current diagnoses other than diabetes? (attention deficit hyperactivity disorder, sleep problem,

mental health problem, asthma, high blood pressure, etc.)”, and for participants without T2D, the question was phrased “Do you have any current diagnoses? (attention deficit hyperactivity disorder, sleep problem, mental health problem, asthma, high blood pressure, diabetes, etc.)”. Participant diagnoses were confirmed in EPIC and the number of total diagnoses recorded in EPIC was collected as an additional descriptive variable. Participants were also asked an open-ended question about their use of medications and vitamins: “Are you on any medications (prescribed medications, over the counter, etc.) or supplements (vitamins, melatonin, etc.)?” Participants with T2D were additionally asked to respond to the question “Do you have a diagnosis of type 2 diabetes?” and, if they answered yes, to specify the year in which they were diagnosed with T2D. Time elapsed since T2D diagnosis in years was calculated by finding the difference, in years, between the intake date and the date of T2D diagnosis recorded in EPIC. Finally, participants with T2D were asked to provide specific details about their T2D treatment regimen, including the frequency and dose of any T2D medication they were taking.

Pubertal stage score. At the intake visit, self-reported information about pubertal maturation was collected using a sexual maturation scale composed of two sets of five numbered line-drawn images (Baird, Walker, Smith, & Inskip, 2017). Each set of progressive images depicts changes in a particular secondary sex characteristic through stages of pubertal development, based on the five Tanner stages of pubertal development for boys and girls (Marshall & Tanner, 1969, 1970). The male version of the scale assesses pubic hair and genital development, while the female version of the scale assesses pubic hair and breast development. Tanner staging by a clinician, the gold standard for assessing pubertal development, has been shown to agree well with adolescent self-report of pubertal development stage using a sexual maturation scale with line-drawn images of the Tanner stages (female breast stage rating: kappa = 0.81, female public hair rating: kappa =

0.91, and male combined pubic hair and genital stage rating: kappa = 0.88) (Duke, Litt, & Gross, 1980; Morris & Udry, 1980). In our study, participants were instructed to select one numbered image from each of the two image sets that best represented their current stage of secondary sex characteristic development. Numbers selected by participants in the two image sets were averaged to create a mean pubertal stage score, where a higher score is indicative of a more advanced overall stage in puberty.

23-Item Pediatric Quality of Life Inventory for 13-18 Year Olds (Peds-QL). The Peds-QL 4.0 Generic Core Scale (J. W. Varni, Seid, & Rode, 1999) was administered at the intake visit to obtain descriptive information about health-related quality of life. Validity and reliability of the PedsQL has been previously demonstrated in both healthy and patient pediatric populations. The scale has been shown to distinguish between healthy children and children with T2D (J. Varni, Seid, & Kurtin, 2001; J. W. Varni et al., 2003). The Peds-QL assesses Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items) and School Functioning (5 items) by asking how much of a problem a particular scale item has posed for the respondent over the past month. Responses are entered on a 5-point Likert scale (0=Never; 1=Almost never; 2=Sometimes; 3=Often; 4=Almost always). A Total Scale Score was calculated for each participant by converting responses to percentage values (0=100; 1=75; 2=50; 3=25; 4=0) and taking the mean of all values. A higher Total Scale Score is indicative of better health-related quality of life. A Peds-QL Total Scale Score cut-off of 70 has been recommended to identify children older than 8 years with a major chronic health condition (I. C. Huang et al., 2009).

Revised 18-Item Three-Factor Eating Questionnaire (TFEQ). The TFEQ (Karlsson, Persson, Sjöström, & Sullivan, 2000), which has been shown to distinguish between different eating patterns in a French population 8 years of age and older (De Lauzon et al., 2004), was

administered at the intake visit to evaluate eating behaviours for descriptive purposes. The TFEQ is composed of 18 self-rated items aggregated into three subscales: Cognitive Restraint (6 items), Uncontrolled Eating (9 items), and Emotional Eating (3 items). Responses to items 1-17 are entered on a 4-point scale (1 to 4), where higher numeric scores on each item reflect higher levels of cognitive restraint, uncontrolled eating, and emotional eating behaviours. For item 18 (Cognitive Restraint subscale), a response is entered by selecting a number on a scale from 1 to 8, where 1 represents no restraint in eating and 8 represents total restraint in eating. Item 18 responses were recoded as follows: 1-2=1; 3-4=2; 5-6=3; 7-8=4. Item scores were summated into raw Cognitive Restraint, Uncontrolled Eating and Emotional Eating scale scores, which were converted to a 0-100 scale using a previously described formula (De Lauzon et al., 2004). Higher TFEQ subscale scores are indicative of greater cognitive restraint, uncontrolled eating or emotional eating behaviours.

Resting heart rate, blood pressure, and mean arterial pressure. At the assessment visit, participants were asked to sit and rest for five minutes prior to the measurement of blood pressure, which was performed twice using an electronic vital signs monitor (Dinamap V100, GE Healthcare, USA). Participants were asked to keep their legs uncrossed during blood pressure readings. If systolic or diastolic blood pressure measurements differed by more than 5 mmHg, a third blood pressure measurement was taken. Mean values for resting systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate provided by the blood pressure monitor were calculated from the two closest values for each participant. Systolic and diastolic blood pressure percentiles by age and sex were then calculated using mean blood pressure values, height percentile for age and sex and exact age in years, as outlined in guidance from the National Institutes of Health (NIH) (National High Blood Pressure Education Program Working Group on

High Blood Pressure in Children and Adolescents, 2005). Height percentiles for age and sex used in blood pressure percentile calculations were based on WHO 2007 reference data (Rodd, Metzger, & Sharma, 2018). Blood pressure norms by age for boys and girls based on NIH 2005 reference data are available in **Appendices C and D**, respectively.

Fat-free mass percentage. At the assessment visit, a body composition analyzer device (TBF-300A Body Composition Analyzer, Tanita Corporation, USA) was used to obtain a measurement of fat-free mass percentage. Participants were asked to remove bulky clothing as well as socks and shoes before the body composition measurement was taken.

Sleep satisfaction. In the week separating the intake and assessment visits (Day 2 – Day 8), participants in the study completed a daily sleep log, which included one item that was used to obtain a self-reported measure of sleep satisfaction for descriptive purposes. This item was developed specifically for this study. Specifically, participants were asked in the sleep log to indicate how they felt when they woke up today, with the following possible responses: Fully rested; Refreshed; Somewhat refreshed; Fatigued; Exhausted. Responses were converted into percentage values (0=Exhausted; 25=Fatigued; 50=Somewhat refreshed; 75=Refreshed; 100=Fully rested) and mean sleep satisfaction was calculated for each participant by taking the average of response scores entered across the week. A higher sleep satisfaction value is indicative of increased sleep satisfaction.

Screen time behaviours. At the assessment visit, screen time and sedentary behaviours were measured via questionnaire for descriptive purposes. The screen time and sedentary behaviours questionnaire includes items adapted from the International Sedentary Assessment Tool, which was constructed using items from other sedentary behaviour instruments found to have acceptable reliability (Prince, LeBlanc, Colley, & Saunders, 2017); it lists ten sedentary

activities and asks participants to specify, for each activity, how many hours and minutes they spend on the activity on a typical week day and on a typical weekend. Responses were converted into hours (e.g., 15 minutes was converted into 0.25 hours); then, estimates of weekday and weekend screen time for each participant were calculated by adding up the total number of hours spent in sedentary activities on week days and weekends, respectively. Frequency of use of multiple screens at once was assessed with another item on the questionnaire that asked “How often do you use more than one screen device at once (e.g., watching videos on computer while playing games on the phone)?”, with the following possible responses: Never; Not that often (approximately 25% of time); Often (approximately 50% of the time); Most of the time (approximately 75% of the time); All the time. Responses were recoded as follows: 0=Never; 0.25=Not that often; 0.50=Often; 0.75=Most of the time; 1=All the time.

Epworth Sleepiness Scale (ESS). At the assessment visit, a self-report measure of daytime sleepiness was obtained using the ESS (Johns, 1991), which has demonstrated good validity and reliability for measuring daytime sleepiness in a Canadian sample of secondary school students (intra-class correlation coefficient = 0.88) (Gibson et al., 2006). The ESS presents eight everyday life situations and asks, “How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?” Participants complete the questionnaire by entering the most appropriate number from the following scale beside each situation: 0=would never doze; 1=slight chance of dozing; 2=moderate chance of dozing; 3=high chance of dozing. Participants were asked to refer to their usual way of life in the past week in responding to questionnaire items; in this study, this was the week preceding the assessment visit during which sleep was objectively measured at home. The ESS score was calculated as the sum of all eight values entered in the

questionnaire. A higher score on the ESS is indicative of a higher level of daytime sleepiness; scores range from 0 (no daytime sleepiness) to 24 (extreme daytime sleepiness).

Positive and Negative Affect Scale (PANAS). During the assessment visit, mood states immediately following a set of cognitively-demanding brain tasks were assessed using the PANAS, which was developed and thoroughly validated in postsecondary students (Watson & Clark, 1988). Later, reliability (Chronbach's alpha of 0.84 and 0.85 for the negative and positive scales, respectively) and construct validity of the instrument were demonstrated in an American adolescent sample (Huebner & Dew, 1995). The PANAS is a 20-item instrument formatted as a list of words that describe different emotions, where 10 items or words measure positive affect and 10 measure negative affect. Participants are asked to indicate to what extent they are feeling the emotion described by each word *at the present moment*, using the following 5-point Likert scale: 1=very slightly or not at all; 2=a little; 3=moderately; 4=quite a bit; 5=extremely. Positive and negative affect subscale scores were calculated as the sums of values entered beside items assessing positive and negative affect, respectively. Negative affect subscale scores were subsequently corrected by subtracting scores from 50, the maximum score that can be attained on the negative affect subscale; this was done to present positive and negative subscale score results such that higher scores on either subscale reflected *better* results on the PANAS. Therefore, higher positive affect scores and higher corrected negative affect scores are indicative of higher-self reported levels of positive affect and lower self-reported levels of negative affect, respectively.

Blood glucose check pre- and post- cognitive testing. This assessment was unique to the CPAT2D study. At the assessment visit, blood glucose readings were obtained from participants with T2D *only* immediately before and immediately after cognitive testing using a glucose metre (Contour next ONE[®]) and test strip (Contour next[®]) to report glycemic control and for safety

monitoring purposes. Standard protocols were followed to perform blood glucose checks. In the SMART2D study, each participant underwent a 2-hour oral glucose tolerance test at the assessment visit prior to cognitive testing (data not shown in this thesis).

Average blood glucose level (glycosylated hemoglobin). Hemoglobin A1c (HbA_{1c}) percentage, which measures blood concentration of glycosylated hemoglobin to provide an average measure of glycemic control over roughly the past three months, was obtained for descriptive purposes. For participants with T2D, the most recent HbA_{1c} reading available in the participant's medical chart in EPIC prior to study participation was collected. Study HbA_{1c} values were available for each control participant through their participation in the SMART2D study.

3.4.2 Habitual Sleep Duration Measurement

Following the intake visit, a habitual sleep assessment was conducted for each participant by objectively measuring nightly sleep duration at home over one week using an actigraph device, the Actiwatch 2[®] (Philips Respironics, Netherlands), worn on the non-dominant wrist by the participant at all times (Days 1-8 of the study). The Actiwatch 2[®] is used to provide objective measurements of sleep duration and efficiency and movement behaviours. Compared to polysomnography, the gold standard sleep measurement tool, actigraph devices have shown high sensitivity (0.89-0.97) in the detection of sleep duration (Meltzer, Montgomery-Downs, Insana, & Walsh, 2012; Meltzer, Walsh, Traylor, & Westin, 2012).

To confirm time-in-bed intervals, participants placed markers in the watch data by pressing the button on the Actiwatch 2[®] for 5 seconds every night at bedtime (lights out) and every morning when they woke up. On Day 8 of the study, study personnel confirmed watch non-wear times, bedtimes and wakeup times with each participant, adjusting actigraph-defined time-in-bed

intervals if required (e.g., if a participant woke up and immediately took off their watch to take a shower, the wakeup time was confirmed with the participant). Actiwatch 2[®] sleep duration data obtained in this study was scored using Philips Actiware Version 6.0.9 (Philips Respironics, Netherlands). In this study, participants had to have at least five nights of valid actigraph-measured sleep to obtain a mean sleep duration measurement.

At home, participants completed a daily sleep log to accompany objective sleep measurements as a substitute for objective sleep data in case of device failure and as a means to validate watch non-wear time. The sleep log was completed in the morning, following each evening of objectively-measured sleep. In the sleep log, participants were asked whether they had pressed the button on their watch as instructed at bedtime and wakeup time. They were also asked to write down (i) their “lights out” time from the previous evening and the time at which they woke up in the morning as well as (ii) intervals of watch non-wear time on the previous day. Daily SMS reminders were also used to remind participants to complete their sleep log and to remember watch specific procedures (e.g., pressing the button on the watch, wearing the watch at all hours except while showering or during swim activities).

Mean values across the sleep measurement week for other actigraph-defined sleep and sleep timing variables were calculated for descriptive purposes. These were mean bedtime across the entire week, on week nights (Sunday through Thursday), and on weekend nights (Friday and Saturday); mean wakeup time across the entire week, on weekday mornings (Monday through Friday), and on weekend mornings (Saturday and Sunday); mean variability in actigraph-defined sleep duration (standard deviation of scored sleep duration); mean sleep efficiency (actigraph-defined total sleep time divided by time in bed); mean wake after sleep onset (minutes of scored wake during the sleep interval), and mean midpoint of sleep (halfway point between bedtime and

wakeup time, calculated by subtracting half of the actigraph-defined time-in-bed interval from the wakeup time).

3.4.3 Cognitive Performance Assessment

Following the habitual sleep assessment, participants visited the HALO laboratory facility at CHEO (Day 8), where they completed two neuromotor cognitive tasks to obtain cognitive performance outcome measurements. The tasks took place after morning anthropometric measurements and administration of study questionnaires. Blood glucose level was assessed immediately before and immediately after the cognitive testing. The sequence of events at the assessment visit is displayed in **Figure 3**.

Figure 3. Schedule of events at the assessment visit (Day 8) in the CPAT2D study.

Time	Event
8:00	Participant arrival at the laboratory
8:00	Verification of sleep, food, and medication log content
8:20	Measurement of BIA, BP, HR, and S _a O ₂
8:35	Administration of questionnaires Screen Time and Sedentary Behaviour Survey Epworth Sleepiness Scale
8:55	Preparation of participant for the cognitive assessment (EMG and goniometer attachment)
10:45	Glycemic index check (pre-task)
10:50	Break + juice
10:55	Simple reaction time task
11:55	Affective shifting task
12:45	PANAS + glycemic index check (post-task) + clean-up
13:35	End of laboratory session

Note. After seven nights of objective sleep measurement, participants in the CPAT2D study visited the research laboratory (Day 8 of the study) for the cognitive assessment. At the assessment visit, study log content was verified by research staff, anthropometric information was gathered and several questionnaires were

administered for descriptive purposes. Participants then completed the cognitive assessment, which was composed of the simple reaction time task and the affective shifting task. For participants with T2D, a glycemic index check was performed for descriptive purposes before and after the cognitive assessment. Following the pre-task glycemic index check, juice was offered to participants during a short break time. This schedule was developed to match the SMART2D study schedule as closely as possible.

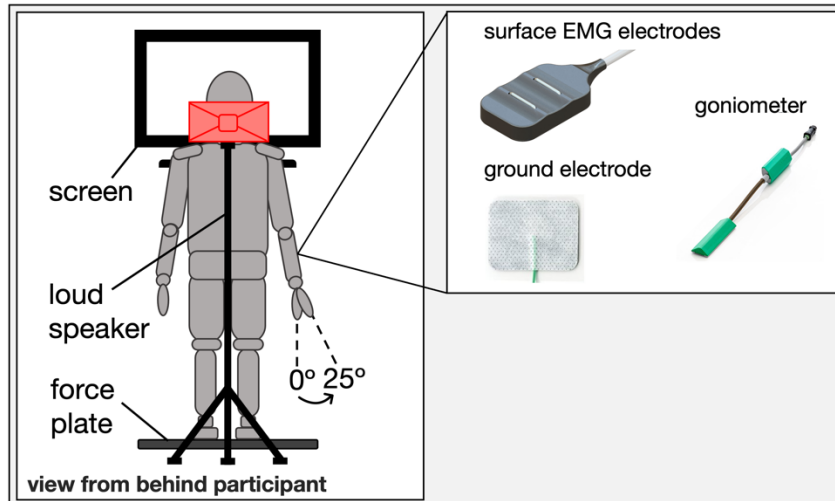
Abbreviations: BIA, bioimpedance analysis; BP, blood pressure; CPAT2D, Cognitive Performance in Adolescents with T2D; EMG, electromyography; HR, heart rate; PANAS, Positive and Negative Affect Schedule; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; S_aO₂, oxygen saturation; T2D, type 2 diabetes.

3.4.3.1 Simple RT Task

The first cognitive task was a simple RT task executed while standing. All protocols, measurements, and data marking and processing procedures related to this task were developed for the SMART2D study by Caroline Dutil and performed by trained personnel for the present study. The duration of the task was approximately 50 minutes. As part of the set-up for this task (**Figure 4**), the participant was instructed to stand barefoot on a force plate: a computer monitor was positioned at eye-level 1.5 metres in front of the participant and a loudspeaker was positioned at ear-level 0.3 metres behind the participant's head. The participant was trained to adopt a 'ready' stance, involving neutral positioning of the spine and the right wrist (i.e., wrist neither flexed nor extended). The participant was fitted with the following: bipolar pre-amplified surface electromyography (EMG) electrodes (DE-2.1 Surface EMG Sensors, Delsys Inc., USA) at the bellies of muscles used in the first task (right extensor and flexor carpi radialis, left and right lateral gastrocnemius, left and right tibialis anterior, and left orbicularis oculi [OOc] muscles); a grounding or reference electrode (Delsys Inc., USA), attached to the medial epicondyle of the right humerus; and a twin axis strain gauge electrogoniometer (TSD130A/SS20L/SS20/BN-GON-110-XDCR, Biopac Systems Inc., USA), attached to the right wrist. At each EMG sensor attachment site, the skin was cleaned using alcohol and an abrasive gel to decrease impedance and an adhesive interface subsequently used to secure each EMG sensor to the skin. The electrogoniometer was

calibrated before the task using two different wrist positions at known angles 40 degrees apart, providing the number of volts per degree of wrist extension movement.

Figure 4. Simple reaction time task set-up.



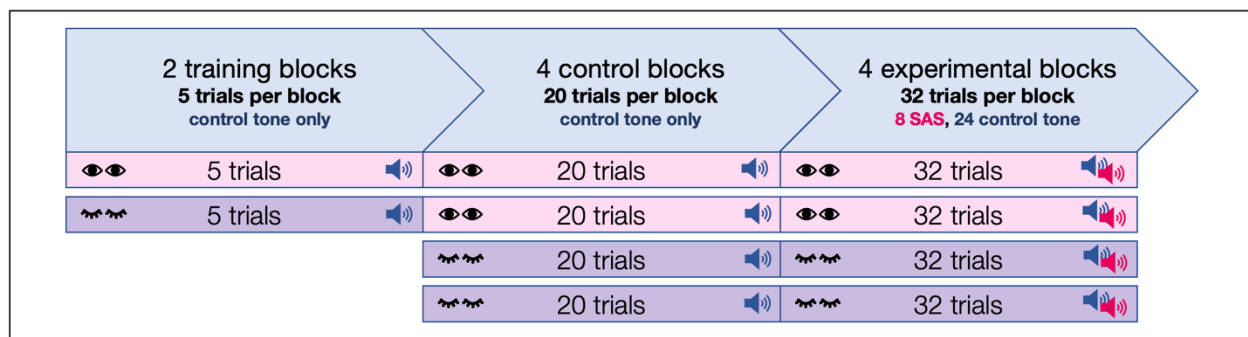
Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on a simple RT task with an auditory imperative stimulus. Participant set-up for the task (pictured) included the attachment of surface EMG electrodes (Delsys Inc., USA) to the skin at the sites of muscles from which electrical activity would be recorded during the task (right extensor and flexor carpi radialis, left orbicularis oculi, right and left tibialis anterior, and right and left lateral gastrocnemius muscles); attachment of a ground electrode (Delsys Inc., USA) to the medial epicondyle of the right humerus muscle; and attachment of an electrogoniometer (Biopac Systems Inc., USA) to the right wrist. A loudspeaker was set 0.3 m behind the participant's head and a computer monitor at eye level 1.5 m in front of the participant. The participant stood bare footed on a force plate and adopted a 'ready stance' involving neutral spine and wrist (0 degree) position.

Abbreviations: EMG, electromyography; RT, reaction time; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

Each trial of the RT task required the participant to prepare a 25-degree ballistic right wrist extension, execute this movement as quickly as possible in response to an auditory 'go' stimulus emitted from the loudspeaker, and re-adopt a neutral wrist position upon presentation of movement RT and wrist extension feedback. Throughout the task, research staff monitored real-time output data and continually reminded participants to prepare the movement, maintain a stable posture, and improve speed and accuracy of the 25-degree wrist extension.

Trial and block organization within the simple RT task is visually depicted in **Figure 5**. The task was comprised of 2 practice blocks (5 trials/block: 1 eyes open block and 1 eyes closed block), 4 control blocks (20 trials/block: 2 eyes open blocks and 2 eyes closed blocks), and 4 experimental blocks (32 trials/block: 2 eyes open blocks and 2 eyes closed blocks). Each trial employed a regular auditory imperative stimulus (control tone: 1000 Hz tone, 100 ms duration, 82 dB intensity); however, in 8 of 32 *experimental* block trials, the control tone was replaced by a startling acoustic stimulus (SAS), a broadband white noise waveform (20 – 20 000 Hz tone, 25 ms duration, 1 ms rise time, 121 dB intensity). Blocks were completed with eyes closed (EC) or eyes open (EO) to modulate difficulty of the postural aspect of the task. The order in which EC and EO task blocks were presented (EC first or EO first) was randomized and counterbalanced across participants. Premotor RT data were collected under four different experimental conditions (**Figure 6**): (1) control tone/EO (2) control tone/EC (3) SAS/EO (4) SAS/EC.

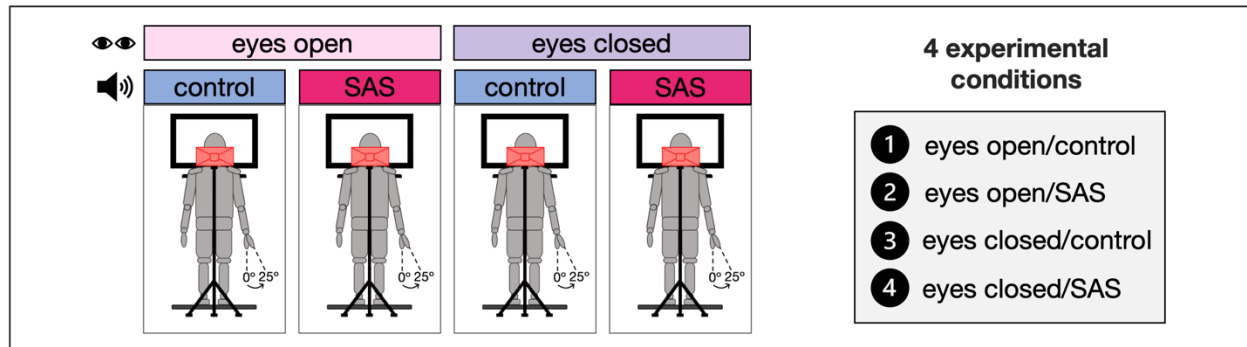
Figure 5. Block format in the simple reaction time task.



Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on a simple RT task with an auditory imperative stimulus (control sound or a SAS), which was completed partially with eyes open and partially with eyes closed. The task was composed of 2 training blocks (5 trials per block: 1 eyes open block and 1 eyes closed block) and 4 control blocks (20 trials per block: 2 eyes open blocks and 2 eyes closed blocks) in which the imperative stimulus was a control tone, as well as 4 experimental blocks (32 trials per block: 2 eyes open blocks and 2 eyes closed blocks) in which the control tone was randomly replaced, in 25% of trials, with a SAS. The order of block presentation (eyes open block first or eyes closed block first) was randomized and counterbalanced across participants.

Abbreviations: SAS, startling acoustic stimulus; RT, reaction time; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

Figure 6. *Experimental conditions in the simple reaction time task.*

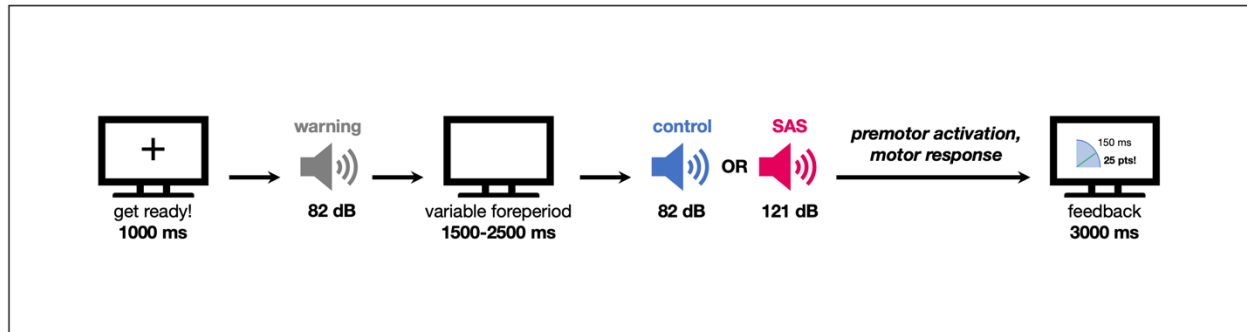


Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on a simple RT task with an auditory imperative stimulus (control sound or a SAS), which was completed partially with eyes open and partially with eyes closed. Premotor reaction time associated with a 25-degree ballistic right wrist extension, the target motor response to the imperative stimulus, was collected from trials under four experimental conditions.

Abbreviations: RT, reaction time; SAS, startling acoustic stimulus; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

Each trial of the simple RT task began with the display of a black fixation cross and text that read “Get Ready!” on the computer monitor for 1000 ms (**Figure 7**). Then, the screen went blank while an auditory warning tone (200 Hz tone, 100 ms duration, 82 dB intensity) was played through the computer speaker. This prompted the participant to prepare the ballistic right wrist extension response. A random, variable foreperiod 1500-2500 ms in duration preceded the delivery of the control auditory ‘go’ stimulus or the SAS ‘go’ through the loudspeaker set behind the participant. The participant released the prepared motor response following the imperative stimulus. Once the movement was executed, feedback regarding RT, wrist angle, and points earned or lost were displayed on the monitor for 3000 ms; feedback was accompanied by a pleasant or an unpleasant sound for fast and slow RTs, respectively. Cumulative points served as added motivation to prepare and execute the movement with as much speed and accuracy as possible.

Figure 7. Trial format in the simple reaction time task.



Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on a simple RT task with an auditory imperative stimulus. Each trial of the simple RT task began with the display of text reading “Get ready!” and a black fixation cross for 1 s. Then, the screen went blank and an auditory warning tone (200 Hz tone, 100 ms duration, 82 dB intensity) was delivered through a loudspeaker; a variable foreperiod of 1.5–2.5 s preceded delivery of the imperative stimulus, which was either a control tone (1 kHz, 100 ms, 82 dB) or a SAS (20–20 000 Hz tone, 1 ms rise time, 121 dB). The imperative stimulus signalled the participant to enact the target response movement, a 25-degree ballistic right wrist extension. Finally, feedback related to movement accuracy (angle) and RT and cumulative points gained during the task were presented on the screen for 3 s.

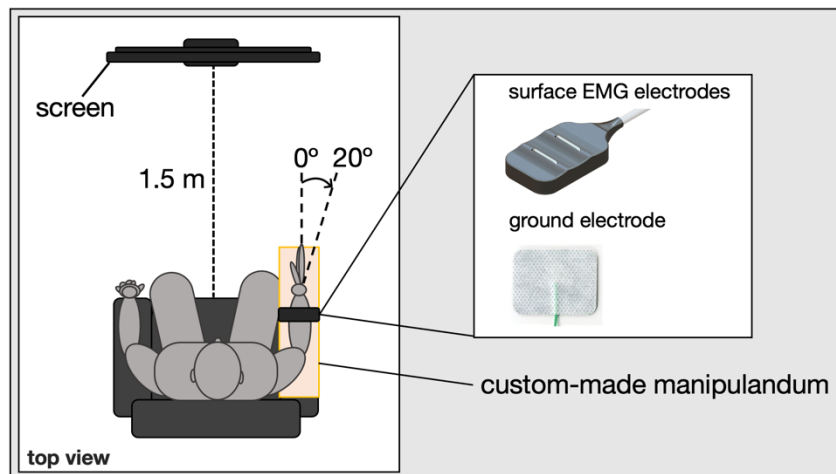
Abbreviations: RT, reaction time; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; SAS, startling acoustic stimulus.

3.4.3.2 Affective Shifting Task

The second task was an affective shifting task (AST). All protocols, measurements, and data marking and processing procedures related to this task were developed for the SMART2D study by Caroline Dutil and performed by trained personnel for the present study. Specifically, a modified version of an AST with food and neutral items (Meule, Lutz, Krawietz, et al., 2014) was used that included foods of different caloric densities and nutritional value, as well as beverages. Neutral items consisted of common household objects or nature objects. Task images were obtained from Food-Pics_Extended, an image database for experimental research on eating and appetite (Blechert, Lender, Polk, Busch, & Ohla, 2019; Blechert, Meule, Busch, & Ohla, 2014). Images were only modified if they contained a definitive grasp or handle (e.g., as in a picture of a mug) on the left side; in this case, images were altered so the item was oriented to the right side.

The duration of the task was approximately 50 minutes. As part of the set-up for this task (**Figure 8**), the participant was seated 1.5 metres in front of a computer monitor set at eye-level, with the right arm resting within a custom-made passive manipulandum containing a potentiometer, in a position involving approximately 90 degrees of elbow flexion, 30 degrees of shoulder abduction and a 90-degree internal right palm rotation (wrist neither flexed nor extended). The passive manipulandum permitted extension and flexion movements through the wrist. The right forearm was stabilized with a Velcro band. Surface EMG electrodes remained attached to the right extensor and flexor carpi radialis muscles and a grounding electrode remained attached to the medial epicondyle of the right humerus.

Figure 8. *Affective shifting task set-up.*

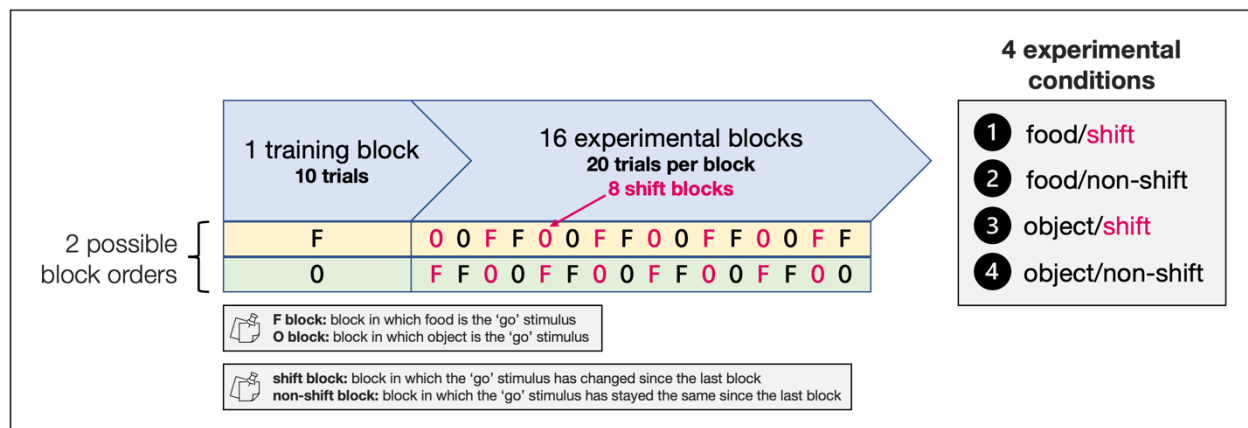


Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on an affective shifting task with a visual imperative stimulus (picture of a food or an object). Participant set-up for the task (pictured) included attachment of surface EMG electrodes (Delsys Inc., USA) to the skin at the sites of muscles from which electrical activity would be recorded during the task (right extensor and flexor carpi radialis) and a ground electrode (Delsys Inc., USA) to the medial epicondyle of the right humerus muscle. The participant was seated in a chair 1.5 m in front of a computer monitor set at eye level with the right arm rested in a custom-made passive manipulandum (potentiometer), in a position involving approximately 90 degrees of elbow flexion, 30 degrees of shoulder abduction and a 90-degree internal palm rotation (0 degree wrist position). A Velcro band was used to stabilize the right forearm.

Abbreviations: EMG, electromyography; RT, reaction time; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

The task was composed of 1 practice block of 10 trials and 16 experimental blocks of 20 trials (**Figure 9**). During each block, each participant was presented with pictures of a food or an object (1:1 ratio) in a random order. Before each block, the participant was made aware of the imperative ('go') stimulus and needed to deduce that the other stimulus was the distractor ('no-go') stimulus for the block. In total, there were eight blocks in which food was the 'go' stimulus (F) and eight blocks in which an object was the 'go' stimulus (O). The block order, either FFOOFFFOOFFFOOFFFO or OOFFFOOFFFOOFFFOFF, was randomized and counterbalanced across subjects and created two levels of task complexity. In non-shift (NS) blocks, the participant maintained the same stimulus-response association from the preceding block; however, in a shift (S) block, the participant had to reverse the stimulus-response association made in the preceding block. To ensure that the first experimental block was a shift block, the imperative stimulus in the practice block was opposite to that of the first experimental block. Errors made in 'no-go' and 'go' trials of the task as well as premotor RT data in 'go' trials were collected under four different experimental block conditions (**Figure 9**): (1) F/S (2) F/NS (3) O/S (4) O/NS.

Figure 9. Block format and experimental conditions in the affective shifting task.



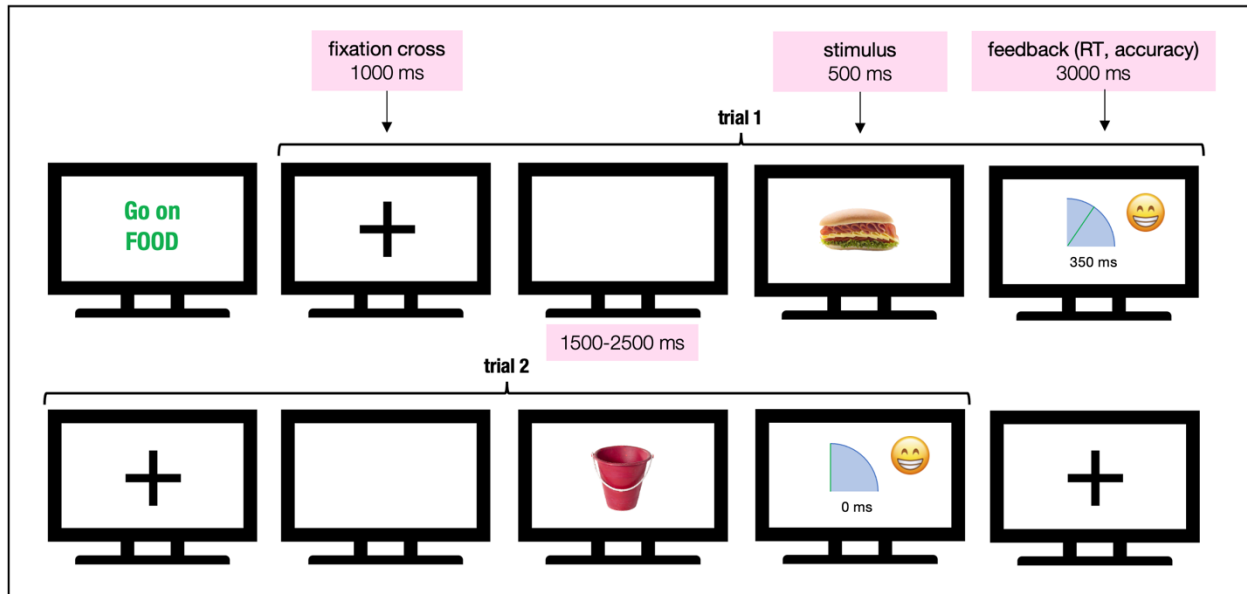
Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on an affective shifting task with a visual imperative stimulus (picture of a food or an object). The task was composed of 1 training block

(10 trials per block) and 16 experimental blocks (20 trials per block). There were 8 experimental blocks in which the imperative stimulus was a food (F blocks) and 8 in which it was an object (O blocks). The block order, OOFFFOOFFFOOFF or FFOOFFFOOFFFOOFF, was randomized and counterbalanced across participants. There were 8 experimental shift blocks (including the first experimental block), blocks in which the imperative or 'go' stimulus had switched since the last block. There were 8 experimental non-shift blocks. Outcome data for the affective shifting task were collected from trials in food/shift blocks, food/non-shift blocks, object/shift blocks, and object/non-shift blocks (4 experimental conditions).

Abbreviations: SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

Participants were trained to produce a fast, reflex-like 20-degree ballistic right wrist extension in response to the 'go' stimulus or to inhibit this movement (maintain neutral wrist position) in response to the 'no-go' stimulus. Each trial began with the 1-s display of a black fixation cross on the computer monitor followed by a 1500-2000 ms variable foreperiod during which the screen went blank (**Figure 10**). Then, the visual imperative stimulus was displayed for 500 ms, prompting participants to decide whether or not to produce the 20-degree ballistic wrist extension and subsequently enact their decision. Upon completion of muscle activity and wrist movement data capture, feedback regarding RT, accuracy, and points earned or deducted was displayed on the monitor for 1500 ms. To discourage participants from moving prior to stimulus presentation, anticipation was penalized with point deduction.

Figure 10. Trial format in the affective shifting task.



Note. This figure was adapted from materials developed by Caroline Dutil for the SMART2D study. The Cognitive Performance in Adolescents with Type 2 Diabetes study assessed, between adolescents with T2D and obesity (cases) and control adolescents with severe obesity but without T2D, performance on an affective shifting task with a visual imperative stimulus (picture of a food or an object). At the beginning of each block of trials, the participant was informed whether a food or an object was the imperative stimulus. Each trial of the task began with the display on the computer monitor of a black fixation cross for 1 s, followed by a blank screen for 1.5-2.5 s (variable foreperiod). Next, the visual imperative stimulus was displayed for 500 ms, signalling the participant to decide on and enact the appropriate motor response, either a 'no-go' response (maintenance of a neutral wrist position) or a 'go' response (a 20-degree ballistic right wrist extension). Following data capture, feedback related to movement accuracy and RT and points earned or deducted were presented on the screen. Food and object images used in the task were obtained from the Food-Pics_Extended image database (Blechert et al., 2019, 2014); the exemplar food and object images in this figure correspond to image codes 0034 and 1243 from the image database, respectively.

Abbreviations: RT, reaction time; SMART2D, Sleep Manipulation in Adolescents at Risk of Type 2 Diabetes; T2D, type 2 diabetes.

3.5 Data Acquisition

Electrical signals within each muscle were captured by EMG sensors and externally amplified and bandpass (20-450 Hz) filtered (to minimize noise) using an 8-channel desktop Bagnoli™ EMG system (Delsys Inc., USA). Separate channels of the EMG system collected rectified data (i.e., converted to absolute values) for each of the muscles studied in the tasks. For each trial of the simple RT task, filtered EMG signals were digitally sampled at a rate of 4 kHz (PCIe-6321, National Instruments Inc., USA) for a total of 5000 ms from the start of the variable

foreperiod (1.5-2.5 s duration) using a custom program in LabVIEW developed by Caroline Dutil and Dr. Anthony Carlsen (National Instruments Inc., USA). For each trial of the AST, filtered EMG signals were digitally sampled at 4 kHz for 4000 ms, beginning 1000 ms before stimulus presentation. EMG data provided outcome measurements of *premotor RT to complete a prepared motor movement* for the simple RT task and *premotor RT in 'go' trials* for the AST.

Angular displacement associated with wrist extension movement was collected by the electrogoniometer for the simple RT task and by the custom-made passive manipulandum in the AST. Potentiometer data from the custom-made manipulandum was digitally sampled at 4 kHz for 4000 ms using a custom program in LabVIEW (National Instruments Inc., USA). Movement kinematics data were collected to identify error trials in either task; therefore, this information ultimately provided the outcome measurements of proportion of commission and omission errors made in 'no-go' and 'go' trials, respectively, of the AST. EMG and kinematics data in the simple RT task and AST were marked as described in **Section 3.6.1**.

3.6 Data Analysis

3.6.1 Data Processing

EMG and movement kinematics data sampled during each trial of the simple RT task and AST were marked using custom programs developed by Caroline Dutil and Dr. Anthony Carlsen in LabVIEW (National Instruments Inc., USA). EMG onset detection for all muscles in either task was performed manually; EMG onset was defined as the time, in ms, at which filtered and rectified EMG activity increased by two standard deviations above baseline of the mean EMG signal (recorded over a 100-ms interval prior to imperative stimulus presentation) for a minimum of 20 ms (Carlsen, Maslovat, Lam, Chua, & Franks, 2011). Detection of errors in either task, including

omission and commission errors in the AST, was also performed manually using movement kinematics data, as described in **Section 3.6.1.1** and **Section 3.6.1.2**.

Control trials of the simple RT task were marked by Irina Podinic and Amelia Eaton; agreement between observers on the marking of right extensor carpi radialis muscle EMG onset was moderate to within 5 ms (Cohen's $\kappa = 0.72$) and strong to within 10 ms ($\kappa = 0.94$) (McHugh, 2012). SAS trials of the simple RT task were marked by Caroline Dutil. 'No-go' trials of the AST were marked by Irina Podinic and Amelia Eaton, and 'go' trials by Caroline Dutil.

Marked task data were exported to Microsoft Excel spreadsheets from the custom marking programs. Error codes attached to trial data were then verified for accuracy, and mean outcome data were calculated across participants in each of the study groups. The procedures for marking EMG and movement kinematics data for each task are explained in further detail below.

3.6.1.1 Simple RT Task: Data Processing

The main outcome in the simple RT task of premotor RT of a prepared motor movement was defined as EMG onset in the right extensor carpi radialis muscle. To obtain this measurement, a marker superimposed against the extensor EMG pattern in the marking program was manually positioned at the time of EMG onset as defined in **Section 3.6.1**.

Wrist kinematics data were visually inspected to identify movement error trials, which were designated using a movement error button in the custom marking program. Movement error trials consisted of trials in which there was (i) no movement or a very small movement angle of under 5 degrees or (ii) an otherwise incorrect wrist movement pattern (e.g., stepped outward movement, or outward-inward-outward wrist movement) instead of the instructed targeted 25-degree wrist extension.

Anticipation errors were verified using extensor EMG onset data; control trials with extensor EMG onset less than 85 ms and SAS trials with extensor EMG onset less than 50 ms were defined as anticipation error trials. For any given participant, if the proportion of SAS or control trials meeting anticipation criteria for SAS and control trials, respectively, exceeded 15 percent, the prespecified extensor EMG onset threshold for identifying an anticipation trial was lowered for the participant. After applying anticipation trial cut-offs in SAS and control trials, they were assessed by examining boxplots of extensor EMG onset data by participant where anticipation trials had been *excluded*; since no extremely low EMG onset data points (data points below quartile 1 [Q1] – 3*interquartile range [IQR]) were found, no anticipation error codes were added. Slow movement errors were identified in control trials only and were defined as extensor EMG onset exceeding 350 ms.

Of the SAS trials, those that did not evoke any startle reaction were classified as error trials as it was uncertain whether the movements executed in these trials were prepared in advance of the imperative stimulus. Force plate data and EMG data from the left OOc muscle were used to confirm startle reactions during SAS trials. An OOc startle reaction was defined as OOc EMG onset (defined in **Section 3.6.1**) within 25-100 ms following the delivery of the imperative stimulus. SAS trials without a startle reaction on OOc EMG were marked using a designated error button. Force plate data were also visually inspected during trial marking to identify any startle reactions on the force plate. Trials with obvious absence of a force plate startle reaction upon visual inspection, as evidenced by a lack of vertical movement (i.e., vertical force displacement on the force plate), were marked using a designated error button. SAS trial force plate startle reactions were later verified using exported force plate data. Trials in which vertical displacement on the force plate (the difference between the minimum and peak Z-axis forces on the force plate) divided

by the baseline vertical axis force value exceeded 2.5%, which corresponded with a minimum force plate displacement of approximately 20 N in our data, were designated as SAS trials with a force plate startle reaction. SAS trials with no startle reaction observed on OOC EMG *nor* the force plate were considered no-startle error trials. Practice trials and all error trials were excluded from statistical analysis of premotor RT performance in the simple RT task.

Once simple RT task data were exported to Microsoft Excel spreadsheets and error codes associated with each trial were verified, mean values for extensor EMG onset (premotor RT) for each participant were calculated across zero-error (1) control tone/EO trials, (2) control tone/EC trials, (3) SAS/EO trials, and (4) SAS/EC trials. Mean premotor RT values under each of the four task conditions were then averaged across participants in the case and control groups to provide the data points required for statistical analysis.

3.6.1.2 Affective Shifting Task: Data Processing

EMG onset in the right extensor carpi radialis muscle provided one of the outcomes of interest for the AST: premotor RT in correct ‘go’ trials. As with the simple RT task data, to obtain a value for extensor EMG onset, a marker superimposed against the extensor EMG pattern was manually positioned at the point in time when extensor EMG activity first increased from baseline, in accordance with the definition of EMG onset (see **Section 3.6.1**).

For a ‘go’ trial to be included in statistical analysis of premotor RT data, a targeted, reflexive outward wrist extension needed to be initiated within 850 ms of imperative stimulus presentation (i.e., extensor EMG onset could not exceed 850 ms), and the peak angle of the executed wrist extension needed to reach at least 5 degrees. However, incorrect wrist movement patterns (e.g., stepped movement, outward-inward-outward wrist movement) were considered

movement errors even if they satisfied premotor RT and peak angle criteria. Wrist kinematics data were visually inspected to identify ‘go’ trials with obvious movement errors, which were marked using a designated error button in the analysis software.

The proportion of omission errors and commission errors made in ‘go’ and ‘no-go’ trials of the task, respectively, constituted two additional performance outcomes for this task. An *omission error* was defined as the failure to initiate a targeted, reflexive movement within 850 ms of the presentation of an imperative stimulus. ‘Go’ trials in which (i) the peak angle of an executed movement was less than 2 degrees in the expected direction (*omission error only*); (ii) the extensor EMG onset exceeded 850 ms, representing a very late movement (*omission error plus slow RT*); (iii) the time taken for the executed movement to reach its peak angle exceeded 300 ms or the movement angle exceeded 2 degrees but not 5 degrees (*omission error plus movement error*), or; (iv) conditions (ii) and (iii) were both met (*omission error plus movement error plus slow RT*) constituted omission error trials. These trials were identified via visual inspection of EMG and movement kinematics data in the marking program and were later verified in Microsoft Excel.

A *commission error* was defined as a wrist extension executed in response to a distractor stimulus. ‘No-go’ trials in which the peak angle of an executed movement exceeded 2 degrees were designated as commission error trials. Commission errors were identified via visual inspection of movement kinematics data in the marking program and later verified in Microsoft Excel. Commission error trials in which (i) the peak angle of the movement was between 2 and 5 degrees or (ii) the time taken for an executed movement to reach its peak angle exceeded 300 ms, which indicated the movement may have been performed with uncertainty, were additionally designated as movement error trials.

Anticipation errors were verified using extensor EMG onset data; any ‘go’ trials or commission error ‘no-go’ trials with extensor EMG onset for an executed movement less than 250 ms were defined as anticipation error trials. Anticipation trials were *not* included in statistical analysis of premotor RT in ‘go’ trials and could *not* simultaneously be designated as commission or omission error trials.

After applying criteria for error trial identification, correct ‘go’ trials were further probed for premotor RT related errors by examining boxplots of extensor EMG onset data for extreme outliers (data points above $Q3 + 3 \times IQR$ or below $Q1 - 3 \times IQR$); this was done separately for food block data and object block data. Any extreme outliers were examined in the context of block difficulty to decide whether the associated trials should be identified as anticipation or omission error trials. Specifically, if extremely slow premotor RT trials in non-shift blocks or if extremely fast premotor RT trials in shift blocks were found, these were designated as omission error and anticipation error trials, respectively. No such trials were found.

We assessed, by trial code (the number identifier for a specific image presented in the task), the proportion of case and control participants that made any error in ‘go’ and ‘no-go’ trials. If over eighty percent of participants made any error in response to a particular image, trial data with this image were to be excluded from analyses; following this assessment, no data associated with a particular image or set of images needed to be excluded from analyses. Practice trials and all error trials were excluded from statistical analysis of ‘go’ trial premotor RT in the AST.

Once AST data were exported to Microsoft Excel spreadsheets and error codes associated with each trial were verified, mean data values were calculated for use in statistical analyses. The following values under four different block conditions (food/shift, food/non-shift, object/shift and object/non-shift blocks) were calculated separately for each participant: (i) mean extensor EMG

onset in zero-error ‘go’ trials, (ii) the proportion of ‘no-go’ trials ($n = 40$) that were coded as commission error trials, and (iii) the proportion of ‘go’ trials ($n = 40$) that were coded as omission error trials. Means for each value across study groups were then calculated.

3.6.2 Statistical Analysis

Data analysis was completed using Microsoft Excel and IBM SPSS Statistics Version 28.0.0.0. The statistical significance level was set at $p < .05$.

3.6.2.1 Descriptive Analyses

Distributions of descriptive characteristics in each study group were summarized using proportions or means with standard deviations, as appropriate. Differences in distributions of categorical descriptive variables between case and control participants were investigated using Fisher’s exact test. Group differences in continuous descriptive variables with normal distribution were assessed with two-tailed independent samples t-tests. Transformations (square root, logarithm base 10, inverse, reflect and transform) were applied to continuous variables with non-Gaussian distribution (significant Shapiro-Wilk test) or extreme outliers (data points above $Q3 + 3*IQR$ or below $Q1 - 3*IQR$) to improve normality of the data. Non-parametric analysis (Mann-Whitney U test) was used to test for group differences in ordinal descriptive variables or continuous variables with non-normal distribution or extreme outliers that could not be improved through data transformations.

3.6.2.2 Simple RT Task Performance

Mean premotor RT in zero-error trials of the simple RT task was analyzed using a 2 (between-subjects factor of *group*: case vs. control) x 2 (within-subjects factor of *eye position*: eyes open vs. eyes closed) x 2 (within-subjects factor of *stimulus type*: SAS vs. control tone) mixed analysis of variance (ANOVA). Investigation of any significant interaction was performed using *t*-tests. Movement error trials, anticipation trials, and SAS trials without any startle reaction were excluded from the analysis.

Mean premotor RT data by eye position and stimulus type across participants in each of the study groups was examined for normality using the Shapiro-Wilk test. Outliers were identified via inspection of boxplots and studentized residuals. Outliers were defined as data points greater than $Q3 + 1.5 \cdot IQR$ or less than $Q1 - 1.5 \cdot IQR$, while extreme outliers were defined as data points above $Q3 + 3 \cdot IQR$ or below $Q1 - 3 \cdot IQR$. Assumptions of equality of variances and equality of covariances were tested using Levene's test and Box's test, respectively. Due to small sample size it was possible that data might not meet all assumptions for the two-way mixed ANOVA test. If assumptions of normality or equality of variances were violated, or extreme outliers were detected, transformations (square root, logarithm base 10, inverse, reflect and transform) were applied as appropriate to the dependent variable and the analysis was repeated to attempt to improve validity of the test results. If transformations were not successful in improving normality, equality of variances or extreme outliers, the planned analysis was carried out using all data points regardless and assumption violations were noted.

After completing the planned analysis, a linear mixed-effects model was performed for the premotor reaction time outcome using the same within- and between-subjects factors to account for a possible subject-level random effect and to make use of all available individual trial data

points, and the impact on the significance of interactive effects was assessed. This analysis was completed using R version 4.1.1.

3.6.2.3 *Affective Shifting Task Performance*

AST performance, as measured using premotor RT in zero-error ‘go’ trials, the proportion of omission errors made in ‘go’ trials and the proportion of commission errors made in ‘no-go’ trials, was analyzed using 2 (between-subjects factor of *group*: case vs. control) x 2 (within-subjects factor of *block difficulty*: shift block vs. non-shift block) x 2 (within-subjects factor of *imperative stimulus*: food vs. object) mixed ANOVAs. Investigation of any significant interaction was performed using *t*-tests. Data assumptions for each of the two-way mixed ANOVA tests were assessed, and a linear mixed-effects model performed for the premotor reaction time outcome, as described for statistical analysis of the simple RT task (**Section 3.6.2.2**).

3.6.2.4 *Effect Size*

The Cohen’s *d* method was used to describe standardized mean difference of an effect, as appropriate; *d* values of 0.2, 0.5, and 0.8 were interpreted as small, medium and large effect sizes, respectively (Cohen, 1988). Partial eta squared (partial η^2) values were presented as part of mixed ANOVA results to provide estimates of the proportion of variance in the dependent variable explained by a particular effect that was not attributed to other effects.

Chapter 4: Results

4.1 Participants

In total, a pool of 25 adolescents with obesity and T2D was identified during the recruitment process. The treating physician obtained permission to be contacted by research from seven adolescents in the pool; of these, one adolescent was not interested in participating and another did not respond when contacted by research. The remaining five adolescents with T2D were assessed for eligibility at an intake visit, recruited and successfully completed the study. Of 36 adolescents included in the SMART2D study, 10 with complete comparator data were individually matched (2:1) to case participants on at least three of four intended matching characteristics of sex, age at intake, mean habitual evening sleep duration and mean pubertal stage score. Three of five case participants were each matched to two SMART2D participants on all four matching characteristics. The two remaining case participants were matched to two SMART2D participants on three of four matching characteristics. For one case participant, no match on sleep duration was found, as the participant had much longer average sleep duration than SMART2D participants. Also, self-reported pubertal stage was not collected from one case participant who did not identify with their sex assigned at birth; for this participant, a proxy report of pubertal stage was used in the matching process by estimating pubertal development based on age and height.

4.2 Descriptive Analyses

Descriptive characteristics of the analytic sample by study group are summarized in **Table 1**. Data are mean $\pm$ standard deviation unless otherwise stated. The analytic sample consisted of five case participants with obesity and T2D (60% female; BMI percentile 98.2 ± 2.0 ; age 16.7 ± 1.1 years) and ten matched control participants with obesity who were at risk of developing T2D (50% female; BMI percentile 99.9 ± 0.2 ; age 15.9 ± 1.3 years). Distributions of self-reported

gender ($p = 1.00$), self-reported race or ethnicity ($p = .08$) and proxy-reported socioeconomic status ($p = .60$) were not statistically significantly different between groups. Successful matching on intended characteristics was demonstrated by similarities between groups in mean age at intake ($p = .30$), mean pubertal stage score ($p = .61$), objectively-measured mean sleep duration ($p = .24$), and sex distribution ($p = 1.00$).

All study participants had at least six valid intervals of habitual sleep recorded using the Actiwatch 2 device. There were no statistically significant differences between groups in the distributions of other objectively-measured sleep (i.e., 7-day sleep duration variability, sleep efficiency, and wake after sleep onset) and sleep timing (mean bedtime and mean wakeup time overall, on weekdays, and on weekends, and mean midpoint of sleep) variables (all $p > .05$). Self-reported sleep satisfaction level across the measured sleep week also did not significantly differ between groups ($p = .94$). However, on average, case participants did have higher scores than control participants on the Epworth Sleepiness Scale, $t(13) = 2.21$, $p = .046$, corresponding with increased self-reported daytime sleepiness during the measured sleep week.

Median BMI percentile was statistically significantly higher in the control group, at 99.95, compared to the case group, at 99.20 ($U = 47.5$, $z = 2.99$, $p = .002$). Mean fat-free mass percentage was 64.4 ± 8.4 percent in the case group and 54.7 ± 5.0 percent in the control group, a statistically significant difference between groups of 9.7 ± 3.4 [mean difference $\pm$ standard error] percent, $t(13) = 2.84$, $p = .014$. Two participants in the case group had measured BMI-for-age less than the 97th percentile (minimum 95.57), despite having a diagnosis of obesity in the medical chart. There were no statistically significant differences in heart rate ($p = .68$), systolic ($p = .20$) and diastolic ($p = .08$) blood pressure percentile, and mean arterial pressure ($p = .07$) between study groups. One participant in the control group had mean systolic blood pressure greater than the 95th percentile

for sex, age and height. The NIH defines hypertension in children as average systolic or diastolic blood pressure greater than or equal to the 95th percentile for sex, age and height on at least three separate occasions of measurement (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2005).

Self-reported screen time on weekdays ($p = .46$) and weekends ($p = .86$), self-reported frequency of simultaneous use of multiple screens ($p = .41$) and self-reported daily minutes of physical activity ($p = .23$) did not differ statistically significantly between study groups. While there were no significant differences between groups in score distribution on the Peds-QL ($p = .33$), 60 percent of case participants and 20 percent of control participants had Total Scale Score on the Peds-QL less than 70, which has been recommended as a cut-off to identify children with lower quality of life due to a major chronic health condition (Huang et al., 2009). Mean scores on cognitive restraint ($p = .85$), uncontrolled eating ($p = .78$), and emotional eating ($p = .81$) subscales of the TFEQ did not statistically significantly differ between groups. On average, control participants did have significantly higher scores compared to control participants on the negative affect subscale of the PANAS, which was administered at the assessment visit immediately after cognitive testing, $t(11.621) = -2.48$, $p = .03$; specifically, the control group self-reported significantly more negative feelings or emotions following the cognitively demanding set of tasks.

Some substance use was reported in the sample. None of the participants identified as smokers. One case participant reported consuming alcohol approximately once per month, while two control participants reported consuming alcohol approximately one to two times per month. One participant in the case group reported using recreational drugs on 3 to 5 occasions, including 1 to 2 times over the last year. Of the control participants, one reported a lifetime recreational drug

use frequency of 1 to 2 times; another control participant reported using recreational drugs 10 to 19 times over the last year and 3 to 5 times over the last 30 days.

Table 1. Descriptive characteristics of the analytic sample.

Characteristic	T2D (n = 5)	No T2D (n = 10)	p
Age at intake (years)	16.7 (1.1)	15.9 (1.3)	.302
Pubertal stage score	4.5 (0.6)	4.4 (0.5)	.608
Sex (% female)	60	50	1.000
Gender (% girl)	40	50	1.000
Race/ethnicity (% non-Caucasian)	60	10	.077
Body mass index percentile	98.2 (2.0)	99.9 (0.2)	.003
Mean resting heart rate (bpm)	79.8 (12.8)	77.2 (10.7)	.677
Mean resting blood pressure percentile			
Systolic	36.7 (24.5)	57.8 (30.8)	.208
Diastolic	27.3 (15.5)	45.3 (18.2)	.083
Mean arterial blood pressure (mmHg)	78.3 (3.9)	84.8 (7.0)	.070
Fat-free mass percentage	64.4 (8.4)	54.7 (5.0)	.014
HbA _{1c} percentage	9.1 (2.1)	5.3 (0.3)	.002
Time elapsed since T2D diagnosis (years)	3.2 (1.7)	—	—
Prescribed medication for T2D (% yes)	100	—	—
Number of diagnoses	2.2 (1.6)	1.6 (1.3)	.446
History of T2D/gestational diabetes (% yes)	80	20	.089
Self-reported minutes of PA per day			.229
<10 (%)	80	40	
10 (%)	0	20	
20 (%)	0	10	
30 (%)	20	20	
60 (%)	0	10	
Proxy socioeconomic status			.604
Medium to medium-high (%)	80	90	
Low to medium (%)	20	10	
Very low to low (%)	0	0	
Objectively-measured sleep variables			
Mean bedtime	11:29:31 PM (1:37:59)	11:49:48 PM (1:05:53)	.639
Mean wakeup	7:57:25 AM (1:17:24)	7:20:47 AM (1:00:13)	.329
Mean WD bedtime	11:20:37 PM (1:34:32)	11:33:08 PM (0:56:25)	.371
Mean WD wakeup time	7:31:38 AM (1:00:21)	6:59:19 AM (0:49:02)	.284
Mean WE bedtime	11:59:18 PM (3:19:07)	12:30:54 AM (1:50:39)	.266
Mean WE wakeup time	9:09:18 AM (1:55:28)	8:14:30 AM (2:01:10)	.417
Mean sleep duration (hours:minutes)	7:46 (1:12)	7:09 (0:45)	.235
Mean sleep duration variability (hours:minutes)	2:17 (1:45)	1:05 (0:34)	.099
Mean wake after sleep onset (hours:minutes)	0:53 (0:35)	0:49 (0:17)	.940
Mean sleep efficiency percentage	84.2 (4.5)	85.0 (3.4)	.165
Mean midpoint of sleep	3:43:29 AM (1:21:36)	3:35:13 AM (0:57:26)	.822
Epworth Sleepiness Scale score	10.2 (2.7)	6.5 (3.2)	.046
Self-reported percent sleep satisfaction level	57.1 (22.2)	57.9 (15.8)	.939

Self-reported WD screen time (hours/day)	17.5 (11.3)	13.9 (7.8)	.464
Self-reported WE screen time (hours/day)	19.7 (10.4)	18.3 (15.0)	.856
Self-reported frequency of multiple-screen use			.412
Never (%)	20	10	
Not that often (%)	0	40	
Often (%)	40	30	
Most of the time (%)	20	10	
All the time (%)	20	10	
Blood glucose level (mmol/L)			
Pre-task	6.3 (2.4)	—	—
Post-task	4.8 (0.9)	—	—
Positive and Negative Affect Schedule			
Positive Affect Score	26.2 (7.9)	27.8 (6.1)	.527
Negative Affect Score (corrected)	38.8 (0.8)	36.1 (3.3)	.030
Three-Factor Eating Questionnaire			
Cognitive Restraint Score	30.0 (17.0)	28.8 (8.2)	.848
Uncontrolled Eating Score	38.3 (11.5)	39.2 (12.7)	.780
Emotional Eating Score	36.7 (24.7)	40.0 (24.8)	.810
Pediatric Quality of Life Questionnaire Score	73.0 (11.8)	74.2 (6.9)	.325

Note: Data are presented as mean (standard deviation) or percentages as appropriate. Blood pressure percentiles for age, sex and WHO-based height percentile were computed using National Institutes of Health 2005 reference data. Higher HbA_{1c} percentages are indicative of lower glycemic control over approximately the last three months; HbA_{1c} results for participants with T2D were retrieved from medical charts (all results dated within three months of study participation), but were obtained through SMART2D study participation for participants without T2D. Electronic medical records were used to confirm dates of T2D diagnosis, prescribed medications for T2D and the number of diagnoses registered in the medical chart. A higher score on the Epworth Sleepiness Scale represents a greater level of self-reported daytime sleepiness. Higher positive affect scores and higher corrected negative affect scores on the Positive and Negative Affect Schedule are indicative of higher self-reported levels of positive affect and lower self-reported levels of negative affect, respectively. Higher scores on subscales of the Three-Factor Eating Questionnaire are indicative of greater levels of self-reported cognitive restraint, uncontrolled eating and emotional eating behaviours. A higher total score on the Pediatric Quality of Life Questionnaire is indicative of better self-reported quality of life. *p*-values represent the significance level of two-sided independent samples *t*-test (continuous variables), Fisher's exact test (dichotomous variables), or Mann-Whitney *U* test (ordinal variables or non-normally distributed continuous variables). Statistical significance is set at $p < .05$.

Abbreviations: HbA_{1c}, glycosylated hemoglobin; PA, physical activity; SMART2D, Sleep Manipulation in Adolescents at Risk of T2D; T2D, type 2 diabetes; WD, weekday; WE, weekend; WHO, World Health Organization.

In the case group, the length of time from T2D diagnosis to the study intake date was 3.2 $\pm$ 1.7 years, and the prevalence of immediate family history of T2D or gestational diabetes was 80%. Median HbA_{1c} percentage in the case group, at 8.9%, was statistically significantly higher than median HbA_{1c} percentage in the control group, at 5.2%, $U = .00$, $z = -3.09$, $p = .002$. For the case group, all HbA_{1c} results obtained from medical charts were dated within three months of the study intake date (mean 2.02 $\pm$ 0.8 months). Medication logs to track adherence to a T2D treatment

regimen were completed by all case participants; only one participant reported forgetting to take daily prescribed medication once during the study, resulting in percent adherence to medication in the case group of 97.1%. At the assessment visit, the blood glucose level of case participants was 6.3 ± 2.4 mmol before cognitive testing and 4.8 ± 0.9 mmol after cognitive testing. The initial glucose reading was taken *before* break time, when juice was offered to participants (**Figure 3**).

4.3 Simple RT Task Outcomes

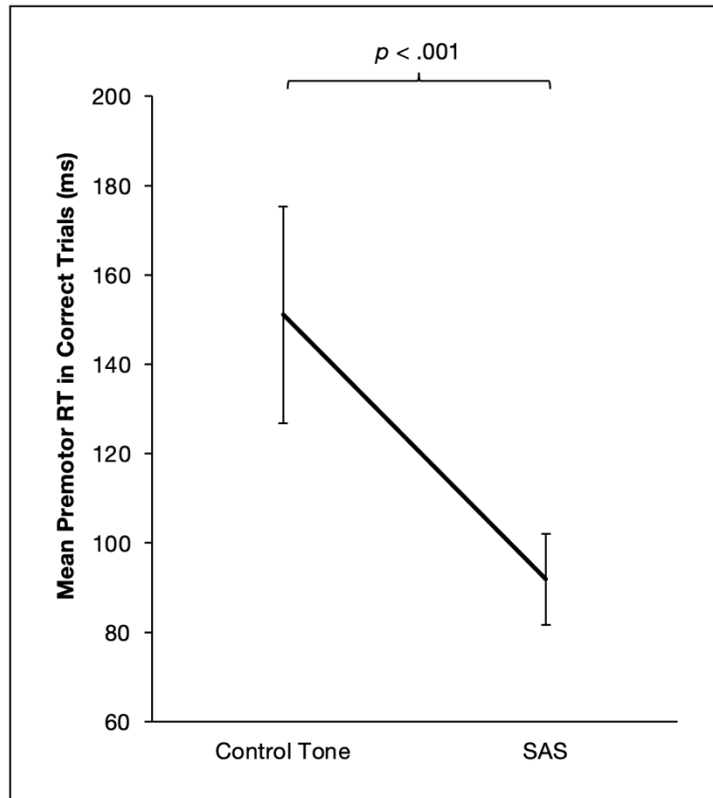
Simple RT task data were collected from a total of 3120 (480 SAS and 2640 control) experimental trials. For two participants, the extensor EMG onset cut-off to identify anticipation errors in control trials was adjusted to 75 ms; after verification of anticipation error codes and boxplot inspection of extensor EMG onset data from non-anticipation trials, no additional error trials were identified. Trials with any error were to be excluded from statistical analysis. After marking and processing of simple RT task data, errors were identified in 11.7% of control trials and 36.7% of SAS trials. Anticipation errors were made in 6.2% ($n = 164$) of control trials and 4.0% ($n = 19$) of SAS trials. Additionally, slow movement errors were identified in 2.6% ($n = 69$) and movement errors in 2.9% ($n = 77$) of control trials. The proportion of SAS trials with any startle reaction was 67.3%. Ultimately, 486 (15.6%) of all trials were excluded from analysis of premotor RT data in the simple RT task.

4.3.1 Premotor RT in Correct Trials

A three-way mixed ANOVA was conducted to assess the effects of study group, eye condition, and auditory stimulus type on premotor RT in zero-error trials of the simple RT task. There were three regular outliers in control group premotor RT data, as assessed by inspection of

a boxplot. The outliers were kept in the analysis as removal of the outliers did not affect conclusions made from the results. Premotor RT was normally distributed in all cells of the study design, as assessed by Shapiro-Wilk's test ($p > .05$). There was homogeneity of variances, as assessed by Levene's test ($p > .05$). There was no statistically significant three-way interaction between study group, eye condition and auditory stimulus type, $F(1, 13) = 1.17, p = .30$, partial $\eta^2 = .11$, indicating that the interactive effect of eye condition and auditory stimulus type on premotor RT did not significantly differ between adolescents with and without T2D. There were also no statistically significant two-way interactions between study group and eye condition, $F(1, 13) = 0.46, p = .51$, partial $\eta^2 = .03$, study group and auditory stimulus type, $F(1, 13) = 0.00, p = .99$, partial $\eta^2 = .00$, and eye condition and auditory stimulus type, $F(1, 13) = 0.004, p = .95$, partial $\eta^2 = .00$. There was a statistically significant main effect of auditory stimulus type on premotor RT, $F(1, 13) = 86.84, p < .001$, partial $\eta^2 = .87$, where premotor RT was faster in trials in which the SAS was delivered as compared to the control tone. On average, mean premotor RT was 59.23 ms shorter in SAS trials compared to control tone trials (**Figure 11**). The remaining main effects were not significant.

Figure 11. Mean premotor reaction time in zero-error trials of the simple reaction time task as a function of auditory stimulus type.



Note. Error bar represents standard deviation (SD). A 2x2x2 mixed ANOVA assessing the effect of study group, eye condition, and auditory stimulus type on mean premotor RT in zero-error trials of the simple RT task revealed no significant interaction effects ($p > .05$) but a significant main effect of auditory stimulus type on mean premotor RT, $F(1, 13) = 86.84$, $p < .001$, partial $\eta^2 = .87$. Mean premotor RT was 151.1 (SD 24.2) ms in control tone trials and 91.9 (SD 10.2) ms in SAS trials. The main effects of study group and eye condition were not statistically significant.

Abbreviations: ANOVA, analysis of variance; RT, reaction time; SAS, startling acoustic stimulus.

4.4 Affective Shifting Task Outcomes

AST data were collected from a total of 2400 ‘go’ trials and 2400 ‘no-go’ trials. For two participants, the extensor EMG onset cut-off to identify anticipation errors was adjusted to 200 ms. Following application of criteria for error trial identification, inspection of boxplots of ‘go’ trial extensor EMG onset data did not reveal any additional error trials. After the marking and processing of AST data, 4.7% ($n = 112$) of all ‘go’ trials were coded as omission errors only, 1.5% ($n = 35$) as omission errors with slow RT, 1.9% ($n = 45$) as both omission errors and movement

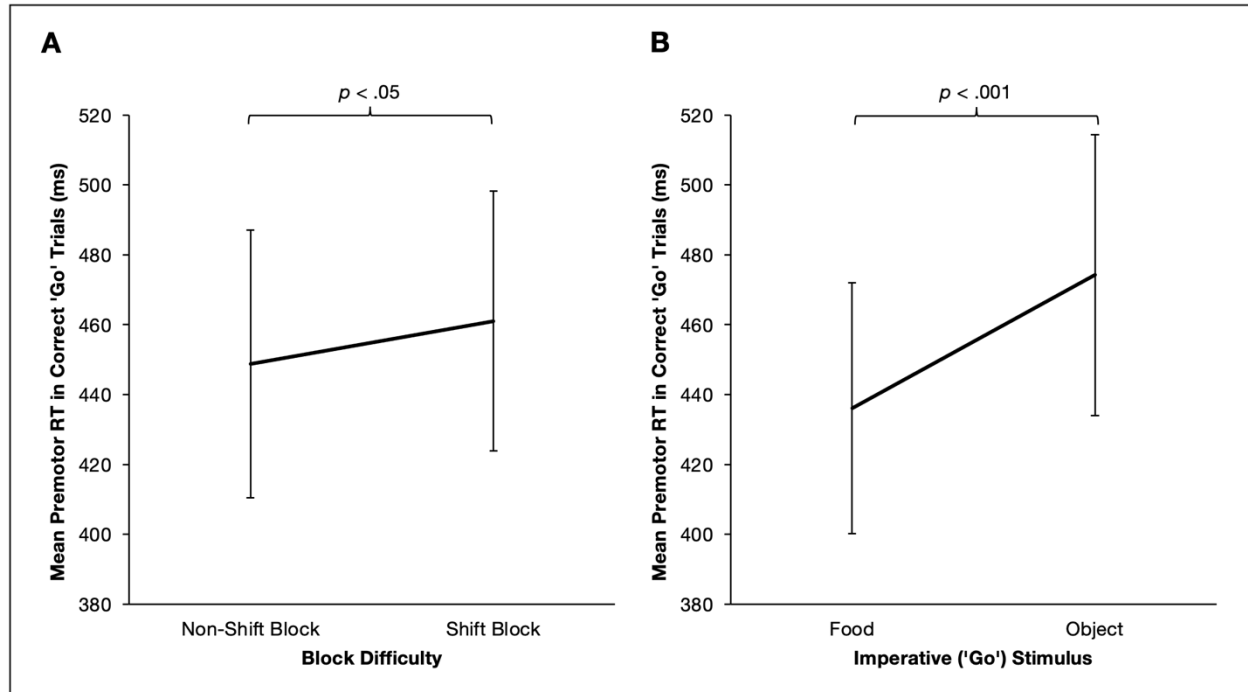
errors, 0.04% ($n = 1$) as omission errors with slow RT and movement errors, 0.7% ($n = 16$) as anticipation errors, and 0.5% ($n = 12$) as movement errors only. All 9.2% ($n = 221$) of ‘go’ trials with errors were excluded from statistical analysis of ‘go’ trial premotor RT performance. Overall, 8.0% ($n = 193$) of all ‘go’ trials were coded as omission error trials. Of all ‘no-go’ trials, 17.7% ($n = 424$) were coded as commission error trials and only 0.8% ($n = 20$) as anticipation error trials.

4.4.1 Premotor RT in Correct ‘Go’ Trials

A three-way mixed ANOVA was conducted to assess the effects of study group, block difficulty, and imperative stimulus type on premotor RT in zero-error ‘go’ trials of the AST. There was one extreme outlier in premotor RT data from the case group under the food and non-shift block condition that could not be improved through data transformation. Outlier data were kept in the analysis to preserve data in the case group due to small sample size. Premotor RT data were mostly normally distributed, as assessed by Shapiro-Wilk’s test; however, there was a significant Shapiro-Wilk test result ($p = .02$) in premotor RT data from participants with T2D for the food/non-shift block condition. The assumption of homogeneity of variances was violated for the food and non-shift block condition, as assessed using Levene’s test ($p = .01$). Data transformations did not improve normality of the data nor equality of variances. There was no statistically significant three-way interaction between study group, block difficulty and imperative stimulus, $F(1, 13) = 1.28$, $p = .28$, partial $\eta^2 = .09$, indicating that the interactive effect of block difficulty and imperative stimulus type on ‘go’ trial premotor RT was not significantly different between adolescents with and without T2D. There were no statistically significant two-way interactions between study group and block difficulty, $F(1, 13) = 1.11$, $p = .31$, partial $\eta^2 = .08$, study group and imperative stimulus, $F(1, 13) = 0.25$, $p = .63$, partial $\eta^2 = .02$, and block difficulty and imperative stimulus, $F(1, 13) =$

0.22, $p = .65$, partial $\eta^2 = .02$. There was a statistically significant main effect of block difficulty on premotor RT in ‘go’ trials, $F(1, 13) = 7.20$, $p = .02$, partial $\eta^2 = .36$. Mean premotor RT was 448.8 ± 38.3 ms in non-shift blocks and 461.0 ± 37.2 ms in shift blocks (**Figure 12A**); therefore, mean premotor RT was significantly longer in more difficult blocks of the task (shift blocks) compared to less difficult blocks of the task (non-shift blocks). The main effect of imperative stimulus on mean premotor RT was also statistically significant, $F(1, 13) = 50.76$, $p < .001$, partial $\eta^2 = .80$. Mean premotor RT was 436.1 ± 35.9 ms in blocks with food as the imperative stimulus and 474.2 ± 40.3 ms in blocks with an object as the imperative stimulus (**Figure 12B**). Therefore, on average, participants exhibited significantly shorter mean premotor RT in ‘go’ trials in response to food as compared with object pictures. There was no statistically significant main effect of group on the outcome, $F(1, 13) = 0.546$, $p = .47$, partial $\eta^2 = .04$.

Figure 12. Mean premotor reaction time in zero-error ‘go’ trials of the affective shifting task as a function of **12A** block difficulty and **12B** imperative stimulus type.



Note. Error bar represents standard deviation (SD). A 2x2x2 mixed ANOVA assessing the effect of study group, block difficulty, and imperative stimulus type on mean premotor RT in zero-error ‘go’ trials of the AST revealed no significant interactive effects ($p > .05$). **12A.** However, there was a significant main effect of task difficulty on mean premotor RT, $F(1, 13) = 7.20, p = .02$, partial $\eta^2 = .36$; mean premotor RT was 448.8 (SD 38.3) ms in non-shift blocks and 461.0 (SD 37.2) ms in shift blocks. **12B.** There was also a significant main effect of imperative stimulus on mean premotor RT, $F(1, 13) = 50.76, p < .001$, partial $\eta^2 = .80$; mean premotor RT was 436.1 (SD 35.9) ms in food blocks and 474.2 (SD 40.3) ms in object blocks. The main effect of group was not statistically significant.

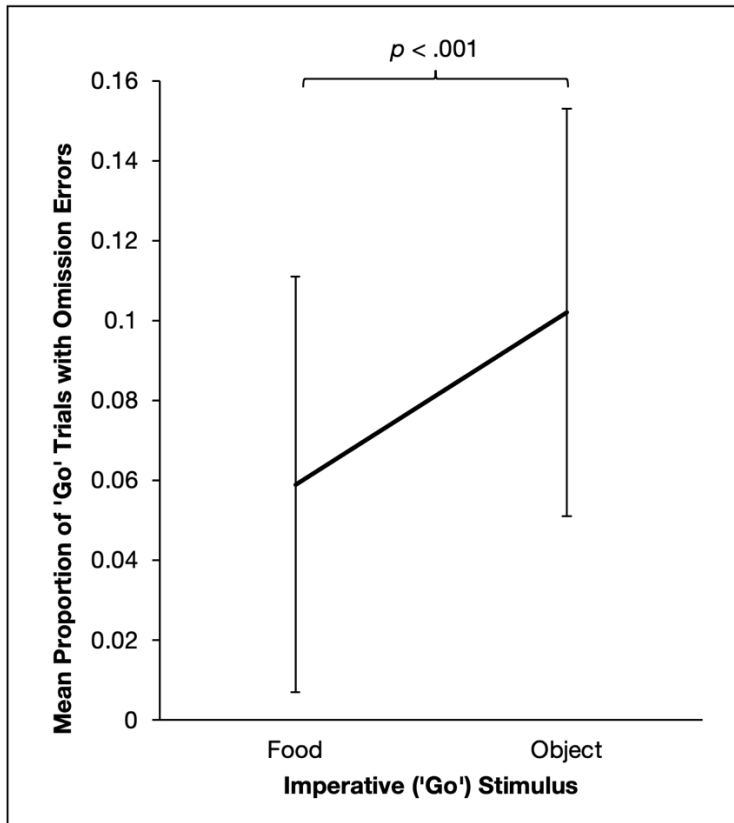
Abbreviations: ANOVA, analysis of variance; AST, affective shifting task; RT, reaction time.

Linear mixed-effects models were performed for reaction time outcomes in either task to assess the impact on the significance of interactive effects after accounting for a possible subject-level random effect and after using all available individual trial data; however, results of linear mixed-effects models were supportive of the main analyses (results not shown).

4.4.2 Proportion of ‘Go’ Trials with Omission Errors

A three-way mixed ANOVA was conducted to assess the effects of study group, block difficulty, and imperative stimulus type on the proportion of ‘go’ trials with omission errors in the AST. Two extreme outliers were identified via visual boxplot inspection in case group data in the object/shift block condition that could not be improved through data transformation. Outliers were retained in the analysis due to small sample size. Outcome data were predominantly normally distributed, as assessed by Shapiro-Wilk’s test; however, the Shapiro-Wilk test was statistically significant in case group data in the object/shift block condition ($p = .04$) and in control group data in the food/non-shift block condition ($p = .04$). Normality of the data did not improve after applying data transformations. There was homogeneity of variances, as assessed by Levene’s test ($p > .05$). There was no statistically significant three-way interaction between study group, block difficulty and imperative stimulus, $F(1, 13) = 0.06, p = .81$, partial $\eta^2 = .01$. There were also no statistically significant two-way interactions between study group and block difficulty, $F(1, 13) = 4.49, p = .054$, partial $\eta^2 = .26$, study group and imperative stimulus, $F(1, 13) = 0.96, p = .34$, partial $\eta^2 = .07$, and block difficulty and imperative stimulus, $F(1, 13) = 1.01, p = .33$, partial $\eta^2 = .07$. There was a statistically significant main effect of imperative stimulus type on the mean proportion of ‘go’ trials coded as omission errors, $F(1, 13) = 27.39, p < .001$, partial $\eta^2 = .68$. That is, a significantly greater percentage of ‘go’ trials with omission errors were identified in blocks where the imperative stimulus was an object, at 10.2 ± 5.1 percent, compared to where the imperative stimulus was a food, at 5.9 ± 5.2 percent (**Figure 13**). The remaining main effects of group and block difficulty were not significant.

Figure 13. Mean proportion of 'go' trials with omission errors in the affective shifting task as a function of imperative stimulus type.



Note. Error bar represents standard deviation (SD). A 2x2x2 mixed ANOVA assessing the effect of study group, block difficulty, and imperative stimulus type on the proportion of 'go' trials with omission errors in the AST revealed no significant interactive effects but a statistically significant main effect of imperative stimulus type on the mean proportion of 'go' trials with omission errors, $F(1, 13) = 27.39, p < .001$, partial $\eta^2 = .68$. On average, omission errors were made in 5.9 (SD 5.2) percent of 'go' trials in food blocks as opposed to 10.2 (SD 5.1) percent in object blocks. The main effects of study group and block difficulty were not significant.

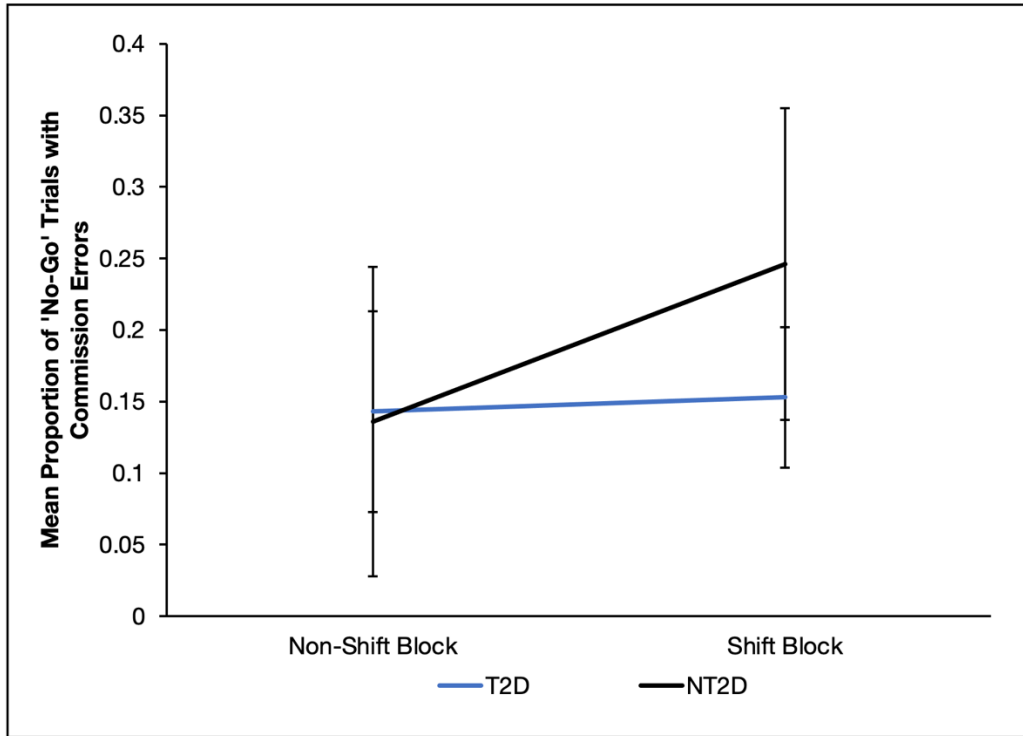
Abbreviations: ANOVA, analysis of variance; AST, affective shifting task.

4.4.3 Proportion of 'No-Go' Trials with Commission Errors

A three-way mixed ANOVA was conducted to assess the effects of study group, block difficulty, and imperative stimulus type on the proportion of 'no-go' trials with commission errors in the AST. One extreme outlier was identified via visual boxplot inspection in case group data and another in control group data from the object and non-shift block condition that could not be improved through data transformation. Outliers were kept in the analysis. Commission error trial

proportion data were predominantly normally distributed, as assessed by Shapiro-Wilk's test; however, the Shapiro-Wilk test was statistically significant in control group data across non-shift blocks where the imperative stimulus was an object ($p = .001$) and where it was a food ($p = .03$). Normality of the data did not improve after applying data transformations. There was homogeneity of variances, as assessed by Levene's test ($p > .05$). There was no statistically significant three-way interaction between study group, block difficulty and imperative stimulus, $F(1, 13) = 0.10$, $p = .76$, partial $\eta^2 = .01$. There were no statistically significant two-way interactions between study group and imperative stimulus, $F(1, 13) = 0.13$, $p = .73$, partial $\eta^2 = .01$, and block difficulty and imperative stimulus, $F(1, 13) = 3.42$, $p = .09$, partial $\eta^2 = .21$. There was a statistically significant two-way interaction between study group and block difficulty, $F(1, 13) = 10.65$, $p < .01$, partial $\eta^2 = .45$. Investigation of the interaction effect revealed that, in the control group only, there was a significantly higher mean proportion of 'no-go' trials with commission errors in shift blocks compared to non-shift blocks, $t(9) = -5.42$, $p < .001$, $d = 1.71$ (**Figure 14**), representing a large effect size (Cohen, 1988). However, there was no statistically significant difference in mean proportion of 'no-go' trials with commission errors between shift and non-shift blocks in the case group, $t(4) = -0.75$, $p = .50$. The main effect of imperative stimulus type on the outcome was not statistically significant, $F(1, 13) = 3.88$, $p = .07$, partial $\eta^2 = .23$.

Figure 14. Mean proportion of 'no-go' trials with commission errors in the affective shifting task by study group as a function of block difficulty.



Note. Error bar represents standard deviation (SD). A 2x2x2 mixed ANOVA assessing the effect of study group, block difficulty, and imperative stimulus type on the proportion of 'no-go' trials with commission errors in the AST revealed a significant two-way interaction between study group and block difficulty, $F(1, 13) = 10.65, p < .01$, partial $\eta^2 = .45$. In the control group, the proportion of 'no-go' trials with commission errors was significantly higher in shift blocks (24.6 [SD 10.9] percent) compared to non-shift blocks (13.6 [SD 10.8] percent), $t(9) = -5.42, p < .001, d = 1.71$. In the case group, on average, the outcome was not significantly different between the shift and non-shift block conditions, $t(4) = -0.75, p = .50$. No other interactive or main effects were statistically significant ($p > .05$).

Abbreviations: ANOVA, analysis of variance; AST, affective shifting task; NT2D, no type 2 diabetes (control group); T2D, type 2 diabetes (case group).

Chapter 5: Discussion

This thesis project analyzed data collected as part of the larger CPAT2D study. In response to preliminary reports of significant associations between T2D and brain structural findings on MRI such as neuronal atrophy or reduced microstructural integrity in adolescents, independent of weight status (Yau et al., 2010), this project endeavored to compare performance between adolescents with T2D and obesity (case participants) and adolescents with obesity but without T2D (control participants) on two neuromotor cognitive tasks. This was the first investigation of cognitive performance in adolescents with T2D to date to account for important potential confounding variables of age, sex, mean pubertal stage, and mean habitual evening sleep duration. While the present findings do not provide reliable evidence of a significant difference in cognitive performance between groups, the results displayed in this thesis were based on data from a preliminary sample of participants and will therefore need to be confirmed once the intended sample size for the study is reached.

5.1 Description of the Comparison Groups

The case and control groups did not significantly differ in the vast majority of descriptive variables collected during the study, highlighting the strength of the chosen comparison group. Successful matching on intended variables was indicated by statistical similarities across groups in age, biological sex, mean pubertal stage and mean habitual sleep duration. HbA1c percentage was significantly lower in the control group compared to the case group, reflecting an anticipated difference in glycemic control exhibited by adolescents with compared to without diagnosed T2D.

Proxy-reported socioeconomic status was not very low in either group, yet low socioeconomic status is associated with T2D (Copeland et al., 2011) and obesity (Janssen, Boyce, Simpson, & Pickett, 2006) in adolescents. However, the participants in this study were exclusively

recruited from the Ottawa area (National Capital Region), which may have resulted in a higher socioeconomic status in our sample than expected. As well, the proxy measure of socioeconomic status does not take into account family structure (e.g., single- vs. dual-income household) or household income, which may mean that socioeconomic status has been overestimated in our sample. Self-reported quality of life in the sample was also not remarkably low; PedsQL score in each group was, on average, higher than 70, a proposed score cut-off for identifying children with reduced quality of life due to the presence of a major chronic health problem (Huang et al., 2009). However, some participants did score below 70 on the quality of life questionnaire. The fairly high prevalence rates of non-Caucasian ethnicity (60%) and family history of T2D (80%) among case participants in this study are consistent with other descriptions of adolescent samples with T2D (Copeland et al., 2011; Edelstein, 2019). In the control group, the high rate of Caucasian ethnicity (90%) is not necessarily representative of the general population of adolescents with obesity in Canada (Valera, Sohani, Rana, Poirier, & Anand, 2015), and is representative of only a subset of SMART2D study participants.

On average, objectively measured habitual sleep duration of case and control participants over a 7-night period was less than 8 hours, the lower limit of sleep duration recommended for children in this age group (Tremblay et al., 2016). Participants from either group reported extremely high amounts of screen time, in excess of nearly 14 hours on an average weekday and 18 hours on an average weekend day; these numbers are likely inaccurate due to over-estimation of time spent on different screen activities or redundant reporting of screen time across multiple survey items. The results nevertheless suggest that adolescents in this sample are not meeting their maximum recommended level of daily recreational screen time of 2 hours (Tremblay et al., 2016). Finally, a majority of participants (53%) reported engaging in less than 10 minutes of physical

activity per day, where 60 minutes of daily moderate-to-vigorous physical activity are recommended for children (Tremblay et al., 2016).

Evidently, the participants in this study may not be meeting movement behaviour guidelines for their age group. Other studies have reported low rates of adherence to movement behaviour guidelines among Canadian children (Janssen, Roberts, & Thompson, 2017; Michaud & Chaput, 2016). However, participants' movement behaviours could also have been negatively impacted by public health measures implemented to slow transmission of illness during the COVID-19 pandemic (Moore et al., 2021). This is particularly true for case participants, all of whom were recruited following the onset of the pandemic. Nonetheless, this finding underlines the importance of targeting multiple modifiable health behaviours, such as sleep, physical activity and time spent in sedentary activities, for health promotion in this population.

Body mass index percentile and fat-mass percentage were, on average, statistically significantly higher in the control group compared to the case group, despite an inclusion criterium for the study specifying BMI percentile ≥ 97 for age and sex. Indeed, participants were recruited if they had a diagnosis of obesity in the medical chart based on most recent weigh-in information. However, participants with T2D were receiving not only pharmacological treatment for diabetes, but other interventions, such as nutritional diabetes education, which could have contributed to a different body weight and composition by the time of their enrolment into the study. Consequently, two case participants had BMI percentiles less than 97, but mean BMI percentile was above 97 in either study group.

5.2 Motor Preparation

The first objective of this project was to compare mean premotor RT in a simple RT task with an auditory imperative stimulus (SAS or control auditory stimulus) between participant groups as an indicator of motor preparation ability. We hypothesized that, on average, case participants overall would exhibit decreased motor preparation ability than control participants, as indicated by significantly longer premotor RT in the simple RT task.

However, the results of three-way mixed ANOVA revealed no statistically significant interactive effects involving study group, eye condition, or auditory stimulus type on premotor RT in zero-error trials of the task. The only statistically significant main effect found was that of auditory stimulus type; on average, participants exhibited significantly faster premotor RT when responding to a SAS as opposed to a control auditory stimulus. This result was expected, despite a SAS being used for the first time to study motor preparation in adolescents with obesity and T2D, as the SAS is known to trigger involuntary release of a prepared motor movement at a very short latency (Valls-Solé et al., 1999). The StartReact effect has been replicated several times, despite methodological variations between studies (Carlsen, Chua, Inglis, Sanderson, & Franks, 2004, 2009; Maslovat et al., 2015; Siegmund, Timothy Inglis, & Sanderson, 2001). Had mean premotor RT values been statistically comparable between SAS and control trials, this could have been suggestive of participants not preparing the target motor response ahead of delivery of the imperative stimulus. The finding of a significant effect of auditory stimulus type in the anticipated direction provides reassurance that motor preparation was being measured throughout the task.

While no significant main effect of study group on premotor RT was found, this result should be interpreted with caution as the intended sample size for the study has not been reached.

Therefore, the study could be presently underpowered to detect significant differences in certain comparisons (see **Section 5.4**).

5.3 Executive Functioning

The second objective was to compare groups on three indicators of executive functioning in an AST, a go/no-go paradigm based task with a visual imperative stimulus that switches between an object image or a food image. We hypothesized that, on average, case participants overall would exhibit decreased executive functioning ability than control participants, as indicated by significantly longer ‘go’ trial premotor RT as well as significantly higher proportions of ‘go’ trials with omission errors and ‘no-go’ trials with commission errors.

5.3.1 Premotor RT in ‘Go’ Trials

Three-way mixed ANOVA did not reveal a statistically significant difference between study groups in premotor RT in ‘go’ trials. However, there was a statistically significant main effect of block difficulty on this outcome. Mean premotor RT was significantly faster in non-shift blocks, where the imperative stimulus was unchanged from the previous block, than in shift blocks, where the imperative stimulus had recently switched. This is unsurprising, as shift blocks are designed to be more challenging by requiring participants to reverse stimulus-response associations they developed in the previous block for optimal task completion (Meule, 2017). In contrast, other studies that assessed the impact of block difficulty on RT in a very similar food-related AST administered to female university students from Germany with normal weight reported no significant differences in RT in shift compared to non-shift blocks (Meule & Kübler, 2014; Meule, Lutz, Krawietz, et al., 2014). There could be several reasons for this, such as

methodological differences (our use of EMG to detect premotor RT rather than a button press to detect movement RT, or the significantly longer duration of our task, that enabled us to collect data from more movement trials) or the use of an adolescent population with obesity and/or T2D in our study.

Additionally, the imperative stimulus type in the task statistically significantly impacted premotor RT in ‘go’ trials; on average, faster premotor RT in ‘go’ trials was observed in response to food compared to object pictures. A possible explanation for this finding could be that the salient stimulus of food in this task is more appealing than the neutral object stimulus to participants, and thereby can impact performance parameters on the AST. Meule *et al.* tested this hypothesis in female university students that completed a food-related AST; as predicted, the study reported significantly faster reaction times in response to food compared to neutral pictures (Meule, Lutz, Krawietz, et al., 2014). Another study examined RT in a go/no-go task that used food-associated and object words between a group of adult participants with obesity and age- and gender-matched healthy control participants. Regardless of weight status, the participants exhibited significantly faster RTs in response to food-related ‘go’ stimuli (Loeber et al., 2012). While subject to change, our finding of slower premotor RT in response to neutral (object) stimuli currently aligns with existing evidence in adults that used a similar task. We comment further on the impact of imperative stimulus type on AST performance in **Section 5.3.4**.

5.3.2 Proportion of ‘Go’ Trials with Omission Errors

Three-way mixed ANOVA did not reveal a statistically significant difference between groups in the proportion of ‘go’ trials with an omission error. However, there was a statistically significant main effect of imperative stimulus type on the outcome. Specifically, on average,

participants omitted to execute ‘go’ responses significantly more in response to object compared to food pictures. This finding is in line with the report by Meule *et al.* of a higher number of omission errors made in response to neutral compared to food targets in a similar AST (Meule, Lutz, Krawietz, et al., 2014) and potentially reflects a difference in the amount of attention (Meule, 2017) that participants give to the two types of imperative stimuli in the task.

There was no significant main effect of block difficulty on the proportion of omission error ‘go’ trials, possibly related to the effect of block difficulty on premotor RT in the same task. If participants took longer to enact a motor response in ‘go’ trials during shift blocks, perhaps added time was spent on target discrimination or decision-making, in turn helping lower the amount of omission errors made in ‘go’ trials of shift blocks. In one of the studies by Meule *et al.*, the opposite was observed: reaction time was not significantly different between shift and non-shift blocks, but omission errors were made more often in shift blocks than in non-shift blocks (Meule, Lutz, Krawietz, et al., 2014). These results along with our own highlight the usefulness of examining multiple performance outcomes in an AST, as participants may prioritize a certain strategy of dealing with task demands (Meule, 2017).

5.3.3 Proportion of ‘No-Go’ Trials with Commission Errors

While this could be an artifact of small sample size, there was a statistically significant two-way interaction effect between group and block difficulty on the proportion of ‘no-go’ trials with a commission error. Investigation of the interaction revealed that statistically significantly more commission errors were made in ‘no-go’ trials during shift blocks compared to non-shift blocks, but this was only true for the control group. As mentioned earlier, increased difficulty associated with the shift block condition could reasonably encourage a greater number of

commission errors to be made. However, more participants need to be recruited to understand whether significant group differences exist related to this task outcome.

Based on findings that premotor RT and the proportion of ‘go’ trials with an omission error were significantly lower in response to food pictures compared to object pictures, imperative stimulus type might also have been expected to impact the proportion of ‘no-go’ trials with a commission error. However, our preliminary results suggest that, while more commission errors were made, on average, when the *distractor* stimulus was food, the main effect of imperative stimulus type on this outcome was *nearly* statistically significant ($p = .07$). In other studies that used an AST in adults, results related to the number of commission errors made in response to food or neutral stimuli are mixed: one study reported no main effect of target type on commission errors (Meule & Kübler, 2014), but another reported that significantly more commission errors were made in response to a food compared to an object distractor stimulus (Meule, Lutz, Krawietz, et al., 2014). The effect of imperative stimulus type on the amount of commission errors made by participants in this study could become significant with greater sample size.

While performance outcomes on the AST provide general insight into participants’ executive functioning, it has been posited that the number of commission errors made in an AST specifically could reflect behavioural inhibition ability, a component of executive function (Meule, 2017). Therefore, the possibility that commission error count on an AST correlates with certain eating behaviours is under investigation. Interestingly, one observational study has reported that decreased ability to inhibit a motor response to a food stimulus in an AST is associated with higher scores on a validated questionnaire measuring momentary food cravings (Food Cravings Questionnaire – State Version), especially on subscales related to desire for food or lack of control over food consumption (Meule, Lutz, Vögele, & Kübler, 2014). More evidence is needed to

understand if performance on an AST relates to specific behaviours, such as certain eating behaviours, outside of the task setting. However, future research in this field will expand interpretations that can be made from performance on neuromotor cognitive tasks like the AST. Interestingly, in our study, case and control participants did not significantly differ in self-reported eating behaviours (R18-TFEQ) and no reliable between-group differences in AST performance have thus far been found.

5.3.4 Imperative Stimulus Type and Performance on the Affective Shifting Task

As mentioned earlier, the finding of an impact of stimulus type on performance outcomes in the AST could be the result of increased affinity or attention toward food, the more salient of the two task stimuli that is also associated with survival. If this were indeed the case, *and* if evidence from an AST suggested that food cues were more easily recognized than neutral cues by our sample of adolescents, this would reaffirm the importance of including interventions targeting diet in the treatment of pediatric obesity or T2D. Such interventions could take the form of personalized nutritional education or counselling about healthy eating attitudes or behaviours; interventions that also aim to change the family's lifestyle habits, or at minimum encourage familial support for behaviour change, might have added effectiveness in this population (Pinhas-Hamiel et al., 1999).

A category effect has also been proposed as a possible explanation for an observed difference in AST performance based on stimulus type, as the object category may be more broad than the food category in the task (Meule, Lutz, Vögele, et al., 2014). Loeber *et al.* attempted to address this effect by using a more narrow category of objects in the AST, such as different articles of clothing; however, in their study, significantly more commission errors were still made in

response to food distractor stimuli, and more omission errors were made in response to clothing items in a subset of hungry participants, but reaction time was not among the task outcomes assessed (Loeber, Grosshans, Herpertz, Kiefer, & Herpertz, 2013).

5.4 General Interpretation

Overall, no statistically significant differences have yet been found between case and control groups in performance on the simple RT task (motor preparation ability) or the AST (executive functioning). This is despite results from studies showing significant associations between T2D and negative features on MRI brain scans, such as volumetric reductions in brain tissue and reduced microstructural integrity of white matter (Yau et al., 2010), and cognitive performance (Brady et al., 2017), in adolescents. Importantly, the results presented in this thesis also do not provide reliable evidence of a *lack* of difference in cognitive performance between adolescents with and without T2D. Due to the small size of this preliminary sample of study participants, the study is not yet sufficiently powered to be able to detect significant differences in the desired data comparisons.

The case participants enrolled in our study to date do not have remarkably lower mean T2D duration or hemoglobin A1c than those in most existing studies of cognitive performance or brain structure in adolescents with T2D (Brady et al., 2017; Bruehl et al., 2011; Nouwen et al., 2017; Yau et al., 2010) that might otherwise contribute to a lack of group differences in cognitive task performance indicators. Also, our control group did not have insulin resistance as determined using an oral glucose tolerance test (results not shown), which has also been associated with smaller hippocampal volume and frontal lobe atrophy on MRI in adolescents (Ursache, Wedin, Tirsi, & Convit, 2012); this is similar to other studies that used control groups either without insulin

resistance or with significantly lower insulin resistance (Bruehl et al., 2011; Nouwen et al., 2017; Yau et al., 2010). Based on these observations, group differences may still become statistically significant upon attainment of the full sample.

If insignificant group differences were to persist, however, we could consider what other factors might have an impact on the results. Perhaps the groups are at comparable risk of reduced cognitive performance due to a shared characteristic that may be a stronger predictor of cognitive health than T2D, such as obesity (Liang et al., 2014); for this possibility to be addressed, another adolescent comparison group without obesity or other chronic disease is needed, which is another aim under the CPAT2D study. Also, during this study, case group adherence to T2D-related medication was very high, but may not reflect a realistic level of medication adherence in teens with T2D, raising the question of whether good medication adherence could have a protective effect on cognitive function in this population. In this vein, Brady *et al.* do not appear to have encouraged medication adherence in their protocol, but report significantly worse performance of adolescents with T2D on certain cognitive assessments they administered compared to adolescents without T2D (Brady et al., 2017).

5.5 Strengths and Limitations

Generalizability of these results, especially before the target sample size is achieved, is very limited. As this is an observational study, temporality between T2D diagnosis and any associated deficit in cognitive performance cannot be assessed. Thus, any significant difference between groups in the measured outcomes cannot be attributed to disease status. If a reliable association between T2D and poorer cognitive performance in adolescents becomes established in the literature, future research should aim to determine when cognitive dysfunction typically

emerges relative to disease diagnosis, or identify the strongest predictors of cognitive dysfunction, in adolescents with T2D. The study is also subject to selection bias as participants were not randomly selected from the population. However, these are expected limitations of studying a rare disease using an observational study.

We experienced prominent barriers to participant recruitment, which did not allow for the intended group sample sizes to be achieved. The COVID-19 pandemic paused in-person research operations at CHEO for an extended period of time, directly impacting recruitment. For a pediatric population with T2D, who may be part of a multigenerational household or have family members with a chronic disease, including T2D, the COVID-19 pandemic could have impacted their willingness to volunteer for a research study. These challenges compound the existing barrier to recruitment of pediatric T2D being a relatively rare disease. Nonetheless, given that approximately 70% of participants contacted to participate in the CPAT2D were successfully enrolled, we are optimistic that, with continued recruitment, the target sample size can be achieved.

There were also notable strengths of this study. Primarily, we add to very limited literature regarding cognitive performance in adolescents with T2D, providing the first assessment of cognitive function using *objective* performance indicators on neuromotor tasks between adolescents with and without T2D while accounting for weight status, sex, pubertal stage and sleep duration. We also provide an extensive description of the sample of adolescents analyzed in the study. Objective measurement of sleep-related variables using wrist actigraphy, including the matching variable of sleep duration, is another important strength of this study.

5.6 Key Points

- Early findings from the CPAT2D study using pilot data from a preliminary sample of adolescents with obesity do not suggest that there are any statistically significant differences between adolescents with and without T2D in performance on neuromotor cognitive tasks measuring motor preparation and executive functioning. However, these results may change when the intended sample size of the study is reached.
- In an affective shifting task, adolescents were less likely to omit *and* were more quick to initiate a target motor response when presented with a food compared to an object picture as the imperative stimulus, suggesting that they may recognize food cues more easily. This effect must be confirmed in a full sample and its implications outside of the task setting are not known. However, it is an interesting finding in adolescents with obesity and/or T2D, for whom diet is an important tool for weight management and glycemic control.
- The majority of adolescents in this sample exhibited lower objectively-measured sleep duration and self-reported daily minutes of physical activity, as well as much higher self-reported daily recreational screen time, than recommended for this age group based on the Canadian 24-Hour Movement Guidelines.

5.7 Conclusion

As part of the larger CPAT2D study, this research project aimed to investigate the association between cognitive performance and T2D in adolescents with obesity. Preliminary data do not suggest that adolescents with diagnosed T2D perform significantly differently on neuromotor cognitive tasks assessing executive functioning and motor preparation than adolescents without T2D. However, these results will be updated once the target sample for the

CPAT2D study is recruited. Addressing the evidence gap related to cognitive performance in adolescents with T2D remains necessary and will inform the need for tools to screen for or prevent against cognitive dysfunction in this population. Until then, clinical monitoring of cognitive function in adolescents with T2D could take the simple form of asking how school is going and how much of a challenge it is to keep up with class material and workload.

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APPENDICES

Appendix A: CHEO REB Approval Letter

From: nanderson@cheo.on.ca <nanderson@cheo.on.ca>
Sent: Thursday, October 8, 2020 9:48 AM
To: Chaput, Jean-Philippe
Cc: Anderson, Natalie
Subject: REB Protocol No 20/102X - Final Approval - Delegated Review

EXTERNAL MAIL*



CHEO Research Ethics Board Approval - Delegated Review

REB Protocol No: 20/102X

ROMEO File No: 20200433

Principal Investigator: Dr. Jean-Philippe Chaput

Project Title: CHEOREB# 20/102X - Cognitive Performance in Adolescents with Type 2 Diabetes (CPAT2D) study: Association between sleep duration and cognitive performance in adolescents with type 2 diabetes and those without

Protocol Status: Active

Approval Date*: October 08, 2020

Approval Expiry Date:** September 15, 2021

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Recruitment Materials	Recruitment Poster	2020/09/09
Recruitment Materials	Recruitment Social Media Version 2	2020/10/05
Other Document	Appendix A_CPAT2D_Safety Protocol	2020/10/05
Protocol	Protocol_CPAT2D	2020/10/05
Assent Form	CPAT2D Study Assent Form	2020/10/05
Consent Form	CPAT2D_Informed Consent	2020/10/05

Documents Reviewed & Acknowledged:

Document Name	Comments	Version Date
Other Document	OCSB Community Involvement Form - CPAT2D	2020/10/08
Other Document	OCSB Community Involvement Activity Record Form_CPAT2D	2020/10/08
Questionnaire/Survey	Questionnaire - Strength & Difficulties (SDQ)	2020/09/09
Questionnaire/Survey	Questionnaire - Pittsburgh Sleep Quality Index (PSQI)	2020/09/09
Questionnaire/Survey	Questionnaire - Severity Measure for Depression (Child age 11-17)	2020/09/09
Questionnaire/Survey	Questionnaire - Pediatric Quality of Life (PedsQL)	2020/09/09
Questionnaire/Survey	Questionnaire - Positive And Negative Affect Schedule (PANAS)	2020/09/09
Questionnaire/Survey	Questionnaire - Epworth Sleepiness Scale	2020/09/09
Questionnaire/Survey	CPAT2D_FoodScreeningAST Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_PubertalQuestionnaire_MALE Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_PubertalQuestionnaire_Female Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_Screen Time and Sedentary Behaviour Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_Sleep Log Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_ThreeFactorEating Version 2	2020/10/05
Questionnaire/Survey	CPAT2D_VAS Version 2	2020/10/05

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed within the delegated stream, which is reserved for projects that involve no more than minimal risk to human participants.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding the ethical conduct of research with humans, as applicable to the research project.
3. Investigators must obtain annual renewal approval prior to the expiry date stated above.
4. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review and approval.
5. The investigator must, prior to use, obtain approval from the Board for changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
6. Investigators must obtain approval from the Board of French version(s) of the consent/assent form(s), unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
7. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs) or unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
8. For SAE reports on clinical drug trials, the investigator must also comply with the hospital-wide Policy regarding, Procedures for Considering Medical Error in the Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial.
9. Investigators must promptly report to the REB any new information regarding the safety of research subjects (e.g., changes to the product monograph or investigator's brochure of drug trials). Where available, any reports produced by the Data Safety Monitoring Board should also be promptly submitted to the REB for acknowledgement.
10. Investigators must notify the REB of any change in study status (closed to accrual, temporary, premature or permanent).
11. Investigators must submit a study closure event form at the conclusion of the study.

If you have any questions, pertaining to this letter, please contact the Research Ethics Board Office.

Regards,

Cécile Bensimon, MA, PhD
Chair, Research Ethics Board
Président, Comité d'éthique de la recherche

* The final approval date for initial delegated study applications approved with or without modifications will be the date the REB has determined that the conditions of approval have been satisfied.

** The expiry date of REB approval for initial study applications will be as follows:

- If the date of approval was **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date of review and approval by the Chair and/or delegate *in the following year*;
- If the date of review and approval was **after** the 15th of the month, the expiry date will be the 15th of the month in which the date of review and approval by the REB *in the following year*.

Appendix B: University of Ottawa REB Approval Letter

03/08/2021

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

Lettre d'approbation administrative | Letter of administrative approval

Numéro de dossier / Ethics File Number

H-07-21-7183

Titre du projet / Project Title

Cognitive Performance in
Adolescents with Type 2
Diabetes (CPAT2D): Association
Between Sleep Duration and
Cognitive Performance in
Adolescents with Type 2
Diabetes and Those
Without (CHEO REB#20/102X)

Type de projet / Project Type

Autre / Other

CÉR primaire / Primary REB

CHEO / CHEO

Statut du projet / Project Status

Approuvé / Approved

Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)

03/08/2021

Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)

15/09/2021

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Caroline DUTIL	École des sciences de l'activité physique / School of Human Kinetics	Chercheur Principal / Principal Investigator
Jean-Philippe CHAPUT	Département de pédiatrie / Department of Pediatrics	Chercheur principal - site d'examen primaire / Primary review site PI
Anthony CARLSEN	École des sciences de l'activité physique / School of Human Kinetics	Co-superviseur / Co-supervisor
Stuart FOGEL	École de psychologie / School of Psychology	Collaborateur / Collaborator
Gary GOLDFIELD	Département de pédiatrie / Department of Pediatrics	Collaborateur / Collaborator
Irina PODINIC	Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health	Étudiant-chercheur / Student-researcher
Amelia EATON	École des sciences de l'activité physique / School of Human Kinetics	Étudiant-chercheur / Student-researcher

Conditions spéciales ou commentaires / Special conditions or comments:

CHEO REB Protocol No: 20/102X (PI: J.-P. Chaput)

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et

2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and

2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled «Special conditions or comments».

Catherine PAQUET

Directeur / Director

Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

Appendix C: NIH Blood Pressure Norms for *Boys* by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B-1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in table 3 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.

Appendix D: NIH Blood Pressure Norms for *Girls* by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B-1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in table 4 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.