Neuropsychological Functioning And Stress Reactivity

In Type 1 Diabetes Mellitus

by

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ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is a chronic disease that requires maintaining tight metabolic control through complex behavioral and pharmaceutical regimens. Subtle cognitive impairments and stress response dysregulation may partially account for problems negotiating life changes and maintaining treatment adherence among emerging adults. The current study examined whether young adults with T1DM physiologically respond to psychological stress in a dysregulated manner compared to non-diabetic peers, and if such individuals also demonstrated greater cognitive declines following psychological stress. Participants included 23 young adults with T1DM and 52 non-diabetic controls yoked to T1DM participants based on age, gender, ethnicity, participant education, and maternal education. Participants completed a laboratory-based social stressor, pre- and post-stressor neurocognitive testing, provided fingerstick blood spots (for glucose levels) and salivary samples (for cortisol levels) at five points across the protocol, and completed psychosocial questionnaires. Related measures ANOVAs were conducted to assess differences between T1DM participants and the average of yoked controls on cortisol and cognitive outcomes. Results demonstrated that differences in cortisol reactivity were dependent on T1DM participants' use of insulin pump therapy (IPT). T1DM participants not using IPT demonstrated elevated cortisol reactivity compared to matched controls. There was no difference in cortisol reactivity between the T1DM participants on IPT and matched controls. On the Stroop task, performance patterns did not differ between participants with T1DM not on IPT and matched controls. The performance of participants with T1DM on IPT slightly improved following the stressor and matched controls slightly worsened. On the Trail Making Test, the performance of participants with T1DM was not different following the stressor whereas participants without T1DM demonstrated a decline following the stressor. Participants with and without T1DM did not differ in patterns of performance on the Rey Verbal Learning Task, Sustained Attention Allocation Task, Controlled Oral Word Association Task, or overall cortisol output across participation. The results of this study are suggestive of an exaggerated cortisol response to psychological stress in T1DM and indicate potential direct and indirect protective influences of IPT.

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Type 1 Diabetes Mellitus (T1DM) is a chronic disease, usually diagnosed in childhood and adolescence, involving the inability to produce insulin, which leads to elevated blood glucose and impairment in nutrient utilization despite elevated glucose levels. When untreated or inadequately controlled, T1DM results in numerous immediate and long-term health problems including coma and death (Peyrot, McMurry, & Kruger, 1999). Avoidance of long-term complications involves maintaining tight blood glucose control through complex behavioral and pharmaceutical regimens.

Emerging adulthood, considered to span the ages of 18-30, is a key developmental period during which adolescents assume increasingly greater independence and responsibility of everyday demands as they transition into adulthood (Arnett, 2000). This transitional period is of particular concern for patients with T1DM who must cope with normative developmental challenges while simultaneously assuming relatively independent treatment responsibility and managing transitions to from pediatric to adult care (for a review of emerging adulthood challenges specific to T1DM see Garvey, Markowitz, & Laffel, 2012). The transition to adult care is viewed as a risky period for young adults with T1DM, characterized by the American Diabetes Association as “a perfect storm during which interruption of care is likely,” placing those who experience disruptions at greater risk for lack of medical follow-up in adulthood (Peters, Laffel, & The American Diabetes Association Transitions Working Group, 2011). An earlier age at which transition to adult care occurs is associated with poorer metabolic control, which may reflect differences in treatment approaches such as less integration of services within adult care (Helgeson et al., 2013). Emerging adulthood is also period of engagement in an array of poor health behaviors (e.g., increased alcohol consumption, smoking, disturbed sleep patterns) and increased risk-taking which occur at similar levels among young adults with and without T1DM despite worse relative consequences for such behaviors for those with T1DM (Palladino et al., 2013). Blood glucose control tends to deteriorate across this period, with poor glycemic control peeking at approximately 18-19 years of age (Bryden et al., 2001). This transitional time is a period of increased risk of morbidity and mortality for individuals with T1DM due to increased acute complications associated with hypoglycemia and ketoacidosis (for a review see Weissberg-

Benchell, Wolpert, & Anderson, 2007). College life appears to place specific demands on young adults with T1DM, which are perceived as interfering in their ability to manage blood glucose levels including: adhering to diet regimens, irregular schedules, lack of parental involvement, peer pressure, drugs and alcohol, fear of hypoglycemia, and limited finances (Ramchandani et al., 2000); however, the increase in demands and stressors may be only partly to blame for the lack of adequate glycemic control observed during this transitional period.

Previous research has examined how disease-related features (e.g., disease duration, age of onset, number of episodes of hypoglycemia) can influence the development of mild cognitive impairments in individuals with T1DM (Gaudieri, Chen, Greer, & Holmes, 2008). While the extent of such impairments should not be overstated, even mild impairments are likely to negatively influence the health outcomes of patients with T1DM as maintaining good blood glucose control is dependent on a dynamic and complex set of behavioral and pharmaceutical regimens (Boyle & Zrebiec, 2007). Moreover, patients with T1DM must be able to navigate medical decision trees (e.g., which treatment choice to use when responding to a given blood glucose reading) often while under stress (e.g., episodes of hypoglycemia can be both a psychological stressor as well as triggering a physiological stress response).

In non-diabetic populations, acute psychological stressors have been demonstrated to impair specific cognitive processes (e.g., Kuhlmann, Piel, Wolf, 2005). Based on the physiological processes underlying T1DM, there is a theoretical argument that such patients are likely to develop a dysregulated physiological stress response, which a handful of studies have begun to demonstrate empirically (Delamater et al., 1988; Dutour, Dadoun, Feissel, Atlan, & Oliver, 1996; Wiesli et al., 2005). One might expect that a dysregulated stress response would further impair cognitive processes during episodes of acute stress in a patient population already at-risk for mild cognitive impairments.

The introduction that follows is divided into a number of sections to examine each of these aspects (i.e., T1DM pathophysiology, cognitive impairments, and stress response dysregulation) separately and provide a rationale for how the stress response may influence cognition in T1DM. To illustrate the complexities of successful disease management, I will begin

with an introduction of T1DM pathophysiology and how inherent alterations in normal physiological processes can undermine successful blood glucose control for young adults with T1DM. The second section will review research concerning observed cognitive impairments in patients with T1DM, previously identified risk factors for such impairments, and how these impairments may interfere with disease management. The third section will focus on one specific aspect of disease-related dysregulation—the physiological stress response—and how this may influence cognition and blood glucose levels in T1DM. The final section will introduce the current study, which will examine how the physiological stress response may become dysregulated in patients with T1DM, and how such dysregulation may negatively influence cognitive processes during stressful events.

Type 1 Diabetes Mellitus

Type I Diabetes Mellitus (T1DM) is an autoimmune disorder that results from the destruction of insulin-releasing ß-cells of the pancreas. Under normal conditions, when blood glucose levels increase, after eating carbohydrates for example, the ß-cells release insulin, which allows cells to absorb glucose, which in turn reduces levels of plasma glucose. Likewise, when healthy individuals experience episodes of hypoglycemia (lower blood glucose levels), insulin levels are suppressed and glucagon is secreted from the pancreatic α-cells, which acts to stimulate glucose production. Under normal functioning, blood glucose levels are tightly controlled by the integrated actions of the α-cells and ß-cells. Further, in healthy individuals episodes of hypoglycemia trigger a physiological stress response, which results in counter regulatory hormones including, epinephrine release (and cortisol if the hypoglycemic episode is prolonged), resulting in an increase in blood glucose levels. Individuals with T1DM lose the feedback control provided by endogenous insulin as well as the control of the glucagon response, which is typically lost between 1 and 5 years after disease onset (Weinger & Jacobson, 1998). This means that patients with T1DM must rely on the epinephrine response to counter-act episodes of hypoglycemia, and for many patients this response becomes attenuated over time (for reviews see Boyle & Zrebiec, 2007; Cryer, 2002; 2009; Weinger & Jacobson, 1998).

Without the use of exogenous insulin, individuals with T1DM will experience uncontrolled elevated levels of blood glucose, which will eventually result in keto-acidotic coma and death if intervention is not initiated. Long-term glucose elevations in poorly controlled diabetes can lead to numerous health complications including heart attack, stroke, gangrene in lower extremities, kidney failure, neuropathy, and blindness (Peyrot et al., 1999, Tomlinson & Gardiner, 2008). Importantly, such health risks can be largely avoided by maintaining near-normal levels of blood glucose (Diabetes Control and Complications Trial Research Group, 1993).

A complication in management of T1DM is that too much insulin, too little food, too much exercise, or a combination thereof can result in hypoglycemia, which can also result in numerous negative consequences including impaired cognition, brain damage, unconsciousness, and death (Boyle & Zrebiec, 2007). As such, the regular process of blood glucose must be tightly controlled through a complex regimen of blood glucose monitoring, insulin administration, and behavioral prescriptions. Moreover, variability in behaviors influencing blood glucose levels (e.g., diet, exercise, alcohol) necessitates close monitoring as well as thorough understanding of the interplay of factors influencing glucose levels and the various response options. Because there are multiple response options for a wide range of blood glucose readings, an individual must be able to determine the best response option for each set of differing circumstances. Therefore, successful management of T1DM not only involves proper medical education and adherence but also a complex set of cognitive abilities involved in navigating potential therapeutic options.

Maintaining tight glycemic control often involves frequent administration of insulin. One consequence of maintaining such tight control can be the recurrent experience of supraphysiological levels of insulin (elevated levels of insulin not reached within natural conditions), which results in hypoglycemia (Allen et al., 2001). Such episodes occur with relative frequency for individuals with T1DM. Specifically, such individuals have reported an average of one to two episodes per week and at least one severe episode per year, resulting in thousands of episodes of hypoglycemia over the lifespan (Cryer, Davis, & Shamoon, 2003; Diabetes Control and Complications Trial Research Group, 1993; MacLeod, Hepburn, & Frier, 1993). Alterations in behaviors prior to sleep that influence blood glucose levels can result in unnoticed episodes of

hypoglycemia during sleep (nocturnal hypoglycemia). Episodes of nocturnal hypoglycemia have been estimated to occur in 12 to 56% of patients enrolled in 11 clinical trials (Allen & Frier, 2003). Nocturnal hypoglycemia is especially dangerous in that both sympathetic response and hypoglycemia awareness are reduced during sleep so that a patient may be unable to respond or unaware of changes in blood glucose levels. As such, in order to avoid nocturnal hypoglycemia, a patient must be able to anticipate how his/her pre-bedtime behaviors may influence his/her nocturnal blood glucose levels.

As detailed above, T1DM represents a complex set of serious health concerns some of which stem from treatment. High quality long-term health requires balancing very tight glycemic control (thereby avoiding the health consequences of hyperglycemia) and limiting episodes of hypoglycemia (thereby avoiding the health consequences of hypoglycemia) (Cryer, 2002). Maintaining such a balance requires rigorous health care management that depends on numerous cognitive abilities such as adequate memory, attention, and responsive problem solving, and maintaining such abilities within highly stressful contexts such as during episodes of hypoglycemia. Unfortunately, such disease-management specific abilities may be hindered by disease-related cognitive impairments (Soutor, Chen, Streisand, Kaplowitz, & Holmes, 2004).

Cognitive Functioning in T1DM

Impaired cognitive functioning is a critical issue in adolescents and young adults with chronic illness, as these problems can impact academic functioning as well as disease management. The young adult population is a difficult population to classify in terms of existing research concerning cognitive impairments observed in individuals with T1DM. Specifically, research in this area is generally categorized as either “adult” (+18 years old) or “children/adolescent” (below 18 years old). While the period of young adulthood may be technically classified as “adult” (i.e., legally above the age of 18) such a category does not accurately depict the period of brain development specific to this age group. Such difficulty in categorization makes drawing inferences concerning deviations from normative cognitive development difficult. As such, the present paper will review both research conducted with

"adults" as well as "children/adolescents," with the acknowledgement that neither group accurately depicts the present population.

In a meta-analysis of cognitive impairments in adults with T1DM, Brands, Biessels, De Haan, Kappelle, & Kessels (2005) concluded that studies generally support the presence of mild to moderate cognitive impairments in patients with T1DM involving mental speed and flexibility compared to non-diabetic controls. More recently, the Diabetes Control and Complications Trial (DCCT, 2007) failed to observe declines in cognitive functions of 1144 patients with T1DM (age of study entry ranged from 13 to 39, M = 27, SD = 7) over an 18-year span, with the exception of reduced psychomotor efficiency in adults who had maintained higher glycated hemoglobin levels. However, this study did not include a non-diabetic control group so it is unclear how to describe participants' cognitive performance during study entry. Additionally, this sample was composed largely of adult patients (89%) with an average disease duration of 6 years, and very few were diagnosed at an early age (specific data regarding the age of diagnosis or percentage of sample with early disease onset was not provided). As such, comparisons of cognitive functioning between individuals diagnosed as children and as adults were not reported. The impact of T1DM and its associated treatments are likely to have differential impacts on early brain development compared to adult brain functioning, which limits the applicability of these findings to populations diagnosed at an early age.

Two recent meta-analyses concerning cognitive impairments in children and adolescents with T1DM have been performed. Gaudieri et al., (2008) examined 15 studies with individuals under the age of 18 (mean age for T1DM = 12.96, for Control groups = 12.55) from 1985-2008, which noted mild impairments in overall cognition, crystallized and fluid intelligence, psychomotor efficiency and motor speed, attention/executive functioning, academic achievement, and visual motor integration (effect sizes generally small). Across studies, heterogeneous definitions (e.g. age 4, 5, & 7) were used to operationalize "early-onset," so that Gaudieri et al. used a broad definition of diagnosis prior to age 7. Such "early-onset" patients were identified as more at-risk for cognitive impairments, which included other domains including verbal and visual learning and memory, and were characterized by moderate effect sizes. Additionally, Gaudieri et al. noted that

previous episodes of hypoglycemic seizures put individuals at a slighter greater risk for cognitive impairments, characterized by nominal to small effect sizes.

Naguib, Kulinskaya, Lomax, and Garralda (2009) examined 24 studies with individuals under the age of 19 (mean ages not provided) published between 1980 and 2005 with an overlap of 10 studies with Gaudieri et al. These studies noted mild impairments in overall IQ with impairments found in the domains of visuospatial ability, motor speed and writing, and sustained attention, reading, and verbal and performance IQ characterized by small effect sizes. Episodes of severe hypoglycemia were identified as a risk factor for more extensive impairments. This relationship between episodes of severe hypoglycemia and more extensive cognitive impairments was characterized by small effect sizes.

More recently, Lin, Northam, Rankins, Werther, and Cameron (2010) reported findings from a 12-year longitudinal study (Northam et al., 1998; 2001), which followed newly diagnosed children with T1DM. After two years, those children who had been diagnosed before age four demonstrated developmental delays. Specifically, their scores on the Wechler Vocabulary and Block Design subtests did not demonstrate developmental gains compared to healthy controls or children with later disease onset. At the 6-yr follow-up, all children with diabetes demonstrated worse performance compared to healthy controls across numerous domains including intelligence, attention, processing speed, long-term memory, and executive skills. At the 12-year follow-up, children with T1DM performed more poorly compared to healthy controls on measures of working memory. Moderate effect sizes were observed for the relationship between early disease onset and worse performance on tasks of associative learning (Glass's $\Delta \approx 0.6$), mental efficiency (Glass's $\Delta \approx 0.3$), divided (Glass's $\Delta \approx 0.5$) and sustained attention (Glass's $\Delta \approx 0.6$) (effect sizes reported in this document are approximations derived from a graphical display provided by Lin et al.). A history of severe hypoglycemic episodes (e.g., loss of consciousness or seizure) was associated with poorer verbal abilities (Glass's $\Delta \approx 0.65$), working memory (Glass's $\Delta \approx 0.8$), and non-verbal processing speed (Glass's $\Delta \approx 0.5$) whereas a history of hyperglycemia was associated with poorer working memory (no effect sizes reported). Additionally, children with multiple risk factors (early-onset, hypoglycemia, or hyperglycemia) performed worse on verbal

abilities, working memory, and mental efficiency, as compared to both healthy controls and children with one or zero risk factors. However, the degree to which multiple risk factors impacted these cognitive domains was not clear, as information regarding effect sizes was not provided.

The pathophysiological basis for reductions in cognitive abilities in individuals with T1DM is not completely understood or well researched. Various potential culprits have been suggested (e.g., early disease onset, hypoglycemia, hyperglycemia), which most likely differentially interact across developmental periods to induce cognitive deficits. Ryan (2006) argues that diabetes-associated chronic hyperglycemia occurring early during development adversely impacts normal brain maturation. Moreover, such an assault on central nervous system development reduces "brain reserve capacity [which serves] as a vulnerability factor for subsequent brain dysfunction" (p. 294, 2006). According to this hypothesis, children with early-onset diabetes are at heightened risk for deleterious effects of any future cerebral insult.

In addition to adversely impacting cognitive development, recurrent episodes of hypoglycemia are concerning because of the transient impact of hypoglycemia on cognitive functioning, which may take up to an hour to return to baseline (for reviews see Bade-White, & Obrzut, 2009; Warren & Frier, 2005). Such episodes may impair concurrent learning of new material as well as interfere in appropriate responding to the abnormal glucose levels.

Episodes of hypoglycemia are also physiological stressors in that such events trigger a physiological stress response. Likewise, supraphysiological levels of insulin act to stimulate a physiological stress response in healthy humans (Fruehwals-Schultes et al., 1999). As will be discussed below, repeated physiological stress activation can lead to dysregulation of the stress response that can lead to impairments in cognition and physiological and psychological health.

Stress

I have previously discussed some of the major points of pathophysiology inherent in T1DM and how these points of dysregulation have been postulated to impact cognitive impairments in T1DM. In this section, I will expand on one specific aspect of disease-related dysregulation—the physiological stress response—that represents an unexplored additional factor in understanding the development of such mild cognitive impairments.

Stress response. Stress has historically been defined as occurring when environmental demands exceed the resources and capacities of an individual (Cohen, Kessler, & Gordon, 1995). Such demands may be physiological, such as an episode of hypoglycemia, or psychological, such as a patient's perception that she feels ostracized due to her disease status. With regard to psychological stressors, Lazarus' cognitive appraisal model of stress asserts that the influence of a potential stressful event is determined more by the perception of that event rather than the event in question (Lazarus & Folkman, 1984). Regardless of the origin (physiological or psychological), stressors elicit a physiological stress response, which includes the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. The present paper will focus on the HPA-axis due to the more extensive literature concerning the HPA-axis and acute psychological laboratory stressors.

The hypothalamic-pituitary-adrenal (HPA) axis is a major stress system that coordinates the highly complex neuroendocrine cascade, which results from a physiological stressor or the perception of stress. The mature, well-regulated HPA-axis exhibits both a daily circadian rhythm (higher circulating levels of cortisol upon awakening, a peak 30 minutes after waking and with hormone levels attenuating across the day) as well as a superimposed stress dependent reaction. In response to stress, stressor specific pathways in the brain converge in the paraventricular nucleus (PVN) of the hypothalamus. Corticotropin releasing factor (CRF) is then released from the hypothalamus and subsequently triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which stimulates the release of glucocorticoids (cortisol in humans) in the adrenal glands. The release of cortisol regulates multiple bodily functions including cognition, energy mobilization, and immune and reproductive functions. Additionally, cortisol then crosses the blood-brain barrier where it acts on glucocorticoid receptors to provide a negative feedback to the brain, thus regulating the release of cortisol. Alterations in any point of this complex circuitry can create dysregulation in other points of the circuit.

While the HPA-axis is an incredibly adaptive system for maintaining homeostasis as well as preparing the body for danger, chronic levels of stress have been linked to dysregulated HPA-functioning as well as a multitude of adverse physiological and psychological pathologies (for

reviews see Boyce & Ellis, 2005; Flinn, 2006; Gunnar & Vazquez, 2001; Lupien, Maheu, Tu, Fiocco, Schramek, 2007). Dysregulation of the HPA-axis during early childhood through adolescence is of particular concern, as these developmental periods appear to be critical windows in the long-term organization of the HPA-axis (see Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). "Organizational" impacts of hormones refer to relatively permanent alterations in brain systems (both structural and functional) as a result of the presence or absence of a given hormone during a specific developmental period. Such brain organization then determines the effects of regulatory hormones in later life. Children and adolescents who experience prolonged activation or under-activation of the HPA-axis are at risk for a multitude of chronic physical and mental health problems in adulthood including altered reproductive, metabolic, gastrointestinal, immune, and psychiatric functioning (Charmandari et al.). Moreover, recent research has demonstrated that adolescence, specifically, may be a particularly salient organizational period in terms of stress responsivity, in that adolescents demonstrate heightened physiological activity of the HPA-axis similar to an "adult" reactivity profile, when facing performance and peer-rejection stressors compared to younger children (Stroud et al., 2009).

Stress and T1DM. As previously described, in T1DM, a hypo-response of the SNS during episodes of hypoglycemia often develops as the disease progresses, which can lead to altered response to hypoglycemia (for reviews see Boyle & Zrebiec, 2007; Cryer, 2002; Weinger & Jacobson, 1998). Prior elevations of cortisol occurring during prolonged periods of hypoglycemia have been found to at least partially account for a later hypo-response of the SNS during episodes of hypoglycemia (Cryer, 2009). While dysregulation of the SNS and HPA-axis has been observed, there is an absence of longitudinal research in this area. Further, much of the existing cross-sectional literature has been conducted in adult populations. As such, the pathway by which such dysregulation occurs is not clear.

Through a series of investigations, Roy and colleagues observed evidence of dysfunction at many points of the HPA-axis circuitry in adult patients with T1DM including cortisol output indicating dysregulation at some point in the system (e.g., increased 24-hour urinary-free cortisol (UFC) output), altered diurnal rhythm (e.g., elevated 9 a.m. plasma cortisol levels, elevated 4 p.m.

plasma ACTH levels), decreased sensitivity to the negative feedback effect of glucocorticoids (e.g., non-suppression to a dexamethasone suppression test), and increased hypothalamic responsiveness (e.g., elevated response to ovine corticotrophin-releasing hormone) (Roy, Collier, & Roy, 1990; Roy, Roy, & Brown, 1998; Roy et al., 1993). Further, Roy and colleagues found that duration of diabetes was related to higher 24-hr UFC outputs and noted a trend between diabetes health complications and 24-hr UFC outputs (Roy, Roy, & Brown). An elevated response to CRH and non-suppression to dexamethasone in adult patients with T1DM have also been observed by other researchers (Ghizzoni et al., 1993; Hudson et al., 1984). Such HPA dysregulation may result from repeated episodes of hypoglycemia, exogenous administration of insulin, prolonged stress from the management of a chronic illness, or a combination of such factors.

While past research has demonstrated a chronic hyperactivity of the HPA-axis in T1DM, little is known about how such chronic activation may influence stress reactivity in this population. Prolonged or frequent episodes of hypoglycemia and administration of insulin are known to trigger the HPA-axis (Cryer, 2002; Weinger & Jacobson, 1998). Additionally, this population is much more likely to experience chronic levels of psychological stress due to daily hassles associated with disease management and associated disruptions within the family environment, disease-related traumas, and the consequence of stigma of growing up with a chronic illness and its associated limitations (Wasserman & Trifonova, 2006). Further, adolescence already tends to be a period of development marked by increases in stressful events during normative development (Bryne, Davenport, & Mazanov, 2007). As such, adolescents with T1DM are likely at a heightened risk for dysregulated stress response due to the chronic levels of psychological and physiological stressors.

Two previous studies have examined stress reactivity in adult T1DM patients. Wiesli et al. (2005) observed cortisol reactivity characterized by large effect sizes in response to a psychological stressor within adults with T1DM regardless of food consumption. Specifically, the authors reported a large increase in salivary cortisol in adult patients with T1DM who underwent

the Trier Social Stress Task after fasting (d = 1.4) and after a meal (d = 1.06)[1], however, not all samples were suitable for analysis, therefore, cortisol analyses were based on a subpopulation of participants (fasting n = 11 out of 20, after meal n =15 out of 20) and may not accurately reflect reactivity in the sample as a whole. While this study demonstrated that adults with T1DM may respond to a standardized stressor task with increased salivary cortisol, a lack of comparison group limits interpretation regarding potential dysregulation of cortisol reactivity in individuals with T1DM (i.e., findings regarding cortisol reactivity were descriptive, but no statistical comparisons across fasting and meal consumption groups were made). Dutour et al. (1996) also examined cortisol reactivity in adults with T1DM and found an elevated neuroendocrine response during a speaking task in front of an evaluative audience in those whose blood glucose levels were characterized as "unstable" compared to those whose blood glucose levels were characterized as "stable"; however, their sample size was small (six subjects per group).

In an adolescent sample, Delamater et al. (1988) found a decrease in plasma cortisol levels after a cognitive task and interpersonal interactions (10-minute discussion with parent regarding a conflictual issue and 10-minute discussion regarding neutral topic); however, these observed changes were most likely due to diurnal rhythms as the stress-tasks occurred in the morning. Additionally, the stress tasks utilized may not have been stressful enough to produce a reliable stress response in that there was no evaluative component and no component of uncontrollability in that the cognitive testing was not very difficult or timed (for a meta-analysis regarding reliable elicitors of stress response, see Dickerson & Kemeny, 2004).

While research in human models has not yet advanced beyond exploratory findings, stronger evidence of dysregulated stress response in T1DM has come from rodent models, although such research has yielded mixed results. In a series of studies, Chan and colleagues observed elevated HPA-axis activity (higher morning circulating plasma concentrations of corticosterone (i.e., the rodent hormonal equivalent to cortisol) and ACTH; Chan et al., 2001) but a reduced stress response in a rodent model of T1DM (Chan, Chan, et al., 2002; Chan et al.,

[1] The effect sizes were calculated from reported means and standard deviations from Wiesli et al., (2005), d = Cohen's d.

2001; Chan et al., 2005; Chan, Inouye, et al., 2002). Additionally, in this series of studies, Chan and colleagues compared normal and diabetic rats' stress responses to hypoglycemia, hyperinsulinemia, and restraint stressors. While the normal rats exhibited unique stress reactions to each type of stressor (least response to hyperinsulinemia and a greater response to hypoglycemia and restraint stress), the diabetic rats had the same stress reaction across types of stressor despite elevated basal plasma corticosteroid levels. Notably, in diabetic rats, response to more stressful episodes (hypoglycemia and restraint stressor) was equivalent to the less stressful experiences (hyperinsulinemia episodes).

Several key points can be derived from Chan and colleagues' body of research. Notably, administration of insulin and episodes of hypoglycemia have independent influences on stress reactivity in normal rats. Additionally, Chan and colleagues provided strong evidence that diabetes is associated with an impaired ability to appropriately regulate the stress response across differing stressors, which has important implications to treatment and management of diabetes in human populations who must face a variety of physiological and psychological stressors while coping effectively with T1DM (e.g., hypoglycemia, social stigma associated with illness).

While Chan and colleagues have advanced basic understanding of HPA dysregulation in diabetic animal models, these researchers did not examine influences of developmental processes on HPA regulation. In a rodent model of T1DM, Moore et al. (2010) found that administration of insulin in a pattern modeling T1DM treatment during early development lead to later increased levels of fear-related behavior and stress reactivity (stress behavior and increased levels of corticosterone following a restraint stressor). Moreover, these alterations did not disappear with normalization of blood glucose and persisted into adulthood.

Stress and Cognition. Under normal conditions, the HPA-axis and the hormonal secretagogues confer beneficial cognitive functioning related to responding to acute stress episodes. Specifically, during an acute stressor, enhanced processing of stress-related features occurs such as focused attention for stress-related cues and enhanced long-term memory for emotional stimuli (Roozendaal, 2002). While well-modulated stress reactivity aids in surviving

and learning from stressful episodes, too much activation, too little activation, or too long an activation can lead to impairments in everyday cognitive functioning and memory of material unrelated to the stressor (for a review see Lupien et al., 2007).

Early research on exogenous administration of corticosteroids has demonstrated that such administration leads to transient cognitive deficits in healthy individuals, including impairment in verbal, spatial, and working memory (Young, Sahakian, Robbins, & Cowen, 1999; Newcomer et al., 1999). Likewise, multiple research groups have observed transient cognitive impairments following acute laboratory stressors, which were associated with endogenous cortisol responses. Domains of transient cognitive impairment include: verbal learning and memory (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996), retrieval of previously learned verbal information (Kuhlmann et al., 2005), working memory when working memory load is high or when tasks require greater executive functions (Oei, Everaerd, Elzinga, van Weil, Bermond, 2006; Schoofs, Wolf, Smeets, 2009), and sustained attention (Lupien, et al., 1990).

Cognitive impairments have been documented in other, non-diabetic, chronically stressed child, adolescent, and adult populations (e.g. De Bellis, Hooper, Spratt, Woolley, 2009; Evans & Schamberg, 2009; Johnsen, & Asbjornsen, 2008; LaGarde, Doyon, & Brunet, 2010; Vasterling & Brailey, 2005), although the effects of acute stress on cognition within these populations has not been studied. Theoretically, the transient cognitive deficits observed after exposure to psychosocial stressors in healthy populations should be exacerbated in cognitively vulnerable populations such as T1DM, which may further impair young adults' ability to manage blood glucose levels.

Current Study

As previously reviewed, management of blood glucose levels requires application of knowledge surrounding a complex set of dynamic factors that can influence blood glucose levels (e.g., understanding how alcohol can influence blood glucose levels). Mild cognitive impairments may impair young adults' ability to select ideal responses from the variety of response options available (e.g., choosing to abstain from alcohol consumption vs. pre-dosing with insulin prior to drinking). Further, many of these disease-related decisions are likely to be sources of stress (e.g.,

managing peer pressure to drink). Stress-induced cognitive deficits are likely to exacerbate pre-existing vulnerabilities to cognitive impairments, which are likely to further hinder young adults' decision-making abilities thus leading to poorer response choices and poorer blood glucose management (e.g., not considering the consequences of drinking and developing a severe episode of hypoglycemia due to "pre-dosing" with insulin prior to consumption). The current study sought to examine the initial components in this sequence: (a) whether young adults with T1DM physiologically respond to psychological stress in a dysregulated manner compared to non-diabetic peers, exhibiting either attenuated or exaggerated physiological responses, and (b) whether young adults with T1DM demonstrate greater cognitive declines in response to psychological stress. A better understanding of the impact of stress on cognition in diabetic patients can help explain how mild cognitive impairments, which may not be readily apparent in standardized settings with limited stress, may lead to clinically significant impairments during critical high-stress moments of disease management. Such an understanding can lead to better interventions for successful transition to young adulthood for these patients such as preventative training in stress management techniques (e.g., relaxation) and psychoeducation concerning the impact of stress. Based on the previous review of the literature, the following hypotheses were made:

1) Compared to non-diabetic young adults, young adults with T1DM would exhibit a greater decline in cognitive functioning after a psychological stressor (e.g., worse performance on post-task cognitive tests compared to pre-task cognitive tests).
2) Compared to non-diabetic young adults, young adults with T1DM would physiologically respond to a psychological stressor in a dysregulated manner (e.g., attenuated or exaggerated cortisol response).

METHODS

Participants

Potential participants were recruited from the psychology research subject pool at Arizona State University, the general undergraduate population at Arizona State University, and the general population in the Phoenix metropolitan area. Recruitment flyers were displayed at locations likely to be seen by young adults with and without T1DM (e.g., college campuses within the metropolitan area, local chapters of diabetes organizations, medical clinics specializing in diabetes treatment). Recruitment information was also distributed via the internet through online message boards (e.g., craigslist), and social networking sites visited by young adults (e.g., Facebook). Exclusion criteria included being non-English speaking. Inclusion criteria included self-reported diagnosis of T1DM, ages 18-30, or meeting matching criteria for T1DM participants. Potential control participants were matched on criteria chosen based on demographic characteristics known to be strong predictors of adult cognitive functioning and/or salivary cortisol levels (e.g., age, gender, participants' education, ethnicity, paternal and maternal level of education). When considering matching on education, preference was given to matching more closely on maternal education than paternal education, as maternal education tends to be a stronger predictor of adult cognitive functioning (e.g., Kaplan et al., 2001). Participants were matched within +/- 2 years of age. Eligible participants were scheduled for participation on an afternoon of their convenience and given instructions for the day of scheduled participation.

Seventy-two individuals participated in the current study including 23 participants with T1DM and 52 non-diabetic controls yoked[2] to the diabetic participants based on key matching variables (i.e., age, gender, ethnicity, participant education level, and maternal and paternal education level). Each T1DM participant was yoked to at least two controls; however, several diabetic participants were yoked to more than two controls in anticipation of the possibility that some controls might require replacement due to aberrations within the protocol. Because the

[2] The term "yoked" refers to one-to-one matching of a population of interest (i.e., diabetic patient group) with control populations, which is frequently a strategy in case controlled studies. "Yoked" is used in the present description to emphasize the related nature of these observations as opposed to group-based matching.

particular analyses employed required a constant number of yoked controls for each diabetic participant, (as described in the data analysis section), “extra” control participants were excluded. In determining which of the overly matched control participants to exclude, the following aberrations resulted in the removal of a total of six controls: premature termination of stressor task (n = 1), diagnosis of schizoaffective disorder with neuroleptic prescription (n = 1), diagnosis of bipolar disorder (n = 1), incomplete data on computer tasks (n = 1), and extreme outlier on outcome variables (n = 2). A final sample of 23 participants with T1DM and 46 yoked controls were included in the subsequent analyses, yielding 23 clusters of related observations; each cluster contained one diabetic participant and two yoked controls. The average age of participants was 22.64 years (*SD* = 3.81). Forty-two (60.87%) participants were female, and 27(39.13%) participants were male. Most participants identified their ethnicity as “Caucasian” (n = 60, 87.00%), followed by “Hispanic” (n = 4, 5.80%), “Black or African American” (n = 3, 4.35%), and “more than one race" (n = 2, 2.90%). The most frequently endorsed level of participant education was “some college” (n = 37, 53.62%) followed by a “college degree” (n = 16, 23.20%), “high school diploma or GED” (n = 8, 11.59%), “master’s, doctorate, law, or medical degree” (n= 5, 7.20%), and “Jr. college or technical school” (n= 3, 4.35%). The most frequently reported current income was “less than $14,000” (n = 72, 60.87%), followed by “$15,000-$29,000” (n = 15, 21.74%), “$30,000-44,999” (n = 4, 5.80%), “$45,000-$59,999” (n = 4, 5.80%), “$60,000-$79,999” (n = 1, 1.45%), “$80,000-$99,999” (n = 1, 1.45%), “$100,000-$150,000” (n = 2, 2.90%). A breakdown of demographic information by diabetic membership (diabetic vs. control) is provided in Tables 4-7.

Procedure

See Figure 1 for a flow chart of study protocol and Figure 2 for a consort diagram of the flow of participants from initial recruitment.

Eligible participants were scheduled for one of two standardized time slots (i.e., 12pm or 3pm) on the day of their preference (Monday through Thursday). On the day of data collection, the lab assistant greeted participants, obtained informed consent, completed screening questions, and collected a screening finger-stick blood sample. If the participant’s blood glucose

screening level was above 350 mmol/L or the participant endorsed any screening questions that would interfere with the analysis of cortisol (i.e., consumption of caffeine, food or alcohol or recent exercise, within the previous two hours, heart problems, or pregnancy), the participant was rescheduled for a different day, if appropriate. The same screening procedure was used for both T1DM and non-T1DM participants. The research protocol began with a 20-minute period of acclimation during which participants began completing questionnaires. Following this time period, baseline saliva samples and finger-stick blood glucose readings were obtained. If the initial blood glucose reading was either less than 80 mmol/L or greater than 250 mmol/L, the participant was provided a small, low-fat snack containing 15 g carbohydrates consistent with recommendations from the American Diabetes Association (i.e., 4 oz. fruit juice; n.d.) or instructed to administer a dose of insulin, and baseline measurements were re-sampled following normalization of blood glucose levels (retested after 10 min). If blood glucose had not normalized to a safe range after the initial retesting, participants were retested up to three times (10 min intervals) prior to rescheduling participation. Subsequently, participants completed the 10-item PANAS (Watson & Clark, 1994) mood survey followed by pre-stressor cognitive testing (see Table 1 for order of pre- and post-stressor cognitive testing). Following pre-stressor cognitive testing, participants repeated the 10-item PANAS and provided a second saliva and finger-stick sample. Participants then completed the stressor task followed by repeating the 10-item PANAS. Saliva samples and blood glucose readings were collected immediately after completion of the stressor task, and 20 and 40 minutes post stressor task, during which time participants completed post-task cognitive testing and questionnaires. Participants were compensated either by $30 (corresponding to approximately $15/hr of participation) or 2 hours of research participation credit.

Assessments and Measures

Social stressor task.

Role-play social stress task. The social confrontation role-play task (Larkin, Semenchuk, Frazer, Suchday, & Taylor, 1998) was designed to replicate a common stressful experience in the lives of college students. Participants were told that they were trying to study for

an important exam, but their neighbor was playing his/her music too loud. During the 10-minute role-play, the participant attempted to get his/her neighbor to turn down the music. The "neighbor", played by a gender-matched research assistant, maintained a neutral expression and delivered a standardized, structured script, indicating refusal to cooperate. College students have reported that this type of role-play relates well to relevant stressors in their lives (Waldstein, Neumann, Burns, & Maier, 1998). No harmful side effects have been noted. In a meta-analysis of 208 laboratory studies of acute stress induction in adults, Dickerson and Kemeny (2004) found that tasks that included both a social-evaluative threat and uncontrollability such as found in this role-play, elicited the largest cortisol response characterized by a large effect size (d = 0.92).

Biological Measures.

Salivary cortisol. Cortisol was collected by passive drool; participants expelled saliva through straws into a sterile 2 mL cryogenic vial. Samples were collected immediately before pre-stressor cognitive testing, immediately prior to the stressor task, immediately after the stressor task, and 20, and 40 minutes following the stressor task. Samples were refrigerated at −20 °C until they were shipped to Biochemischen Labors (Trier, Germany) to be assayed. Cortisol values are not significantly affected by transport over a period of several days without refrigeration (Clements & Parker, 1998). Assays were conducted in duplicate using a time-resolved immunoassay with fluorometric detection (DELFIA) (Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). Intra-assay coefficients of variation (CVs, i.e., the degree to which duplicate analyses of each sample differ) were between 4.0% and 6.7%, and inter-assay CVs (i.e., the degree to which measurements across plates of samples differ) ranged from 7.1% to 9.0%. Cortisol reactivity was analyzed using the area under the curve with respect to increase (AUC_i) and area under the curve with respect to ground (AUC_g). This method is a standard analysis technique in endocrine and neuroscience research for assessing repeated measurements over time (Pruessner, Kirschbaum, Meinschmid, & Hellhammer, 2003).

Blood glucose. Blood glucose readings were collected by a fingerstick and read by a standard commercial blood glucose meter. Measuring blood glucose levels via fingerstick is a part of standard T1DM disease management, and patients are required to collect numerous

readings throughout the day. As such, this method of sampling should not be novel or aversive for T1DM participants. Fingerstick blood collection may be novel and mildly aversive for non-diabetic participants; however, all participants were fully informed of the use of fingerstick blood sampling and the potential for mild discomfort in this study during the informed consent. Single-use disposable lancet devices (OneTouch® SureSoft™) and single-use test strips were used for each sample collection, and the blood glucose meter was sanitized between users according to the manufacturer's directions eliminating any issues of cross contamination. Study personnel followed World Health Organization (WHO) recommendations for Standard Precautions and the Centers for Disease Control and Prevention (CDC) recommended practices as they pertain to diabetes care in performing fingersticks and handling blood spots (WHO, 2007; CDC, 2005). Blood spot samples were collected immediately before pre-stressor cognitive testing, immediately prior to social stress task, immediately after the stressor task, and 20, and 40 minutes following the stressor task. Blood glucose reactivity was analyzed using the area under the curve with respect to increase (AUC_i) and Area under the curve with respect to ground (AUC_g). This method is a standard analysis technique in endocrine and neuroscience research for assessing repeated measurements over time (Pruessner, Kirschbaum, et al., 2003).

Cognitive Testing.

Sustained Attention Allocation Task. Based on the Rapid Visual Information Processing Task (Wesnes & Warbuton, 1984), the Sustained Attention Allocation Task requires integrated skills of sustained visual attention and working memory. During this task participants are presented with a series of single digits on a computer screen at a rate of 100/minute for four minutes. Participants are instructed to press the space bar as quickly as possible with their dominant hand every time a sequence of three consecutive odd or even digits is presented. The number of distractor digits presented between valid response series ranges from 5 to 25, with approximately 10 valid response sequences per minute. The order of digit presentation is the same for all participants. Correct responses are recorded as "hits" when the key is pressed within 100 and 1200 ms following the presentation of the third digit in a valid sequence. Responses are recorded as "misses" when the space bar is pressed after invalid digits (errors of commission) or

when the participant fails to press the space bar after a correct digit (errors of omission), A Microsoft Excel script was used to present stimuli and record responses for the task. The difference between hits and misses was used to quantify attentional performance. This task was administered in both pre- and post-stressor batteries. Higher scores reflect better performance.

Rey Verbal Learning Test (RVLT). The RVLT is a measure of verbal learning and memory, which has been extensively used in both clinical and healthy samples (see Mitrushina, Boone, Razani, & D'Elia, 2005 for a review) and is considered to be one of the most sensitive measures available of verbal memory (Lezak, Howieson, & Bigler, & Tranel, 2012). There have been many varieties of administration procedures across studies using the RVLT (Mitrushina et al.); the present study followed the standard protocol set out in Strauss, Sherman, and Spreen (2006, p. 784). Specifically, the participant was presented with a list of 15 words at a rate of one second between each word after which the participant was asked to recall as many of the words as he/she could remember. Five consecutive trials of the same 15 words were administered followed by presentation and recall of a 15-word interference list and then a delayed recall of the original list (short-delay recall). Approximately 20 minutes later the participant was asked to recall words from the original list again (long-delay recall) followed by a recognition task in which participants were asked to identify words from the original list among a collection of words from the original list, the interference list, and a selection of new words. In the present study, procedures from presentation of the original list through the short delay recall occurred during the pre-stressor cognitive task and the long-delay recall and recognition tasks occurred during post-stressor cognitive testing. There are a multitude of scores that can be derived from RVLT with total score across learning trials, the delayed recall score, and Trial 5 score being the more reliable measures (Strauss et al.); however, the present study used the number of words recalled on the fifth learning trial to reflect pre-stressor total learning and the number of words recalled after a long delay as measures of post-stressor verbal memory. Higher scores reflect better performance.

Controlled Oral Word Association Test. The COWAT is a measure of verbal fluency, the efficiency by which verbal information is organized and recalled, which is thought to be multi-

determined by a variety of cognitive abilities including auditory attention, short-term memory, initiation, cognitive flexibility, inhibition, mental processing speed, and long-term storage of vocabulary (see Mitrushina et al., 2005 for a review). The COWAT consists of two versions of three letters each (C, F, & L and P, R, & W), which were selected due to equivalence in number of words occurring in the English language that begin with each letter combination (C, F, & L and P, R, & W). The correlation between performance on letter combinations CFL and PRW is high (*r* = .82; Benton, Hamsher, & Sivan, 1994). In a randomized design, Schum, Sivan, & Benton (1989), observed equivalence between these versions when administered to children (6-12 years old; i.e., CFL administered to half and PRW administered to half). Participants were given 60 seconds to generate as many non-proper words in the English language as possible. The present study used letters C, F, and L in the pre-stressor cognitive battery and P, R, and W in the post-stressor cognitive battery. The total number of valid words generated was summed across the three trials so that one score was used for pre-stressor verbal fluency (i.e., letters C, F, & L) and one score was used for post-stressor verbal fluency (i.e., letters P, R, & W). Higher scores reflect better performance.

Stroop Test. The Stroop Test is traditionally viewed as a measure of cognitive inhibition (see Mitrushina et al., 2005 for a review). There are many versions of this task; however, varieties typically include a trial in which participants read a list of color-words (e.g., red, blue, yellow), and then an interference trial in which participants are asked to name the color of color-words printed in incongruent ink color (e.g., name the color of the word “red” printed in yellow ink). The interference trial is a more difficult task in that participants must inhibit an over-learned response (reading) in order to complete a more novel one (naming colors). The present study will use the Golden Stroop task (Golden, 1978; Golden & Frechwater, 2002) for both the pre and post-stressor battery. This tasks consists of three stimulus cards, a Word Page with 100 color words (red, green, blue), a Color Page with 100 series of Xs printed in red, blue, or green ink, and a Color-Word page with 100 color words (red, blue, green) printed in incongruent ink color. The participant is instructed to read words or name the ink color as quickly as possible within a 45 second time frame. The test yields three scores based on the number of items completed on

each of the three trials. The present study used an interference score calculated as the difference between the interference trial and the color naming trial. This task was administered in both the pre- and post-stressor cognitive battery. Scores from the interference trial are typically negative, with lower scores (i.e., more negative) reflecting greater interference.

Trail Making Test. The TMT was originally developed as part of the Army Individual Test Battery (1944) and was then included as part of the Halstead-Reitan Battery. Currently, the TMT is one of the most frequently used neuropsychological tests to measure executive functions (Mitrushina et al., 2005). The TMT is a visual-motor tracking task requiring a range of abilities including: motor-spatial, basic sequencing, visual tracking, mental flexibility, and attention (see Mitruchina et al. for a review). In full, the TMT is comprised of two distinct trials, part A (TMA) and part B (TMB); however, the TMB is a more difficult task due to differences in structural complexity of the stimuli and additional sequencing demands. Taylor has argued that TMB can be administered in isolation without greatly impacting performance (1998). The present study will administer only the TMB during the pre-stressor testing to reduce fatigue and practice effects. TMB consists of encircled numbers 1-13 and encircled letters A-L. Examinees are instructed to draw lines connecting the circles in sequence alternating between numbers and letters (e.g., 1-A-2-B, etc.) as quickly as possible, with total time to completion recorded. A short set of sample items is provided prior to administration. An alternative version to the TMT was developed by DesRosiers and Kavanagh (1987). In DesRosiers and Kavanagh's alternative form, the relative positions of the circles were retained from the original TMT; however the sequence was inverted. The original validation study found the alternative formats to be highly correlated to the original formats (TMA/TMC r = 0.73; TMB/TMD r = 0.80; DesRosiers & Kavanagh), which has been replicated (TMA/TMC r = 0.70 ; TMB/TMD r = 0.78; Franzen, Paul, Iverson, 1996). LoSasso, Rapport, Axelrod, and Reeder (1998) found TMD to be more difficult than TMB, making it less impacted by practice effects. The current study used TMB in the pre-stressor cognitive test battery and TMD in the post-stressor cognitive test. Total time to complete was recorded. Lower scores reflect better performance.

Questionnaires.

Demographics. Participants completed demographics concerning their age, gender, race/ethnicity, level of education, childhood family income, and level of parents' education. T1DM participants also reported on insulin pump usage and age of disease onset.

Cortisol covariates. The following were provided by the participant: time of waking, hours of sleep on previous night, average daily caffeine use, average weekly alcohol use, cigarette use, hormonal contraception use, medication use, time of last menstrual cycle (for females) (Kudielka, Hellhammer, & Wüst, 2009).

Positive and Negative Affect Schedule (PANAS). The PANAS (Watson & Clark, 1994) is a 10-item measure of positive and negative affect. Baseline mood can influence the stress response, and is therefore assessed as a potential covariate (Folkman & Moskowitz, 2007; Forbes & Dahl, 2005). The PANAS has been found to have good internal reliability (Cronbach's $\propto$= .85 for negative affect scale; Cronbach's $\propto$ = .89 for positive affect scale; Crawford & Henry, 2004). In the current study, a similar level of internal consistency was observed for baseline positive affect (Cronbach's $\propto$ = 0.84), but was questionable for baseline negative affect (Cronbach's $\propto$ = 0.68) and did not improve with deletion of any items.

Depression Anxiety Stress Scales 21 (DASS-21), stress subscale. The DASS-21 is a 21-item instrument measuring current symptoms of depression, anxiety, and stress that was shortened from the original DASS (Lovibond & Lovibond, 1995). Each of the three scales consists of 7 items which are responded to using a 0-3 likert-scale (0 = did not apply to me at all, 3 = applied to me very much, or most of the time). The present study used the stress subscale. An example item from the stress scale is "I found myself getting upset by quite trivial things." The range of possible scores for each scale is 0-21. Internal consistency for each scale has been found to be high in large community sample (Cronbach's $\propto$ = 0.90 for Stress subscale; Henry & Crawford, 2005). In the present study, internal consistency was observed to be acceptable (Cronbach's $\propto$ = .79).

Data Analysis

For a tabular depiction of study design see Tables 2 and 3.

Preliminary analyses. Descriptive statistics, correlation matrices, skewness, kurtosis, and univariate graphical displays were examined for all variables of interest. The assumptions of normality were examined for each variable of interest, and transformations most appropriate to the shape of the distribution were attempted to correct deviations from normality following the recommendations set forth by Tachbachnick and Fidell (2001, p. 92). For variables that did not benefit from transformations and were found to be heavily influenced by the presence of univariate outliers, individual scores were winsorized by assigning a raw score one unit larger (or smaller) than the next non-outlier score in the distribution, but retaining rank order in the case of more than one outlier (Tabachnick & Fidell, 2001, p. 45).

Establishing within-cluster equivalence on matching criteria. T-tests were run to confirm group equivalence on the matching variables.

To examine equivalence on matching criteria within clusters, a series of related measures one-way ANOVAs[3] were performed for each matching criteria with diabetic membership as the three-level related measures factor (diabetic, yoked control 1, yoked control 2).The two yoked controls for each diabetic participant were randomly assigned to yoked control condition (yoked control 1 versus yoked control 2). A planned contrast tested the difference between the diabetic member and the average of the two yoked controls for each cluster of participants (see Table 2 for a depiction of the contrast used in the analyses).

Identification of cortisol covariates. A number of factors that could influence cortisol activity were considered for inclusion as covariates in the main analyses predicting cortisol AUC_i and AUC_g. These included blood glucose AUC_g, and AUC_i, time since waking, number of hours slept in previous evening, smoking status, average daily number of serving of caffeine intake, average servings of alcohol consumed during a week, body mass index (BMI), waist to hip ratio (WHR), hormonal contraception use by female participants (yes/no), days since last menstrual period began for female participants, baseline positive and negative affect, number of cortisol-affecting medications (e.g., cholesterol medications, benzodiazepines, SSRIs; Granger, Hibel,

[3] These analyses are more commonly referred to as repeated-measures; however, the term related was selected for the present study to more accurately reflect the nature of the design.

Fortunato, & Kapelewski, 2009) taken other than insulin or hormonal contraception, and score on the DASS stress scale. The influence of insulin pump status was included to examine the potential for an interaction with diabetic group status (diabetic, non-diabetic) because of its significance to the treatment of T1DM. A cluster of cases (one diabetic and two yoked controls) that contained a diabetic who employed an insulin pump was coded as an insulin pump cluster; all other clusters were coded as non-insulin pump clusters. While gender and age are both known to influence cortisol reactivity, the yoking procedure equated the diabetic and yoked controls on these variables. As such, these variables were not included in potential covariates.

Potential covariates were examined separately for each of the cortisol outcomes (e.g., AUC_i or AUC_g). Variables were selected as covariates in the main analyses of cortisol outcomes if the potential covariate was significantly correlated with the cortisol outcome under consideration ($p < .05$) or if the magnitude of the correlation was strong (e.g., $r \geq .40$ or $r \leq -.40$). For variables that were either strongly related or significantly related, evidence that the yoking process did not equate for the potential covariate across levels of diabetic membership within clusters was also required (e.g., no difference between the diabetic member and the average of the two yoked controls for each cluster of participants). A planned contrast tested the difference between the diabetic member and the average of the two yoked controls for each cluster of participants (see Table 2 for a depiction of the contrast used in the analyses). A potential covariate was then included if the planned contrast was statistically significant at a level of $p < .05$ or if the effect size for the planned contrast was large (e.g., $\eta_p^2 \geq .26$; Cohen, 1988). Potential interaction terms (e.g., insulin pump status) were included if the interaction term was significantly correlated with the cortisol outcome under consideration ($p < .10$) or if the magnitude of the correlation was strong (e.g., $r \geq .40$ or $r \leq -.40$). The statistical significance threshold level for correlation with cortisol outcomes was set somewhat higher for interaction terms given that the sample size on which these analyses were based was smaller (e.g., only based on diabetic participants).

Identification of cognitive covariates. A number of factors that could influence executive functioning, attention and processing speed were considered for inclusion as covariates in the main analyses: number of hours slept in previous evening, baseline positive and negative

affect, number of medications used other than insulin or hormonal contraception, cortisol AUC_i, and cortisol AUC_g. The influence of insulin pump status was also considered because of its significance to the treatment of T1DM. A cluster of cases (one diabetic and two yoked controls) that contained a diabetic who employed an insulin pump was coded as an insulin pump cluster; all other clusters were coded as non-insulin pump clusters. Early age of disease onset, (prior to age 7 versus 7 and older) was also considered. A cluster of cases that contained a diabetic whose age of onset was prior to age 7 was coded as young onset; all other clusters were coded as older onset. Early age of onset was anticipated to be examined as a potential interaction with diabetic group status (diabetic, non-diabetic) given the importance of early disease onset in predicting cognitive impairment in T1DM (as previously discussed in the introduction); however, given the very small number of participants with diabetes diagnosed prior to the age of 7 observed in the present study (n = 3), this variable was no longer considered for inclusion as a potential interaction term. Variables known to predict general cognitive functioning that the yoking procedure equated within clusters (e.g., participants' education, maternal education, childhood family income) were not considered for inclusion as covariates.

Potential covariates were examined separately for each of the cognitive outcomes. Given the small samples size available for the main analyses, strict criteria were used in determining inclusion of covariates. As previously detailed, selection of potential covariates was based on past research concerning influences on cognition in general without the application of a stressor as well as associations specific to cognitive deficits in T1DM. No known or reliable covariates have been identified from the limited literature regarding the effect of physiological stress on cognition within using repeated measurement (i.e., the majority of research regarding the effects of stress on cognition has used a no-stress control group for comparisons; e.g., Al'Absi, Hugdahl, & Lovallo, 2002; Bohnen, Houx, Nicolson, & Jolles, 1990). As such, potential covariates were chosen to account for differences in baseline cognitive functioning prior to stress induction, which is consistent with recommendations set forth by Tabachnick and Fidell (2001, p. 424) concerning the selection of covariates in repeated measures designs.

Covariates to control for differences in baseline cognitive functioning were included in the main analyses if they were significantly related to the pre-stressor cognitive test ($p < .05$) or if the magnitude of the correlation was strong (e.g., $r \geq .40$ or $r \leq -.40$). For variables meeting this criteria, evidence that the yoking process did not equate the potential covariate across levels of diabetic membership within clusters was also required (i.e., through same data analysis design as described in establishing equivalence on matching criteria).

To examine equivalence on potential covariates within clusters, a series of related measures one-way ANOVAs were performed for each potential covariate with diabetic membership as the three-level related measures factor (diabetic, yoked control 1, yoked control 2). A planned contrast tested the difference between the diabetic member and the average of the two yoked controls for each cluster of participants (see Table 2 for a depiction of the contrast used in the analyses). A potential covariate was then included if the planned contrast was statistically significant at a level of $p < .10$ or if the effect size for the planned contrast was large (e.g., $\eta_p^2 \geq .26$; Cohen, 1988).

Potential interaction terms (e.g., insulin pump status) were included if the interaction term was significantly correlated with the cortisol outcome under consideration ($p < .10$) or if the magnitude of the correlation was strong (e.g., $r \geq .40$ or $r \leq -.40$). The statistical significance threshold level for correlation with cortisol outcomes was set somewhat higher for interaction terms given that the sample size on which these analyses were based was smaller (e.g., only based on diabetic participants).

Testing assumptions of related measures ANOVA. For each main analysis, the assumptions of related-measures ANOVA were tested according to the recommendations set forth by Tabachnick and Fidell (2001). Skewness and kurtosis values for each level of the design (e.g., diabetics vs. controls in the one-way related measures design) were assessed for violations of normality. Homogeneity of variance was assessed by examining the ratio of the largest variance to smallest variance within all levels of the design, which was then evaluated against the $F_{max} \leq 10$ threshold. The assumption of sphericity was tested through Mauchly's test.

Primary Analyses.

***Primary analyses of cortisol outcomes*.** Primary analyses were conducted separately for each cortisol outcome. To assess differences between diabetic and control participants on cortisol outcomes, separate one-way related-measures ANOVAs were conducted on the cortisol outcomes of interest (e.g., AUC_i and AUC_g) with diabetic membership (diabetic, yoked control 1, and yoked control 2) as the related measures factor with a planned contrast performed in lieu of the omnibus ANOVA to maximize power for the hypotheses of interest as recommended by Tabachnick and Fidell (2001, p. 296). A planned contrast assessed the difference between diabetic participants and the average of the two yoked controls on the cortisol outcomes (see Table 2 for display of study design and planned contrast). As reviewed in the results section, no covariates were retained in the analyses of cortisol outcomes.

***Primary analyses of cortisol outcomes* with inclusion of a between-subjects factor.** If insulin pump status was identified as a potential interaction term (e.g., as demonstrated by a significant correlation with outcomes), a 2 X 3 mixed related-measures ANOVA was performed on the cortisol outcome of interest with the between-subjects measure being the two levels of the covariate of interest (e.g., insulin pump vs. no insulin pump). If the interaction term (e.g., interaction of between-subjects variable with planned contrast of diabetic membership described previously) was significant, separate one-way related measures ANOVAs were conducted within each level of the between-subjects factor. If the interaction term was not significant, the between-subjects factor was removed from the model due to the unknown theoretical significance of insulin pump status on cortisol levels in T1DM, following the recommendations set forth by Aiken and West (1991, p. 105).

Primary analyses of cognitive outcomes with no identified covariate. For cognitive outcomes without covariates, cognitive changes from pre- to post-stressor were analyzed by conducting 2 x 3 related measures ANOVAs with the pre and post-stressor scores as the two-level repeated measure and diabetic membership (diabetic, yoked control 1, and yoked control 2) as the three-level related measures factor with a planned contrast performed in lieu of the omnibus ANOVA to maximize power for the hypotheses of interest as recommended by Tabachnick and Fidell (2001, p. 296). A planned contrast assessed the interaction between

change in performance from pre- to post-stressor tasks and the contrast of diabetic membership (e.g., contrast of diabetic participant vs. the average of the two yoked controls), which tests the hypothesis that diabetics and yoked controls differ in their change in cognitive performance from pretest to posttest (see Table 3 for depiction of study design and planned contrasts).

Primary analyses of cognitive outcomes covariate(s). For cognitive tasks requiring adjustment for covariates, the score from the post-stressor task was adjusted for the score on the pre-stressor task as well as the covariate(s). Specifically, the post-test score was regressed on the pretest score plus the covariate. The residuals of the regression analysis (i.e., post-test score with corresponding pretest score and covariate partialed out) were adjusted post-stressor scores that served as the dependent variable for the analysis of the impact of diabetes on performance. A one-way related measures ANOVA was then conducted on the adjusted post-stressor score with diabetic membership (diabetic, yoked control 1, and yoked control 2) as the related measures factor. A planned contrast assessed the difference between the diabetic participant and the average of the two yoked controls (see Table 2 for depiction of study design and planned contrast).

Primary analyses of cognitive outcomes **with inclusion of a between-subjects factor.** To examine whether insulin pump status interacted with diabetes membership, a between-subjects factors was added to the previously described related-measures designs. If the interaction between the between-subjects factor and the related-measures factors was significant, separate lower-level analyses were carried out at each level of the between-subjects factor. For example, for insulin pump status, a separate one-way related measures ANOVA was conducted at each level of insulin pump status (i.e., for clusters in which there was a diabetic with an insulin pump and clusters in which there was a diabetic not on an insulin pump).

RESULTS

Preliminary Analyses

Evaluation of yoking procedure. Non-repeated measures t-tests were employed to confirm group equivalence on the matching variables. The 23 diabetic participants were contrasted with the 46 yoked controls. On average, diabetic participants were not statistically different from control participants on any matching factor ($p \geq .24$ for all t-tests, see Table 5 for descriptive information). While group equivalence was demonstrated, more important to the present study design (i.e., related measures) was demonstration of within cluster equivalence.

Overall, the series of related measures ANOVAs demonstrated within cluster equivalence on matching criteria within the pre-determined acceptable level of difference (e.g., participants were matched within +/- 2 years of age and maternal education was given preference over paternal education in identifying most closely matched participants).

With regard to within-cluster equivalence of participants' age, the difference between the age of the diabetic participants and the average of the two yoked control participants was significant, $F(1,22) = 6.37$, $p = .02$, $\eta_p^2 = 0.23$). While the diabetic participants were observed to be older than the average of their two matched peers, the observed difference between the diabetic participants ($M = 23.00$, $SE = 0.84$,) and the average of the matched pairs ($M = 22.46$, $SE = 0.79$) was less than one year, well within the criteria used for matching (+/-2 years). There was also a difference between the paternal level of education of the diabetic participants ($M = 3.78$, $SE = 0.37$) and the average of the two yoked control participants ($M = 4.28$, $SE = 0.37$) that reached significance, $F(1,22) = 4.87$, $p = 0.04$, $\eta_L^2 = 0.18$;[4] however, groups were not different on participant's level of education, maternal education, or childhood family income, supporting equivalence on developmental demographic factors most predictive of adult cognitive functioning (e.g., Kaplan et al. 2001; Richards, Hardy, Kuh, & Wadsworth, 2001).

With regard to group equivalence of ethnicity, there was not a significant difference in the proportions of ethnicities represented within each group (e.g., diabetic vs. control, see Table 5).

[4] η_L^2 = lower limit of partial eta squared, which is provided when assumption of sphericity is violated.

With regard to the equivalence of ethnicity within clusters, 21 out of 23 (91.30%) diabetics were exactly matched to the ethnicity of their respective yoked control participants. Exact ethnicity matches were unable to be recruited for two diabetics who indicated “more than one race” as their primary ethnic identification. In these cases, potential participants were recruited if they matched one of the ethnic categories endorsed by the diabetic participant, and every attempt was made to vary the ethnicity of the yoked control participants across the ethnicities endorsed by the diabetic participant while balancing contributions from other matching variables.

Descriptive statistics, tests of normality, and outlier screening for cortisol analyses. All cortisol variables and potential covariates were screened for univariate outliers and violations of normality.

The raw cortisol values from one participant with T1DM were outside the normal physiological range of afternoon salivary cortisol levels (time 1 = 42.15 nmol/L, time 2 = 41.25 nmol/L, time 3 = 19.51 nmol/L, time 4 = 50.13 nmol/L; Aardal & Holm, 1995; Lo, Ng, Azmy, & Khalid,1992). This participant and the two yoked control participants were excluded from further analyses involving cortisol. One participant did not have complete data available for computation of AUC_i due to early termination after post-stressor cognitive tasks; therefore, this cluster was not included in cortisol analyses. The final analysis sample for cortisol outcomes included 21 clusters of participants.

Of the potential covariates examined for inclusion in the main cortisol analyses, the distributions of several variables appeared to be heavily influenced by the presence of a few univariate outliers [average daily servings of caffeine (1 diabetic, 1 control extremely high), average weekly servings of alcohol (1 control extremely high), blood glucose AUC_i (1 diabetic extremely low), DASS stress (1 diabetic extremely high)]. The non-normality of blood glucose AUC_g did not appear to be primarily driven by the presence of outliers. As an initial attempt to correct for violations of normality, each variable was transformed in the manner most appropriate to the shape of the distribution following the recommendations set forth by Tachbachnick and Fidell (2001, p. 92). Upon visual examination of the distributions, q-q plots, and indicators of skewness and kurtosis, following transformations, only blood glucose AUC_g benefited from

transformation (square root transformation). To reduce the impact of the univariate outliers for the variables that did not benefit from transformations, individual scores were winsorized by assigning a raw score one unit larger (or smaller) than the next non-outlier score in the distribution, but retaining rank order in the case of more than one outlier (Tabachnick & Fidell, p. 45). While the effect of winsorizing did improve the normality of the distributions, winsorizing did not significantly influence the correlations among the potential covariates and cortisol outcomes. As such, winsorzing lessened the violation of the normality assumption of ANOVA without altering which potential covariates were included in the main analyses.

Due to safety procedures built into the laboratory protocol (i.e., consumption of juice when blood glucose dropped below 80), variability in protocol standardization (i.e., whether the participant consumed juice during participation) was a possible confound to cortisol analyses. To examine how such variability in standardization might introduce error into subsequent analyses, a related measures logistic regression was conducted to examine if the probability of diabetics differed from the average probabilities of the two yoked controls with regard to variability in standardization, which revealed no difference within clusters, Wald $\chi^2 = 1.99$, $p = .16$, OR[5] = 2.42.

A related measures ANOVA was also conducted to examine if diabetics differed from the average of the two yoked controls with regard to variability in protocol start time, which revealed no difference within clusters, $F(1, 20) = .08$, $p = .78$, $\eta_p^2 < .01$. An additional related measures ANOVA was also conducted to examine if diabetics differed from the average of the two yoked controls with regard to variability in time elapsed from start time to initial cortisol sample, which revealed no difference within clusters, $F(1, 20) = 0.76$, $p = .39$, $\eta_p^2 = .04$.

Means, standard deviations, medians, ranges, skewness and kurtosis of the cortisol variables and potential covariates by group (i.e., diabetic vs. control) are included in Tables 10 and 11, and frequencies of categorical variables are included in Table 12. Correlation matrices for potential covariates that were significantly correlated with either cortisol AUG_i or AUG_g at a level of $p < .05$ or that had a correlation of strong magnitude ($r \geq .40$ or $r \leq -.40$) for either diabetic

[5] OR = Odds Ratio

or control participants are provided in Table 13 for total sample (collapsed across diabetic and control participants), Table 14 for control participants and Table 15 for diabetic participants. Correlations for the total sample were used in determining potential covariates. Of these possible covariates, no variables met pre-determined criteria for inclusion as a covariate ($p < .05$ or $r \geq .40$ or $r \leq -.40$ for total sample). Usage of an insulin pump was strongly negatively correlated with AUC_i ($r = -.40$, $p = .08$), which was within the threshold for inclusion as an interaction term (e.g., $p < .10$, or $r \geq .40$ or $r \leq -.40$). Because insulin pump status is not possible to equate within cluster (i.e., yoked controls are never on an insulin pump) and the interaction of insulin pump status with the planned contrast of diabetic membership described previously (e.g., diabetic participant versus the average of the two yoked control participants, see Table 2 for planned contrast) is of theoretical importance, this variable was retained as a between subjects variable.

With regard to cortisol AUC_g, waist to hip ratio was significantly positively correlated with cortisol AUG_g ($r = .25$, $p = .05$) for the entire sample (collapsed for diabetic and control participants). To examine equivalence on waist to hip ratio within clusters, a related measures one-way ANOVA was conducted where the related measures factor was diabetic membership. A planned contrast compared the waist to hip ratio of the diabetic participant with the average of the two yoked control participants. The difference between the waist to hip ratio of the diabetic participants and the average of the two yoked control participants was not significant, $F(1,20) = .72$, $p = .41$, $\eta_L^2 = .01$. Given equivalence within clusters on waist to hip ratio this variable was not included as a covariate in the main analyses of cortisol AUC_g.

The number of cortisol-influencing medications was found to be significantly negatively correlated with cortisol AUG_g ($r = -.34$, $p = .007$) for the entire sample (collapsed for diabetic and control participants). To examine equivalence on number of medications affecting cortisol taken within clusters, a related measures one-way ANOVA was conducted where the related measures factor was diabetic membership. A planned contrast compared the number of medications taken by the diabetic participant with the average of the two yoked control participants. The difference between the number of medications taken by the diabetic participants and the average of the two yoked control participants was not significant, $F(1,20) = .35$, $p = 0.56$, $\eta_L^2 = 0.01$. Given

equivalence within clusters on number of medication taken, this variable was not included as a covariate in the main analyses of cortisol AUC_g.

For both diabetics and controls, skewness and kurtosis fell below recommended cut-offs for use of maximum likelihood estimation; this was true for all variables included in the main analyses of cortisol (skewness < 2, kurtosis < 7; West, Finch, & Curran, 1995). While log transformations are commonly performed in analyses involving cortisol AUC, such a transformation resulted in a much larger deviation from normality in the present data (e.g., AUC_i skewness = -6.95, kurtosis = 46.96). As such, the non-transformed values were used in the main analyses.

Descriptive statistics, tests of normality, and outlier screening for cognitive analyses. All cognitive variables and potential covariates were screened for univariate outliers and violations of normality. Of the cognitive outcomes, there was one diabetic participant whose scores on the computerized sustained attention allocation task (SAAT) indicated lack of task engagement (e.g., the number of times the participant pressed the space bar was suggestive of continuous bar pressing without regard to stimuli). Therefore, this participant and the two yoked controls were excluded from the remainder of SAAT analyses. There were univariate outliers on Trails B and the pre-stressor Stroop task; however, upon inspection of the raw scores, there was no indication that the scores were invalid (e.g., the scores were within plausible raw scores for adequate effort). Transformations were used to neutralize the effect of the outliers and improve violations of normality. Trails B appeared to violate assumptions of normality, which were improved with a log transformation. A log transformation was also applied to Trails D to ensure equivalence across pre and post measurement. The distribution of trial 5 of the RVLT list-learning task also violated assumptions of normality with a negative skew due to the performance of a few individuals. An inverse transformation was applied to trial 5 of RVLT as well as the delayed recall trial to which trial 5 is compared in the main analyses. These transformations improved the distribution of these variables as shown in graphical displays, q-q plots, and measures of skewness and kurtosis and did substantially alter the results of the analyses.

Means, standard deviations, medians, ranges, skewness and kurtosis of the cognitive variables and potential covariates by group (i.e., diabetic vs. control) prior to transformations are

included in Tables 16-18. Correlation matrices for potential covariates are provided in Table 19 for the total sample (collapsed across diabetic and control participants), Table 20 for control participants, and Table 21 for diabetic participants. Within these tables, correlations were provided for variables that were significantly correlated with cognitive outcomes at a level of $p <$ .05 or that had a correlation of strong magnitude ($r \geq .40$ or $r \leq -.40$) for diabetic participants, control participants, or total sample. Correlations for the total sample were used in determining potential covariates. No variables approached a significant correlation with any of the cognitive outcomes. Therefore, the main analyses for these outcomes were conducted without the inclusion of covariates. Insulin pump status was significantly negatively correlated with Trails B ($r = -.45$, $p = .03$), and was negatively correlated with performance on the Stroop task at the trend level ($r = -.37$, $p = .08$), meeting criteria for inclusion as interaction terms for these variables. Because insulin pump status is assigned at the cluster level (i.e., the cluster is designated as containing a diabetic with an insulin pump or not), and the interaction of insulin pump with the planned contrast of diabetic membership described previously (see Table 2 for depiction of the planned contrast) is of theoretical importance, this variable was retained as a between subjects variable for Trails and Stroop tasks.

Primary Analyses for Cortisol

Cortisol AUC_i. A 2 X 3 mixed between-subjects related-measures ANOVA was performed on cortisol AUC_i with insulin pump usage as the between subjects factor (cluster with a diabetic on an insulin pump versus cluster with a diabetic not on an insulin pump) and diabetic membership as the three-level related measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance ($F_{max} = 1.71$) or sphericity ($W = .95$; $\chi^2 = .86$, $p = .65$).

There was a marginally significant interaction between the insulin pump factor with the related measure factor (i.e., diabetic vs. yoked control 1 level vs. yoked control 2), $F(1,19) = 3.88$, $p = .06$, $\eta_p^2 = .17$ on cortisol AUC_i (see Figure 3). Planned follow-up repeated measures ANOVAs were run separately for the two levels of the insulin pump factor (i.e., insulin pump vs. no insulin pump). For clusters in which the diabetic participant was on an insulin pump, there was no difference between the cortisol AUC_i of participants with T1DM ($M = 30.76$, $SE = 2511.95$) and

the pooled average of the two yoked control participants, (*M* = -637.32, *SE* = 3408.85; *F*(1,10) = .05, *p* = .82, η_p^2 = .01). Among clusters in which the diabetic participant was not on an insulin pump, mean AUC_i for diabetic participants (*M* = 5826.12, *SE* = 2614.13) was significantly greater than the pooled average of the yoked control participants (*M* = -4537.85, *SE* = 3097.77; *F*(1,9) = 6.45, *p* = .03, η_p^2 =.42).

Post-hoc analyses of cortisol AUC_i. Post-hoc visual inspection of plots of the different groups' average raw cortisol values across participation (i.e., T1DM participant on an insulin pump, T1DM participant not on an insulin pump, and the two matched control groups) suggested that cortisol levels for control participants yoked to T1DM participants not on an insulin pump generally declined across the protocol with a peak cortisol value at the first sample (see Figure 4), prior to initiation of experimental protocol (e.g., pre-stressor cognitive testing or stressor task). Additionally, visual inspection of plots of total AUC_i across groups (see Figure 3) suggested that control participants yoked to T1DM participants not using an insulin pump demonstrated lower overall AUC_i compared to all other groups, although the magnitude or statistical significance of this difference was not apparent from the graphical display.

Because AUC_i is a summary score of reactivity relative to a participants' initial cortisol level, further post-hoc exploration was undertaken to examine to what degree previous findings (i.e., difference in AUC_i between diabetics not using an insulin pump and yoked controls) might be influenced by elevated initial cortisol levels within the yoked control group rather than due to differences in cortisol reaction to the interpersonal stressor.

To examine within cluster-equivalence on initial cortisol levels, a 2 X 3 mixed between-subjects related-measures ANOVA was performed on initial cortisol level with insulin pump usage as the between subjects factor (cluster with a diabetic on an insulin pump versus cluster with a diabetic not on an insulin pump) and diabetic membership as the three-level related measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance (F_{max} = 5.71) or sphericity (W = .80; χ^2 = 4.03, *p* = .13).

There was a significant interaction between the insulin pump factor with the related measure factor (i.e., diabetic vs. yoked control 1 level vs. yoked control 2), *F*(1,19) = 4.62, *p* = .05, η_p^2 = .20

on initial cortisol levels. Planned follow-up repeated measures ANOVAs were run separately for the two levels of the insulin pump factor (i.e., insulin pump vs. no insulin pump). For clusters in which the diabetic participant was on an insulin pump, there was no difference between the initial cortisol sample of participants with T1DM (*M* = 4.97, *SE* = 0.80) and the pooled average of the two yoked control participants, (*M* = 4.91, *SE* = 0.88; *F*(1,10) = .02, *p* = .91, η_p^2 = .001). Among clusters in which the diabetic participant was not on an insulin pump, mean initial cortisol level for diabetic participants (*M* = 3.67, *SE* = 0.42) was significantly lower than the pooled average of the yoked control participants (*M* = 5.56, *SE* = 1.05; *F*(1,9) = 6.75, *p* = .03, η_p^2 =.43).

Additional non-repeated measures t-tests were performed to compare the initial cortisol level of the two control groups and to compare the two diabetic groups (on and off insulin pump). When examining only control participants, the initial cortisol level of control participants yoked to diabetic participants not using an insulin pump (*M* = 5.56, *SD* = 3.15) was not different from that of control participants yoked to diabetic participants using an insulin pump (*M* = 4.91, *SD* = 2.69, *t* = .73, *p* = .47, *d* = .22). Additionally, when examining only diabetic participants, the initial cortisol level of diabetic participants not using an insulin pump (*M* = 3.67, *SD* = 1.32) was not different from the initial cortisol level of the diabetic participants using an insulin pump (*M* = 4.97, *SD* = 2.66, *t* = -1.40, *p* = .18, *d* = .62).

To examine possible differences in whether peak cortisol values occurred during the first sample, participants were coded as having a peak cortisol value at the first sampling period or having a peak cortisol value at a time other than the first sampling period. A greater proportion of control participants (21/42) had a peak cortisol level at the first sampling period compared to diabetic participants (5/21, χ^2 = 3.96, *p* = .047, Φ[6] = -0.25). The proportion of control participants matched to diabetic on an insulin pump (11/22) with a peak cortisol value at the first sampling time did not differ from the proportion of the control participants matched to diabetic not on an insulin pump (10/20; χ^2 = 0.00, *p* = 1.00, Φ = 0.00). There was also no difference between the proportion of diabetic participants on an insulin pump (3/11) with a peak cortisol value at the first

[6] Φ= phi coefficient, a measure of effect size for chi-square tests.

sampling period and the proportion of diabetic participants not on an insulin pump with a peak cortisol value at this time point (2/10, χ^2 = .15, *p* = .70, Φ =.09).

In examining individual plots of control participants' raw cortisol values across participation, there appeared to be variability in subsequent cortisol levels. Specifically, of the 21 control participants who demonstrated peak cortisol levels at the first sampling period, the majority also demonstrated later fluctuations, with rising and falling cortisol levels (n = 13/21) although such fluctuations did not reach the initial peak level. A smaller proportion of control participants who peaked at the initial sampling period exhibited a continuous decline in cortisol levels (n = 8/21).

To examine if the control groups (i.e., control participants yoked to diabetic participants using an insulin pump versus control participants yoked to diabetic participants not using an insulin pump) differed on variables potentially related to cortisol AUC_i, t-tests and chi-squared tests were run on these variables (i.e., age, number of medications, waist to hip ratio, time slept the previous night, time from participation start to first saliva sample, stress (from DASS), average daily caffeine intake, body mass index, time since waking, days since last menstrual (for females), average alcohol consumption, education level, gender, smoking status, maternal education, paternal education, childhood family income, nonstandard protocol administration, initial positive affect, and initial negative affect . To control for the increased type 1 error rate from conducting so many post-hoc analyses, a more conservative p-value was set (i.e., $p < .01$). No differences between controls yoked to diabetics on or off an insulin pump were observed across these variables at the conservative level or traditional criteria (i.e., $p < .05$).

Within diabetic and non-diabetic participants, different variables were related to AUC_i (see Tables 14-15). Specifically, smoking status was negatively correlated with AUC_i within the diabetic participants, but was not correlated to AUC_i within control participants. Likewise, male gender was positively associated with higher cortisol AUC_i within control participants, but was not correlated to AUC_i within diabetic participants. Baseline positive affect was negatively correlated with AUC_i within control participants and was positively, although not significantly correlated with AUC_i within diabetic participants. Moreover, as detailed above, there was a significant difference

in the proportion of control participants with a peak cortisol value at the first sampling period compared to the portion of diabetic participants with a peak cortisol value at this sampling period.

Given that the difference observed in the primary analysis of cortisol AUC_i may be due in part to the differential initial response of cortisol a post-hoc ANOVA was conducted to examine if there were differences between the two diabetic groups (e.g., with and without insulin pump). While smoking status and perceived stress were both negatively correlated with cortisol AUC_i among diabetic participants, these variables were also correlated with each other. As recommended by Tabachnick and Fidell, only one of several correlated covariates was selected to be included in the model (2001, p. 424). Given prior research regarding the effect of habitual smoking on cortisol attenuation (e.g., Morgan et al., 2004; Badrick, Kirschbaum, & Kumari, 2007), smoking status was included as a covariate.

After controlling for the effect of smoking status, there was a trend toward a main effect of insulin pump status, $F(1,18) = 3.40$, $p = 0.08$, $\eta_p^2 = 0.16$. Specifically, diabetic participants using an insulin pump ($M = -55.06$, $SE = 2237.63$) had lower cortisol AUC_i compared to diabetic participants not using an insulin pump ($M = 5920.52$, $SE = 2346.88$).

Cortisol AUC_g. A one-way related ANOVA was performed on cortisol AUC_g with diabetic membership as the three-level related measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance ($F_{max} = 1.03$) or sphericity ($W = .74$; $\chi^2 = 5.67$, $p = .06$).

There was no difference between the cortisol AUC_g of participants with T1DM ($M = 30.76$, $SD = 8331.19$) and the pooled average of the two yoked control participants, ($M = -637.32$, $SD = 10819.92$), $F(1,20) = .11$, $p = .75$, $\eta_p^2 = .01$).

Post-hoc analyses of cortisol AUC_g. Given the previously described problems with the use of current control groups in analyses of cortisol within the present sample, differences in AUC_g of diabetic participants with and without insulin pumps were compared. There was no difference between the cortisol AUC_g of diabetic participants on an insulin pump ($M = 24300.82$, $SE = 3554.29$) and diabetic participants not on an insulin pump ($M = 23683.23$, $SD = 3727.77$), $F(1,19) = .01$, $p = .91$, $\eta_p^2 = .001$.

Primary Analyses for Cognitive Tasks

Trails. A 2 X 3 X 2 mixed related-measures ANOVA was performed on the transformed pre- and post-stressor Trails scores. Insulin pump usage was the between subject factor (cluster with a diabetic on an insulin pump versus cluster with a diabetic not on an insulin pump); diabetic membership was the three-level related measures factor (diabetic, yoked control 1, yoked control 2); pretest versus posttest was the repeated measures factor. There was no violation of homogeneity of variance (F_{max} = 4.21) or sphericity (W = 0.82; χ^2 = 3.93, p = 0.14).

The interaction between insulin pump status, diabetic membership, and change from pre to post-stressor on Trails was not significant, $F(1,21) = 1.75$, $p = 0.20$, $\eta_p^2 = 0.08$. Because the theoretical significance of insulin pump status on cognitive abilities is unknown, insulin pump factor was removed from the model as recommended by Aiken and West (1991, p. 105).

Following the removal of the between-subjects factor (e.g., insulin pump status), a 2 X 3 related measures ANOVA was performed on pre- and post-stressor Trails scores with diabetic membership as the three-level repeated measures factor (diabetic, yoked control 1, yoked control 2). A planned contrast assessed the interaction between change in performance from pre- to post-stressor tasks and the contrast of diabetic membership (e.g., contrast of diabetic participant vs. the average of the two yoked controls), which tests the hypothesis that diabetics and yoked controls differ in their change in Trails performance from pretest to posttest (see Table 3 for depiction of study design and planned contrasts). There was no violation of homogeneity of variance (F_{max} = 2.92) or sphericity (W = .90; χ^2 = 2.23, p = .32). There was a significant interaction between diabetic membership and change on Trails from pre to post, $F(1,22) = 4.75$, $p = .04$, $\eta_p^2 = .18$ (see Figure 5). As expected, the post-test Trails D test was more difficult than the pretest Trails B test. Pairwise comparisons revealed that the control participants took more time to complete the post-stressor Trails than the pre-stressor Trails (MD[7] = .35, SE = .08, t = 4.26, p = .0001), whereas the time it took diabetic participants to complete Trails did not differ from pre to post (MD = 0.15, SE = .09, t = 1.74, p = .10).

[7] MD = Mean Difference

Stroop. A 2 X 3 X 2 mixed related-measures ANOVA was performed on transformed pre- and post-stressor Stroop interference scores with insulin pump usage as the two-level between subjects factor (cluster with a diabetic on an insulin pump versus cluster with a diabetic not on an insulin pump) and diabetic membership as the three-level repeated measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance (F_{max} = 2.08) or sphericity (W = .97; χ^2 = .67, p = .72).

There was a significant interaction between insulin pump status, diabetic membership, and change from pre to post-stressor on Stroop interference task, $F(1,21) = 6.68$, $p = .02$, $\eta_p^2 = .24$ (see Figure 6). Follow-up related measures ANOVAs were carried out separately at each of the two levels of the insulin pump factor (i.e., has insulin pump vs. does not have insulin pump).

For clusters in which the diabetic participant was on an insulin pump, there was no violation of homogeneity of variance (F_{max} = 1.42) or sphericity (W = .85; χ^2 = 1.82, p = .40). A planned contrast assessed the interaction between change in performance from pre- to post-stressor tasks and the contrast of diabetic membership (e.g., contrast of diabetic participant vs. the average of the two yoked controls), which tests the hypothesis that diabetics and yoked controls differ in their change in Stroop performance from pretest to posttest (see Table 3 for depiction of study design and planned contrasts).There was a significant interaction between diabetic membership and change on pre-stressor Stroop interference to post-stressor interference, $F(1,12) = 8.52$, $p = 0.01$, $\eta_p^2 = .42$ (see Figure 6). Pairwise comparisons of pre- versus post-stressor scores revealed that the performance did not change from pretest to posttest for control participants (*MD* = 3.35, *SE* = 3.27, t = 1.02, p = .32)[8]. For diabetic participants, there was a trend toward an improvement in Stroop performance from pre to post- stressor (*MD* = -3.15, *SE* = 1.73, t = -1.82, p = .09).

For clusters in which the diabetic participant was not on an insulin pump, there was no violation of homogeneity of variance (F_{max} = 2.08) or sphericity (W = .86; χ^2 = 1.17, p = .56). The interaction between diabetic membership contrast (diabetic vs. average of two yoked controls),

[8] MD= mean difference of pre-stressor score minus post-stressor score, negative MD reflects improvement on Stroop task from pre to post-stressor administration.

and change from pre to post-stressor on the Stroop interference score was not significant, $F(1,9) = 1.12$, $p = .32$, $\eta_p^2 = .11$.

COWAT. A 2 X 3 related-measures ANOVA was performed on pre- and post-stressor COWAT scores with diabetic membership as the three-level repeated measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance ($F_{max} = 1.81$) or sphericity ($W = .91$; $\chi^2 = 1.97$, $p = .37$).

The planned comparison of the interaction between diabetic membership contrast (diabetic vs. average of two yoked controls), and change from pre to post-stressor on COWAT was not significant, $F(1,22) = .59$, $p = .45$, $\eta_p^2 = .03$.

RVLT. A 2 X 3 related measures ANOVA was performed on transformed pre- and post-stressor RVLT scores (Pre-stressor = Trial 5, Post-stressor= Delayed Recall Trial) with diabetic membership as the three level repeated measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance ($F_{max} = 1.23$) or sphericity ($W = .90$; $\chi^2 = 2.23$, $p = .33$). The planned comparison of the interaction between diabetic membership contrast (diabetic vs. average of two yoked controls), and change from pre to post-stressor on RVLT was not significant, $F(1,22) = .66$, $p = .43$, $\eta_p^2 = .14$.

SAAT. A 2 X 3 related measures ANOVA was performed on pre- and post-stressor SAAT scores with diabetic membership as the three level repeated measures factor (diabetic, yoked control 1, yoked control 2). There was no violation of homogeneity of variance ($F_{max} = 1.43$) or sphericity ($W = .99$; $\chi^2 = .17$, $p = .92$). The planned comparison of the interaction between diabetic membership contrast (diabetic vs. average of two yoked controls), and change from pre to post-stressor on SAAT was not significant, $F(1,21) = .06$, $p = .80$, $\eta_p^2 < .01$.

Post-hoc comparisons of participants with T1DM on and off an insulin pump.

Current and childhood family income. Given the theoretical significance of socioeconomic status to insulin pump use, post-hoc comparisons were made to assess differences in childhood family income and current household income between diabetic participants using and not using an insulin pump. No differences were observed in current household income for diabetic participants using a pump ($M = 1.85$, $SD = 1.28$) compared to diabetic participants not using a

pump (*M* = 2.10, *SD* = 1.85, *t* = 0.39, *p* = .70). However, diabetic participants not using an insulin pump (*M* = 2.70, *SD* = 1.57) reported lower childhood family income compared to diabetic participants using an insulin pump (*M* = 5.31, *SD* = 1.44, *t* = -4.15, *p* < .001).

DASS stress score. Given the theoretical significance of reductions of sources of stress to insulin pump use, post-hoc comparisons were made to assess differences in DASS stress score between diabetic participants using a pump and not using an insulin pump. Diabetic participants using an insulin pump reported higher levels of perceived stress on the DASS (*M* = 7.64, *SD* = 3.64) compared to diabetic participants not using an insulin pump (*M* = 4.40, *SD* = 3.41, *t* = -2.10, *p* = .05).

DISCUSSION

The purpose of the present study was to examine differences between young adults with T1DM and matched non-diabetic peers with regard to neurocognitive and hormonal stress reactivity. Based on previous literature, it was hypothesized that compared to matched peers, young adults with T1DM would demonstrate a dysregulated cortisol reaction (i.e., hyper or hypo response) in response to an interpersonal stressor. Likewise, it was hypothesized that compared to matched peers, young adults with T1DM would demonstrate a relatively greater decline in neurocognitive functioning across the same interpersonal stressor.

Summary of Findings

Cortisol reactivity. The results of the present study provide mixed support for the above hypotheses. With regard to cortisol reactivity (as measured by AUC_i), differences between young adults with and without T1DM were dependent on whether the young adult with T1DM was using an insulin pump. Specifically, young adults with T1DM using an insulin pump did not differ from matched peers without T1DM. In contrast, young adults with T1DM not using an insulin pump demonstrated greater cortisol reactivity compared to matched peers without T1DM.

When examining only participants with T1DM (the reasons for which are discussed at length in a later section) there was a trend for those using an insulin pump to exhibit lower cortisol reactivity than those not on a pump. There was no statistically significant difference between young adults with and without T1DM with regard to total cortisol hormonal output (as measured by area under the curve with respect to ground) across the interpersonal stressor task.

Neurocognitive reactivity. With regard to neurocognitive changes across the interpersonal stressor task, findings were dependent on the specific task. On a measure of attention and processing speed (i.e., Trail Making Test, or TMT; Lezak et al., 2012), young adults with and without T1DM demonstrated distinct patterns of neurocognitive stress reactions. It was hypothesized that individuals with T1DM would show greater decline from pre to post stressor performance. However, the performance of young adults with T1DM on the TMT was not statistically different from pre to post stressor performance whereas young adults without T1DM demonstrated a decline in performance from pre to post stressor administration. On a measure of

cognitive interference, or one's ability to inhibit an overly learned response in favor of a new one (the Stroop Task; Lezak et al.), differences in performance from pre to post stressor task between young adults with and without T1DM were dependent on insulin pump usage. Young adults with T1DM not using an insulin pump did not differ from matched peers without T1DM in performance across pre to post stressor administration of the Stroop. In contrast, young adults with T1DM using an insulin pump differed from matched peers without T1DM in their performance from pre to post-stressor administration of the Stroop. Young adults with T1DM using an insulin pump slightly improved across the stressor task whereas matched peers without T1DM remained stable. No other differences emerged for all other indicators of cognitive performance.

Interpretation of Cortisol Reactivity Findings

Collectively, these results add to an emerging body of literature suggesting an exaggerated cortisol reaction in response to psychological stressors in individuals with T1DM. There are several theoretical lenses through which the present findings can be interpreted. The present discussion will focus on two: exacerbation of pathophysiological underpinnings inherent in T1DM and the influence of socioeconomic status (SES) on health disparities.

Exacerbation of pathophysiological underpinnings inherent in T1DM. As previously reviewed in the introduction, past research has generally demonstrated chronic hyperactivity of the HPA-axis in T1DM (Roy et al., 1990; Roy et al., 1998; Roy et al., 1993), which may be due, in part, to repeated episodes of hypoglycemia, exogenous administration of insulin, prolonged stress from the management of a chronic illness, or a combination of such factors (Cryer, 2002; Wasserman & Trifonova, 2006). However, only a handful of studies have explicitly examined cortisol stress reactions in response to psychological stress in T1DM (e.g., Delamater et al. 1988; Dutour et al., 1996; Wiesli et al., 2005), none of which have made comparisons of individuals with T1DM to a non-diabetic control group.[9]

[9] Dutour et al. (1996) had a group of non-diabetic fourth-year medical students as participants; however, no statistical comparisons were made between the non-diabetic group and the groups with T1DM. Moreover, the non-diabetic group were not matched to the groups with T1DM on any variables and were of different educational backgrounds, different age ranges, and did not experience the same stressor task.

Blood glucose control. Of the three studies that have examined cortisol reactivity in response to psychological stressors in T1DM (e.g., Delamater et al. 1988; Dutour et al., 1996; Wiesli et al., 2005), the strongest support for dysregulation (i.e., attenuated or exaggerated response to stress) of the cortisol stress response comes from the work of Dutour and colleagues. When comparing participants with T1DM on the basis of "brittle" versus "stable" T1DM,[10] Dutour et al. observed an exaggerated cortisol response in participants with "brittle" T1DM. Despite study limitations described in the introduction, Dutour et al. provides support for an exaggerated cortisol reaction to psychological stressors in T1DM and suggests that such dysregulation is due to unstable blood glucose control. The present study did not directly assess blood glucose control (i.e., did not measure HbA1c); however, assuming insulin pump use may act as an indicator of blood glucose control (see section below for review of insulin pump use), the present findings are consistent with Dutour et al. in that an exaggerated cortisol response was observed in young adults with T1DM who do not use insulin pumps when compared to two different groups: matched peers without T1DM and young adults with T1DM who use an insulin pump. In contrast, no difference in cortisol reactivity was observed between young adults with T1DM who use insulin pumps and matched peers.

Insulin pump usage. Given the centrality of insulin pump use to the present findings, a brief review of the mechanism of action and associated benefits of insulin pump therapy is provided. Insulin pump therapy, or continuous subcutaneous insulin infusion (CSII), mimics insulin-delivery patterns of individuals without diabetes (for a review see Pickup, 2012). The mechanism by which CSII improves blood glucose stability is through the use of more rapid-acting insulin compared to the insulin prescribed in standard multiple daily injections (MDI). Rapid-acting insulin has a much lower variation of absorption (±3%) compared to long-lasting insulin (±50%, Pickup). Lower variation of absorption reduces wide swings in blood glucose levels as well as severe episodes of hypoglycemia.

[10] Brittle diabetes was defined by Dutour et al. as number of hypoglycemic evens (>10 per month) and hyperglycemic peaks requiring the addition of rapid insulin (>20) per month.

There are numerous brands and types of insulin pump therapy devices, which vary in which technological features are incorporated into the basic CSII design. One general class that is gaining in popularity is sensor-augmented pump therapy (SAPT), which incorporates CSII with a continuous blood glucose monitoring device (CMD).[11] A recent meta-analysis by Yeh et al. (2013) concluded that the benefit (i.e., better blood glucose stability, avoidance of severe hypoglycemia, patient satisfaction) of insulin pump therapies appears dependent on several factors: the type of device (stronger benefit from SAPT compared to CSII alone), age of patient (children and adults generally benefit more from CSII compared to adolescents), and patients' blood glucose control prior to pump initiation (patients with poorer pre-pump control see largest improvement).

A burgeoning literature has also suggested that insulin pump therapy may be associated with benefits beyond improved blood glucose control such as improved dietary habits (e.g., Markowitz et al., 2013; Peters et al., 2013). Research concerning other benefits such as improved quality of life has been inconclusive and largely anecdotal (e.g., Hirose, Beverly, & Weinger, 2012; Pickup, 2012); however, one randomized clinical trial has reported a wide range of quality of life improvements with the strongest improvements in diabetes-specific quality of life domains such as decreased fear of hypoglycemia (e.g., Rubin, Peyrot, STAR 3 Study Group, 2012).

Mechanisms by which insulin pumps may influence cortisol stress reactivity. In the present study, an exaggerated cortisol response was observed for young adults with T1DM not using insulin pumps (compared to matched peers as well as young adults with T1DM using insulin pumps), whereas no difference was observed between young adults with T1DM using insulin pumps and matched peers. This finding is suggestive that use of insulin pump therapy may be beneficial to other endocrine systems beyond glucose control, such as the HPA axis. Insulin pumps may impact cortisol stress reactivity by decreasing the intensity and frequency of both physiological and psychological stressors. Prolonged or frequent episodes of hypoglycemia

[11] Continuous monitoring devices (CMD) are also available as a stand-alone device and function by providing near continuous monitoring of blood glucose levels some of which are able to alert users when blood glucose levels deviate outside of a specified range (for more extensive description see Yeh et al, 2013; Wagner, Tennen, & Wolpert, 2012).

and administration of insulin are known to trigger the HPA-axis (Cryer, 2002; Weinger & Jacobson, 1998). By stabilizing blood glucose levels, insulin pumps allow for avoidance of severe hypoglycemic episodes, which would suggest that the HPA-axis is also less frequently stimulated. Less frequent stimulation of the HPA-axis would likely reduce allostatic load, the chronic wear-and-tear of chronic activation of natural physiological responses to stress, and lead to improvements across numerous physical and psychological health conditions attributed to the accumulated effects of allostatic load (McEwen & Gianaros, 2010).[12] Similar to the hypothesized causal relationship between HPA-axis perturbations and development of Type 2 Diabetes Mellitus (Rosmond, 2003), exaggerated cortisol stress responses may act to exacerbate the pathophysiological mechanisms inherent in diabetes (Reagan, Grillo, & Piroli, 2008). For these reasons, improved regulation of the HPA-axis may have reciprocal influences on blood glucose control in young adults with T1DM.

In addition to a direct physiological reduction in HPA-axis stimulation, insulin pumps likely affect HPA-axis functioning through a reduction in exposure to daily hassles, reduction in health-related anxieties, and promotion of more adaptive coping. Illustratively, in a randomized clinical trial comparing improvement in quality of life between patients receiving sensor-augmented insulin pump therapy (SAPT) or multiple daily injections (MDI), individuals assigned to SAPT reported substantial reductions in hypoglycemia fear, hypoglycemia-avoidant behavior, treatment problems, blood glucose monitoring burden, interference in daily activities, diabetes worries, and psychological well-being after one year (Rubin et al., 2012). Collectively, these improvements may reflect a reduction of diabetes-related daily hassles and anxieties with concomitant benefits to the HPA-axis.

Accumulation of minor daily hassles can exert a powerful negative effect on health and well-being (e.g., Almeida, 2005; Cohen, Gunthert, Butler, O'Neil, & Tolpin, 2005; DeLongis, Coyne,

[12] One determinant of the direction of cortisol reactivity dysregulation (i.e., exaggerated or attenuated) caused by allostatic load is the underlying pathophysiology of co-morbid diseases (Miller, Chen, & Zhou, 2007). Hypo-cortisolism in Addison's disease versus hyper-cortisolism in Cushing's syndrome represent most extreme example of this continuum of potential dysregulation.

Dakof, Folkman, & Lazarus, 1982; Zautra, 2003). Although less is known about hassles and cortisol relations in diabetic populations, there is evidence that greater daily hassles may be associated with perturbations in the cortisol response to psychological stressors with studies reporting both attenuated (e.g., Roy, 2004) and exaggerated (e.g., Peters, Godaert, Ballieux, & Heijnen, 2003) cortisol response in healthy adult males. According to the cognitive appraisal model of stress (Lazarus & Folkman, 1984), how a given hassle or stressor influences health is determined by the perception of the event (i.e., to what extent the event is perceived as exceeding the individual's resources or capacities). The appraisal of an event will then determine both physiological disturbance (i.e., activation of physiological stress response) as well as engagement in specific coping strategies (e.g., avoidance versus approach). Specific cognitive processes can alter the perception of a threat. In a recent meta-analysis, Denson, Spanovic and Miller (2009) observed that anxious thought processes (i.e., rumination and uncontrollable repetitive thoughts) were associated with exaggerated cortisol response to psychological stressors. Similarly, ruminations over diabetes-specific worries (e.g., fear of hypoglycemia) likely lead to exaggerated cortisol response for young adults with T1DM. The present study did not measure frequency of daily hassles, however, young adults with T1DM using an insulin pump reported greater perception of stress compared to young adults with T1DM not using an insulin pump. This is somewhat inconsistent with the above hypothesis that insulin pumps may confer benefits through a reduction of daily hassles associated with diabetes management. However, reduction of daily hassles specifically associated with diabetes may reduce activation of the HPA-axis independent of reducing overall perception of stress across domains of life. In a large-scale randomized clinical trial comparing quality of life improvements after one-year of insulin pump therapy versus multiple daily injection,[13] Rubin and colleagues observed significant improvements in diabetes-related quality of life related to insulin pump use, but did not observe differences in general quality of life across mental and physical domains. Given that the current study did not

[13] n = 334 adults with T1DM, n = 147 children/adolescents, n = 147 parents

assess daily hassles (general or diabetes-specific) or the perception of diabetes-specific stress, the independence of global versus diabetes specific stressors on the HPA-axis is speculative.

The cognitive appraisal model of stress argues that specific coping strategies influence engagement in adaptive or maladaptive health behaviors (Lazarus & Folkman, 1984) in response to perceived stressors. Coping strategies can be conceptualized along a continuum of "approach" versus "avoidance," with approach strategies generally thought to reflect a more adaptive coping compared to avoidance strategies (Wilkinson, Walford, & Espnes, 2011). The way in which individuals T1DM appraise and cope with stressors appears to influence metabolic control with greater negative appraisals of stressors and more use of avoidance coping strategies found in adolescents with T1DM with "poor" metabolic control (as defined by HbA1c levels) compared with those with "good" metabolic control (Delamater, Kurtz, Bubb, White, & Santiago, 1987). In a 5-year longitudinal study, Sultan, Epel, Sachon, Vaillant, and Hartemann-Heurtier (2008) found that baseline use of adaptive coping strategies in adults with T1DM (i.e., greater use of approach strategies) predicted decreases in state anxiety and better blood glucose control five years later. Engagement in insulin pump therapy may facilitate more adaptive coping strategies allowing for greater engagement in adaptive health behaviors as reflected by improved dietary habits following insulin pump therapy initiation (e.g., Markowit et al., 2013; Peterset al., 2013). However, given that the present study did not assess coping strategies, the above interpretation is speculative.

The influence of socioeconomic status on health disparities. Living in low socioeconomic conditions exposes individuals to numerous sources of chronic stress such as poor housing and neighborhood quality, pollutants and toxins, crowding and congestion, and noise exposure (for a review see Evans & Kim, 2010). Growing up with lower socioeconomic resources exerts powerful effects on later adult health outcomes, above and beyond the effects of current, adult SES (for a review see Cohen, Janicki-Deverts, Chen, & Matthews, 2010). McEwen and Gianaros (2010) argue that the association between low SES and poorer health outcomes may be due to accelerated allostatic load (McEwen, 1998). In support of the allostatic load hypothesis, lower SES has been associated with indicators of accelerated aging across both

peripheral and central biological systems including cerebral, autonomic nervous system, cardiovascular, metabolic, and immune functioning (for reviews see McEwen & Gianaros, 2010; Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010). While lower SES has been repeatedly associated with cortisol perturbations, no consistent direction of dysregulation (e.g., blunted versus exaggerated) has been observed (for a review see Dowd, Simanek, & Aiello, 2009). As detailed by Miller, Chen, and Zhou (2007), chronic stress can lead to either elevated or suppressed HPA-axis activity with pathological consequences resulting from deviations in either direction. The authors argue that the direction of cortisol deviation following exposure to chronic stress is influenced by multiple stressor-specific factors: time since onset, required adaptational demands, induced emotions, controllability, and psychiatric (e.g., effects of stress-induced depression versus stress-induced PTSD).

The relatively higher SES of insulin pump users may provide greater resources (both physiological and psychosocial) with which individuals can cope with stress as well as fewer sources of stress, which may protect against chronic stimulation of the HPA-axis above and beyond the direct impacts of insulin pump therapy. The annual, national cost associated with T1DM is estimated at $14,926 billion dollars with an annual per person cost of $14,856 (Dall et al., 2009). These costs are disproportionately felt by under- or non-insured families.[14] These families not only bear a higher percentage of costs, but are also unable to take advantage of third-party fee negotiations (for a more detailed discussion see Dall et al., 2009). Low SES has been observed to negatively influence metabolic control (for a review see Seeman et al., 2010). Within a pediatric T1DM specialty clinic, Hassan, Loar, Anderson, and Heptulla (2006) found worse blood glucose control, less likelihood of engagement in intensive treatment (i.e., intensive MDI or insulin pump therapy), and greater likelihood of depression in patients growing up in lower SES relative to more affluent patients.

[14] According to the Juvenile Diabetes Research Foundation (Spain, 2008), insulin pump devices cost, on average $5,000 with basic supplies costing $100 per month and reimbursement of costs is variable across insurance providers, although most plans cover pump associated costs.

Within the present study, post-hoc analyses revealed that young adults with T1DM using an insulin pump reported higher childhood family income compared to young adults with T1DM not using an insulin pump. As suggested by Hassan et al. (2006) there are at least two possible mechanisms explaining the observed difference in economic status and insulin pump use in the present study: the direct effects of health care access disparity and the indirect effects associated with low SES (e.g., less frequent self-monitoring, less diabetes knowledge, reduced self-efficacy; Chaturvedi, Stephenson, & Fuller, 1996) leading to poor candidacy for insulin pump therapy.

Interpretation of Neurocognitive Reactivity

The present research was the first known study to examine neurocognitive stress reactivity in T1DM, the results of which suggest a differential response in young adults with T1DM compared to matched non-diabetic peers dependent on specific cognitive tasks. Due to the distinct functions represented by tasks used in the present study, the discussion of findings is organized by domains of neurocognitive functioning assessed in the present study.

Sympathetic nervous system facilitation of attention and processing speed. On a measure primarily reflecting attention and processing speed (i.e., Trail Making Test, TMT), the performance of young adults with T1DM remained stable whereas the performance of matched peers without T1DM tended to worsen following an interpersonal stressor. This may reflect differences in stress responses not assessed by the present study, such as activation of the sympathetic nervous system (SNS). Given that the present study did not assess markers of SNS activation, the interpretation provided below is thus theoretical with regard to explaining the current findings. Activation of the SNS can disrupt or facilitate the “attentional matrix” through global mechanisms of catecholamines on cerebral glucose and oxygen perfusion rate (i.e., combined top-down modulation from frontal, parietal, and limbic systems and bottom-up regulation from ascending reticular activating system; Mesulam, 2000). The effects of SNS stimulation are considered to reflect the general Yerkes-Dodson curvilinear theory of arousal such that too little or too much activation results in disrupted attention whereas moderate activation results in improved attention (see Mendl, 1999). While speculative, differences between the performance of young adults with and without T1DM on the TMT may reflect different thresholds

at which SNS increase occurs. Despite chronic SNS tonal over-activation, a blunted epinephrine response to hypoglycemia and other physical stressors has been repeatedly observed (see Cryer, 2009) and is thought to be due to desensitization of components of the SNS (i.e. noradrenergic system; see Parekh, 2009). The potentially lethal effect of this has been noted in regard to responding to episodes of hypoglycemia (i.e., hypoglycemia unawareness). Such chronic tonal activation of SNS combined with reduced sensitivity of the SNS may result in a relative flat of attentional response during times of mild stress.

No differences were observed on the Sustained Attention Allocation Task, which is thought to reflect both sustained attention and working memory; however, given a lack of reports of normative data, test-retest reliability or cross-validation with other established measures of sustained attention, it is unclear what specific neuropsychological functions this task measures (e.g., Lawrence, Ross, Stein, 2002; Petrie & Deary, 1989; Warburton & Mancuso, 1998; Wesnes & Warburton, 1984). Further, should T1DM confer a relative attentional benefit during acute stress, this benefit would not necessary translate to the SAAT given the high degree of working memory (generally reflective of frontal-system control, see Mesulam, 2000) demands of this task.

Curvilinear effect of cortisol and differential effects on verbal learning, memory and fluency. The present study did not observe differences in performances on tests of verbal learning and memory (RVLT) or verbal fluency (COWAT) between participants with and without T1DM. Neuroanatomically, verbal memory consolidation and retrieval is thought to rely on medial temporal lobes with a primary role played by hippocampal systems (for a review see Mesulam, 2000). Verbal fluency tasks (e.g., COWAT) require rapid retrieval of semantic information and are thought to be dependent on both hippocampal (retrieval of verbal information) and frontal systems (working memory; see Strauss et al., 2006). These null findings may be, in part, due to a curvilinear effect of cortisol on learning and memory, as well as executive functions such as working memory (see Lupien et al., 2007). While the current study was not designed to assess a mediational effect of cortisol on neurocognitive stress reactivity (i.e., due to lack of statistical power), a consideration of the general curvilinear effect of cortisol on neurocognition provides a useful lens through which to consider the present null findings.

Exogenously administered corticosteroids exhibit a curvilinear dose-dependent effect on domains of neurocognitive functioning associated with brain regions with a high density of glucocorticoid receptors (i.e., frontal lobe and hippocampus), with frontal systems being relatively more sensitive compared to hippocampal systems.[15] Low levels of glucocorticoid administration confer a neurocognitive benefit with these domains of cognition while higher doses impair these functions (Lupien,Gillin, & Hauger, 1999; Lupien et al., 2002, Lupien, Wilkinsons, et al., 2001). The curvilinear effect of glucocorticoids is also reflected by the meta-analytic finding that the cognitive effects of glucocorticoids are dependent on time of day (Het, Ramlow, & Wolf, 2005). When administered in the morning, when endogenous cortisol levels are highest, exogenous administration generally inhibits cognitive processes. In contrast, when administered in the afternoon, when endogenous cortisol levels are generally at a nadir, exogenous administration of glucocorticoids generally facilitates cognition.

Studies of stress-induced endogenous release of cortisol are inconsistent with regard to cognitive domains impaired by psychological stressors and the role of cortisol in producing such deficits. In cases of extreme stress during which very high levels of endogenous cortisol are released, the relationship between elevated cortisol and cognitive impairment appears more readily detected (e.g., Taverniers et al., 2010, Taverniers, Taylor, & Smeets, 2011). Findings from laboratory-based studies using more mild psychological stressors stimuli similar to that of the present study have been mixed with some studies observing impairments (e.g., Al'Absi, Hugdahl, & Lovallo, 2002), some failing to observe impairments (e.g., Hoffman & al'Absi, 2003), and others observing impairments in select domains (e.g., Bohnen et al., 1990; Kulmann et al., 2005). Moreover, elevated cortisol reactivity in response to stress has been associated with both improved cognitive functioning (e.g., Myer, Smeets, Giesbrecht, Quaedflieg, & Merckelbach,

[15] As reviewed by Lupien et al. (2007), a primary mechanism by which acute glucocorticoid administration is thought to influence neurocognitive functioning is through differential actions on glucocorticoid receptors and the relative distributions of each receptor type across distinct neuroanatomical regions. Specifically, cognitive functions are theorized to be enhanced when mineralocorticoid receptors (MR) are saturated, but glucocorticoid receptors (GR) are minimally activated, resulting in a high MR/GR activation ratio. In contrast, cognitive functioning is thought to be impaired when MR/GR activation ratio is low.

2013) as well as impaired performance (e.g., Al'Absi et al., 2002). Inconsistency in these findings is likely due to differential effects of mild increases of cortisol dependent on time of day (e.g., Het et al., 2005).

Within the present study, it was hypothesized that participants with T1DM would exhibit a greater decline in neurocognitive performance following an interpersonal stressor when compared to matched peers. Notably, the present study took place during the afternoon to facilitate capturing cortisol stress reactivity; however, stressors occurring during the afternoon, when cortisol levels are at a nadir, do not consistently impair neurocognitive processes thought to be most sensitive to the effects of cortisol reactivity (learning, memory, and working memory; e.g., Hoffman & al'Absi, 2004; Myer, et al., 2013). It is possible that overall cortisol levels stayed within a range that would impair or facilitate neurocognitive functioning in an equitable fashion across participants with and without T1DM. This is supported by the lack of statistical differences observed in overall cortisol output (AUC_g) between participants with and without T1DM. It is also possible that divergent patterns of cortisol reactivity produced similar of changes in neurocognitive functioning reflective of the curvilinear effect of cortisol. Participants with T1DM that were not on an insulin pump were found to have elevated cortisol reactivity compared to matched peers. Within this group, both high and low cortisol responses could have, theoretically led to a similar pattern of neurocognitive decline reflective of over and under saturation of cortisol receptors. Likewise, participants with T1DM treated with an insulin pump did not statistically differ from matched peers in terms of cortisol reactivity, which would also be theoretically consistent with a similar neurocognitive pattern on these tests. Collectively, the above interpretations, while supported by theory and previous research, were not directly assessed within the present study and are solely speculative in nature.

Significant differences on performance of the Stroop tasks were observed between young adults with and without T1DM that were dependent on whether the young adult with T1DM was using an insulin pump. The Stroop task is dependent on frontal systems and thus may be vulnerable to cortisol reactivity. However, interpreting the findings from the Stroop task through the lens of cortisol reactivity is somewhat more difficult in that the performance of young adults

with T1DM not using an insulin pump was not different from matched peers, and neither group demonstrated significant change across the stressor. While young adults with T1DM using an insulin pump generally improved across the stressor compared to matched peers, it is unclear to what extent this improvement can be explained by differences in cortisol as these relationships were not originally hypothesized within the present study and not directly assessed. Further, no significant differences between the cortisol reactivity of participants with T1DM on an insulin pump and matched peers were observed. Performance patterns on the Stroop task may be better accounted for by other process described below.

Promotion of adaptive coping reflected by the Stroop task: Indirect benefits of insulin pumps. Within the present study, young adults with T1DM on an insulin pump demonstrated a benefit from repeated exposure to the Stroop task whereas matched peers did not benefit from repetition. In contrast, young adults with T1DM not treated with an insulin pump did not statistically differ from matched peers in patterns of performance across administrations of the Stroop task. The current findings are suggestive that coping with T1DM within the context of adequate resources (assuming insulin pump therapy represents relative greater access to resources) may confer specific cognitive benefits during subsequent stressful experiences, which then reciprocally facilitate contextually adaptive and flexible responding.

Performance on the Stroop task requires management of dual task demands of goal maintenance simultaneous with inhibiting habitual responding. While the translation of cognitive abilities represented by neuropsychological tasks to real-life situations remains uncertain (for a discussion see Marcotte & Grant, 2009), the specific cognitive abilities represented by the Stroop task appear uniquely suited to promote a more flexible response to stress (i.e., inhibiting an overlearned response) while facilitating goal achievement (i.e., maintaining focus on goal).

One lens through which to view these findings is that coping with the stress of a chronic illness, such as T1DM, with adequate internal and external resources may lead to an inoculation effect against future stressors. The concept of stress inoculation is related to that of resilience, but focuses on a process by which repeated stress exposure may facilitate adaptive responses to future stressors (for a review see Luecken, Roubinov, & Purdom, 2011). One mechanism by

which exposure to repeated stressors may lead to adaptive coping strategies is suggested by Huether (1996; 1998) who argues that coping strategies that are adaptive are acquired through an alteration of controllable and uncontrollable stressors. Huether explains that the presentation of repeated controllable stressors aids to cement effective patterns of appraisals and coping through strengthening neuronal connections, whereas the presentation of uncontrollable stressors serves to help extinguish maladaptive patterns of coping and provides a necessary prerequisite for the reorganization of neuronal networks and behavioral patterns (through activation of the stress response).

The bulk of the literature supporting stress inoculation effects comes from studies of rodents and nonhuman primates exposed to repeated mild stressors. Nonhuman primate models have been particularly useful in demonstrating the beneficial impact of mild/moderate stressors during early development on physiological and behavioral stress responses later in development (see Lyons & Parker, 2007 for a review). More recently, a cerebral benefit of stress inoculation has been observed as evidenced by increased ventromedial prefrontal cortex (Katz et al., 2009) as well as increased hippocampal neurogenesis (Lyons et al., 2010), areas involved in learning in memory. Support of stress inoculation in humans is more limited. The experience of mild stressful events in childhood has been associated with reduced cardiovascular reactivity to a laboratory stress test (Boyce & Chesterman, 1990) and the use of positive coping strategies in adulthood (Khoshaba & Maddi, 1999). Luecken (2002) and Luecken, Kraft, Appelhans, and Enders (2009) found that young adults who lost a parent in childhood and reported a warm relationship with their surviving parent had higher social support and smaller stress-related increases in negative emotion during daily life stressors than nonbereaved young adults who reported similarly caring relationships during childhood. Thus, successfully coping with a stressor early in life may enhance individuals' personal competence in coping and thus enable such individuals to appraise potential stressors as "challenges" instead of as "threats."

Enrollment in insulin pump therapy often requires intensive training not only on insulin pump use, but also on diabetes management in general as well as intensive physician monitoring during initial stages (Pickup, 2012). Engagement in insulin pump therapy appears to provide spill-

over effects reflective of greater engagement in healthier behaviors such as improved diet adherence (e.g., Markowitz et al., 2013; Peters et al., 2013) and improvements in quality of life (e.g., Rubin et al., 2012). Collectively, these insulin pump "extras" may provide young adults with T1DM effective coping skills to successfully manage T1DM. Successful management of T1DM may act to provide young adults with T1DM a sense of mastery not available to non-diabetic peers. This sense of mastery may then facilitate an approach to future stressors through the lens of a "challenge" rather than a "stressor," which may translate into greater task engagement across the present study regardless of the presence of an interpersonal stressor. In contrast, matched peers without T1DM who likely have not benefited from such an inoculation, may view the post-stressor administration of tasks through the lens of a "stressor" rather than a "challenge," and thus be less engaged in the task demands. Although we cannot rule out the possibility that peers without T1DM have not had life experiences that might cause an inoculation, the matching procedure used in the current study, successfully equated clusters of young adults with T1DM on an insulin pump and matched peers on maternal education, race/ethnicity, and childhood family income, which have been conceptualized as demographic indices of childhood stress (see Luthar & Zigler, 1991). Additionally, populations with chronic health conditions have been shown to experience a greater level of daily hassles, which were more strongly related to later health outcomes compared to major life events (DeLongis et al., 1982).

Methodological Considerations When Interpreting Results

Post-hoc analyses revealed a pattern of differential initial and peak cortisol levels that may have biased the present findings. Regardless of the mechanism by which differential initial and peak cortisol levels occurred, these differences may have influenced the present findings and a more in-depth discussion of these possible biases and associated implications is provided.

Lower initial cortisol sample in participants with T1DM not using an insulin pump and differential peak cortisol between participants with and without T1DM. As detailed in the results section, initial cortisol levels were lower for participants with T1DM not using an insulin pump when compared to matched controls. In contrast, there was not a statistically significant difference between initial cortisol levels of participants with T1DM using an insulin pump and

matched controls. There was also not a significant difference in initial cortisol levels between the two control groups. Additionally, participants with and without T1DM differed in whether or not cortisol levels peaked at the first sample: a significantly greater proportion of control participants had a peak cortisol value at the first sampling period compared to the proportion of participants with T1DM who had a peak cortisol value at this sampling period. In contrast, a similar proportion of participants with T1DM with and without insulin pumps demonstrated a peak cortisol level at the initial sample period. There are two possible mechanisms by which such a pattern may have occurred: 1) differential impact of initial fingersticks among participants depending on level of familiarity with fingersticks, and 2) attenuated baseline cortisol levels in participants with T1DM not on insulin pumps.

Possible differential experience of fingersticks. Although the experimental protocol was designed to offer a standardized interpersonal stressor experience, one interpretation of the above pattern of findings is that participants may have had differential reactions to the protocol. Specifically, one aspect of the protocol involved repeated fingersticks which may have been more aversive to those participants less familiar with daily blood glucose tests (i.e., non-diabetic control participants and potentially young adults with T1DM using insulin pump therapies). The current study did not sample salivary cortisol or assess positive or negative affect prior to initial finger-stick blood spot screening. Therefore, the degree to which baseline cortisol patterns in all groups except participants with T1DM not using an insulin pump reflects anticipatory stress (e.g., anticipating a novel aversive stimuli) versus pain induction (through fingersticks) is uncertain and may reflect the influence of both.

The influence of fingersticks on cortisol reactivity has not been directly examined; however, fingersticks likely represent a novel, aversive stimuli for finger-stick naïve individuals such as young adults without diabetes. The likelihood that fingersticks represent an aversive stimuli for insulin pump users is less clear due to the unknown frequency of finger-stick use within this sub-population of T1DM.[16] Novel, aversive stimuli are well-known to activate the HPA-axis

[16] Alternatives to finger-stick blood glucose monitoring are available. Insulin pump use does not eliminate the need for external blood glucose monitoring (some pumps lack monitoring devices

(for a review see Steckler, 2005). The heightened pain sensitivity found in the finger-tip (Schady, Torebjörk, & Ochoa, 1983) is suggestive that puncture of other less sensitive skin sites such as during venipuncture would provide an approximation of the potential effect of fingersticks on cortisol. Studies using a venipuncture-stressor paradigm have been found to elicit a cortisol response for some participants across genders and developmental periods (e.g., Hillman, Dorn, Loucks, Berga, 2011; Hubert, Möller, & Nieschlag, 1989; McCarthy et al., 2009; Sontag-Padilla et al., 2012; Susman, Dorn, Inoff-Germain, Nottelmann, & Chrousos, 1997). Application of a painful stimuli (e.g., cold pressor tasks) is generally shown to produce a more reliable activation of the sympathetic nervous system compared to HPA-axis activation (see Smeets et al., 2012), which would suggest that activation of the HPA-axis would be largely driven by anticipation of a finger-stick rather than the physiological effect of pain induction.

For individuals initially diagnosed with diabetes (both type 1 and type 2), the pain and discomfort of fingersticks are noted as a barrier to blood glucose monitoring (Cradock & Hawthorn, 2002). Fear of blood and injury are related both to less frequent blood glucose checking and poorer blood glucose control in adults with T1DM (Berlin et al., 1997). The aversive nature of fingersticks is also reflected by the burgeoning industry of devices that can provide accurate measurement of blood glucose at alternative, less painful sites such as the forearm (Lee, Weinert, Miller; 2002) and eliminate the need for skin puncture (e.g., mid-infrared spectroscopy measurement of skin glucose concentration, Pleitez et al., 2013). Although these findings indicate that individuals with T1DM are not immune to negative perceptions of fingersticks, it is plausible that a T1DM population not using insulin pump therapy may be more likely to have habituated to the pain and emotional distress of fingersticks compared to relatively

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and pumps with monitors require regular external calibration), however, the recommended frequency of external monitoring is “greatly reduced” when continuous blood glucose monitors (CMD) or devices that incorporate CMD such as sensor-augmented insulin pumps are used (Juvenile Diabetes Research Foundation, n.d.). Additionally, socioeconomic disparities in health care access translate to greater use of more expensive, state-of-the-art disease management technologies such as insulin pumps and monitoring devices not dependent on fingersticks (Brown et al., 2004).

more finger-stick naïve populations. However, anxiety surrounding fingersticks was not assessed thus differential experiences of fingersticks is entirely speculative.

Attenuated baseline cortisol levels in participants with T1DM not on insulin pumps potentially due to poorer metabolic control. An assumption implicit in the above interpretation regarding fingersticks is that the cortisol pattern from the first sampling period reflects *elevated* baseline cortisol within control participants and participants with T1DM using an insulin pump. However, if one assumes the reverse, that the cortisol pattern is reflective of *attenuated* baseline cortisol within participants with T1DM not using an insulin pump, a consideration of alternative interpretations is warranted. An attenuated baseline cortisol in participants with T1DM not using an insulin pump may reflect an altered diurnal rhythm in addition to exaggerated cortisol reactivity. Given that this study did not assess diurnal cortisol, this interpretation is extremely speculative. Moreover, this interpretation is not consistent with past research, which has found elevated morning and afternoon plasma cortisol and failure to suppress cortisol following administration of dexamethasone (reflective of negative feedback failure; Roy et al., 1990)[17] and increased total 24-hour urinary-free cortisol output (Roy et al., 1998)[18] within adults with T1DM compared to healthy controls. Another possible explanation is that participants with T1DM not using insulin pumps failed to demonstrate the normative anticipatory stress response that occurs on days in which individuals are anticipating a psychological stressor (e.g., Lovallo, Farag, & Vincent, 2010) due to psychological processes not assessed in the current study. Regardless of the mechanism, differences in baseline cortisol levels may have influenced the primary findings, and this will be explored below.

Influence of differential initial and peak cortisol on cortisol reactivity. The precise nature of how such initial elevated cortisol levels prior to the experimental induction might influence observation of later cortisol reactivity is unclear. In healthy individuals, stress-induced

[17] Average disease duration was 12.0 years (*SD* = 7.2). Disease duration was not correlated with plasma cortisol levels, but was correlated postdexamethasone plasma levels of cortisol collected on a different day (reflective of negative feedback failure).

[18] Average length of duration of T1DM was 13.56 years. Increased urinary cortisol was related to longer disease duration and higher frequency of other diabetic complications.

hormonal activation should lead to rapid inhibitory feedback of glucocorticoids on the subsequent release of ACTH at the hypothalamic level, lasting between 5 to 15 minutes (Fulford & Harbuz, 2005). Such rapid inhibitory feedback might then interfere or alter subsequent HPA-axis experimental activation. Additionally, given the temporal periodicity of possible stressors that participants could experience across the current study's protocol (periodic fingersticks, cognitive testing, and interpersonal stressor), the HPA-axis of some control participants may have been periodically stimulated so as to maintain elevated levels of cortisol. A stress response would then be obscured by the fact that no "true" baseline cortisol value was obtained for most participants (i.e., on average, the first cortisol sample occurred 31.95 minutes after the initial screening finger-stick, *SD* = 8.38). Mathematically, should a person reach a maximum level of cortisol prior to experimental stress induction, repeated activation would not be apparent from the calculation of area under the curve with respect to increase given that reactivity is assessed from initial baseline sample.

The influence of elevated initial cortisol levels may have influenced AUC_i differently for high responding insulin pump users compared with control participants. Specifically, while insulin pump users also demonstrated an elevated initial cortisol level, they were no more likely to "peak" at this time point than participants with T1DM not using an insulin pump. In contrast, a greater proportion of control participants demonstrated a "peak" response at this initial sampling compared to participants with T1DM.

Within control participants from the present study, the peak cortisol response at baseline appeared to influence control participants' later cortisol responses in a variable manner. In examining individual plots of control participants' raw cortisol values across participation, there appeared to be variability in subsequent cortisol levels. Specifically, of the 21 control participants who demonstrated peak cortisol levels at the first sampling period, the majority also demonstrated later fluctuations, with rising and falling cortisol levels (n = 13/21) although such fluctuations did not reach the initial peak level. A smaller percentage of control participants who peaked at the initial sampling period exhibited a continuous decline in cortisol levels (n = 8/21).

Effect of differential initial cortisol levels on neurocognitive stress reactivity. The influence of cortisol levels on neurocognitive processes was not part of the study design or analysis. However, a large literature documenting the effects of glucocorticoids on neurocognitive functioning (for a review see Lupien et al., 2007) suggests that point-to-point changes in cortisol not captured by AUC_i may relate to performance on cognitive tasks at specific times during the protocol.

Differential timing of cortisol increases may have obscured cognitive performances at baseline and post-stressor. Such interference may have eliminated or reversed differential patterns between participants with and without T1DM on tasks involving dependent on brain regions with greater glucocorticoid receptor densities (i.e., COWAT, RVLT, & Stroop task dependent on frontal and hippocampal systems). A larger proportion of the control participants demonstrated a peak cortisol level at the first sample and higher initial cortisol levels. These individuals may have benefited from this relatively higher level of cortisol during the first administration of the cognitive tasks, artificially boosting their pre-stressor baseline neurocognitive test performance. Viewed from this perspective, a relative worsening of performance following a stressor (i.e., lack of practice effect on the Stroop task) may reflect the impact of relatively decreasing cortisol levels later in the protocol (i.e., the other side of the curvilinear relationship between cortisol and cognition). In contrast, a smaller proportion of individuals with T1DM demonstrated a peak cortisol level at the first sample, and in general, demonstrated an increase in cortisol from the baseline levels, which may, in part, explain an improvement on the Stroop task for those individuals on insulin pumps.

General Limitations

In addition to the potential selection-history confound described above, several other factors complicate interpretation of the present findings. First, while the present study was designed to occur in the afternoon to best capture the effects of psychological stressors on cortisol response, such a time period likely hindered observing cognitive deficits due to stress as these impairments are best seen in the morning when cortisol levels are higher as previously described in great detail (Het et al., 2005). Second, while the number of participants with T1DM is

comparable to previous studies examining HPA-axis reactivity in T1DM, the size of the present sample was potentially underpowered to observe subtle cognitive deficits, which previous meta-analyses have described as small in terms of effect size.

A third limitation that also reduced power to observe subtle cognitive deficits was the use of cognitive tests that produced floor (most participants performing at very low levels) and ceiling effects (most participants performing at very high levels). Specifically, most participants learned and retained a large proportion of words from the word list learning task used (RVLT). While the RVLT is very sensitive in measuring verbal learning and retention in older populations, it is less sensitive with younger populations (Strauss et al., 2006). In contrast, most participants performed poorly on the sustained attention task used (SAAT). Specifically, few participants were able to correctly respond to many target stimuli without also responding to many distractor foils. The use of such insensitive cognitive tests further reduces statistical power to observe stress-induced deficits in cognitive performance. Fourth, while the current study did not assess pre-stressor cognitive deficits, an underlying theory on which hypotheses regarding neurocognitive stress reactivity were based was that stress-induction would exacerbate cognitive deficits in cognitively "vulnerable" populations. Previous meta-analyses have identified early disease onset (i.e., below age 7) as a risk factor in predicting cognitive deficits in T1DM (Gauderi et al., 2008); however, the present study sample contained very few participants diagnosed with T1DM at an early age.

Fifth, the present study did not measure an objective indicator of blood glucose control (i.e., HbA1c) and did not obtain information concerning the type of insulin pump used by participants with T1DM. As previously stated, an assumption made in interpreting some of these findings is that participants on insulin pumps have better overall blood glucose control compared to participants not on an insulin pump; however, as previously reviewed, insulin pumps alone (without a continuous blood glucose monitoring component) have not reliably demonstrated better overall blood glucose control.

Sixth, the present study used a sampling period of 20-minute intervals designed to capture the effects of the interpersonal stressor on salivary cortisol. These sampling intervals are likely too long to accurately capture blood glucose changes. Blood glucose reactivity and output

were not related to cortisol outcomes, which likely reflects differential timing of the stress response for blood glucose and salivary cortisol. Changes in blood glucose can occur very rapidly and sampling periods of 1-5 minutes have been suggested to best capture metabolic reactions (Wagner, Tennen, & Wolpert, 2012).

Seventh, the index used in the present study to capture cortisol reactivity (i.e., AUC_i) is a summary indicator of HPA-axis reactivity. AUC_i was used in the present data as its computation accounts for both baseline hormone levels as well as changes across time (Pruessner et al., 2003). As detailed by Fekedulegn et al. (2007), AUC_i is always negative when cortisol levels are declining and positive when cortisol levels are increasing. However, when patterns of cortisol change involve both increases and decreases, AUC_i can be either positive or negative depending on the ratio of net increase to decrease. Moreover, AUC_i can be problematic when attempting to observe nuances within patterns of reactivity (e.g., increases at one point, but then decreases at a subsequent point). Highly correlated patterns of responding can result in considerable differences in AUC_i and different patterns of responding can result in identical values of AUC_i.

Study Strengths

The current study was the first known to the author to attempt several advances in the field of neurocognitive and neuroendocrine functioning in T1DM. As reviewed in the introduction, the human literature regarding neuroendocrine stress reactivity within T1DM is extremely limited and marked by a lack of equitable comparison groups. The current study is the first to compare neuroendocrine and neurocognitive stress reactivity in T1DM to a matched control group. Secondly, the present study used a much more narrow age range of 18-30, allowing for better control of the effect of age on cortisol reactivity. In addition to allowing better control over the potential influence of age-related changes in the HPA-axis, the age range represented by the present study population is a developmental period of specific interest to the treatment of T1DM. Third, the current study is the first known study to examine differences in hormonal regulation between individuals with T1DM on and off insulin pump therapies and represents a unique contribution of the present study to the insulin pump therapy literature.

Beyond the strengths of the present study specific to T1DM, this study also introduced a methodological model for detecting subtle cognitive impairments that can be potentially applied to studying a wide range of diseases that result in cognitive impairments. The induction of a stressor may aid in illuminating cognitive deficits at earlier stages of disease processes when intervention is still possible (e.g., prior to neuronal death). One example of how such a model may be applied to other diseases beyond diabetes is in the field of Alzheimer's disease research. As reviewed by Resia et al. (2011), there is a convergence of evidence that the pathophysiological basis of Alzheimer's disease begins years to decades prior to symptom manifestation. As advocated by the National Institute of Aging, developing diagnostic guidelines for preclinical stages of Alzheimer's disease will likely require advances in neuropsychological assessment. In addition to the development of more sensitive neuropsychological instruments, application of novel assessment methods (i.e., through a stress induction paradigm) may aid in the detection of preclinical cognitive impairments across a wide array of diseases with central nervous system effects.

Future Directions

The current study offers a number of directions for future research. Most importantly, these results highlight the potential role of insulin pumps in reducing the negative impact of T1DM on other outcomes beyond blood glucose control. Given the preliminary nature of the present findings due to study limitations, replication of these findings is essential. Research concerning neurocognitive functioning in T1DM should use targeted recruitment of individuals with T1DM who were diagnosed in early childhood (i.e., below the age of 7) to maximize power to detect stress-induced cognitive impairments potentially related to early onset. Given the rising popularity and accumulating evidence of the benefits of insulin pumps, studies should be careful to recruit an equal number of individuals with T1DM who are on and off insulin pumps. Moreover, a powerful direction to build from the current study would be to examine neuroendocrine and neurocognitive stress reactivity before and after initiation of insulin pump therapy within the same individuals. Findings from the current investigation also suggest that future studies utilizing non-diabetic control groups should assess blood glucose through pain-free means (e.g., mid-infrared

spectroscopy measurement of skin glucose concentration, Pleitez et al., 2013) to eliminate the potential differential experience of stress between individuals with and without diabetes or better yet, use continuous blood glucose monitoring devices, which allow precise execution of monitoring intervals best representative of blood glucose changes (for a discussion of inclusion of continuous monitoring devices in behavioral research, see Wagner et al., 2012). Experimental evaluation of cortisol reactivity due to fingersticks alone and in combination with a psychological stressor in finger-stick naïve populations is an important line of research given that finger-stick blood spots remain the least expensive method to assess blood glucose.

The present study used AUC_i as a summary index to capture cortisol reactivity. The drawbacks of AUC_i as detailed elsewhere (see Limitations section). Future research not constrained by the same limitations of the current study (i.e., sample size and clustered data, variability in sampling periods due to adherence to blood glucose safety procedure), would benefit from pursuing alternative approaches in capturing cortisol reactivity. Ideally, to best capture such pattern of responding, mixed regression models such as hierarchical linear models, growth curve models, and random coefficient models would be used (Blackwell, Mendes de Leon, & Miller, 2006). Other alternatives detailed by Fekedulegn et al. (2007) include reactivity (difference between first and last sample), slope of the line through the baseline and last measurement (reactivity divided by time from baseline to last measurement), and slope of the regression line fitted through the raw cortisol data. An additional statistical method has been used by Morris and colleagues (Morris, Rao, & Garber, 2012; Morris, Rao, Wang, & Garber, 2013), who computed cortisol AUC_i based on the second through last cortisol measurements, controlling for initial cortisol level.

A strength of the present study was the use of a psychological stressor as a paradigm to assess subtle cognitive deficits. Future research should make use of this paradigm in assessment of subtle cognitive deficits across diseases with central nervous system effects. As previously noted, the National Institute on Aging has specifically advocated for methodological improvements in neurocognitive assessment of subtle cognitive changes associated with preclinical stages of Alzheimer's disease (Reisa et al., 2011), which is only one example of how

this paradigm might be applied to other diseases. In applying such paradigms in the future, protocols should take place in the morning to maximize observation of stress-induced cognitive impairments (Het et al., 2005). Further, careful consideration of test battery selection to avoid floor and ceiling effects observed in the present study will improve the ability to detect such subtle changes.

Conclusions and Clinical Implications

The current research sought to examine neuroendocrine and neurocognitive stress reactivity in young adults with and without T1DM. It was hypothesized that compared to matched peers, young adults with T1DM would demonstrate 1) a dysregulated cortisol reaction and 2) greater neurocognitive decline in response to an interpersonal stressor. The results of this study provide mixed support for these hypotheses. Young adults with T1DM not using an insulin pump demonstrated an exaggerated cortisol response when compared to matched peers, suggesting that relatively poorly controlled T1DM may be associated with elevated cortisol reactivity. However, the hypothesis that young adults with T1DM would exhibit a greater cognitive decline in response to stress when compared to matched peers was not supported. Across most neurocognitive tasks (i.e., RVLT, SAAT, COWAT) no difference in performance pattern was observed between young adults with T1DM compared to matched peers. While different performance patterns were observed on the Trail Making Test and the Stroop task, these patterns were not in the hypothesized direction. Young adults with T1DM appeared to remain stable while matched non-diabetic peers appeared to deteriorate on the Trail Making Test, a test measuring attention and processing speed. Young adults with T1DM using an insulin pump demonstrated a benefit from repeated administration of the Stroop Task, a test of cognitive interference, whereas matched peers did not.

The present findings add to an emerging literature documenting elevated cortisol reactivity in response to psychological stressors in individuals with T1DM. Previous research suggests that the magnitude of over-activation of the HPA-axis is associated with longer disease duration, which is concerning given the present study's focus on young adults (suggesting that this exaggerated response may become more pronounced over time). Hyper-activation of the HPA-

axis has been theorized to exacerbate medical complications associated with T1DM (e.g., retinopathy, cardiovascular complications; Roy et al., 1998) and potentially play an etiological role in diabetes-related depression (Brown, Varghese, & McEwen, 2004). While not assessed in the present study, chronically elevated tonal SNS activation coupled with sympathetic nervous system response desensitization may also influence the health and well-being of young adults with T1DM (see Cryer 2009, Parekh, 2009). Performances on a measure of attention and processing speed, which are sensitive to SNS activation, were flat in young adults with T1DM but declined within matched peers following the stressor, a pattern consistent with possible decreased cerebral noradrenergic sensitivity within young adults with T1DM. Dysregulated stress responses may undermine the calibration of adaptive coping strategies and engagement in healthy behaviors in young adults with T1DM, which would likely be more difficult to establish in later adulthood (see Del Giudice, Ellis, & Shirtcliff, 2011), although such theories were not hypothesized or assessed within the present study.

In addition to highlighting areas of impaired functioning in T1DM, the current findings are suggestive that insulin pump therapy may potentially ameliorate such dysregulation. Several mechanisms by which insulin pumps may be protective are suggested by previous research and theory. However, the present study was not designed to evaluate these processes and their influences are thus speculative. Benefits of insulin pump use are likely due to both direct and indirect effects. Direct effects may include reduction in the frequency with which the HPA-axis is stimulated through better metabolic control as well as decreased daily hassles and diabetes-related anxieties. Potential indirect effects include a theorized promotion of adaptive coping strategies and health behaviors, as well as benefits associated with a relatively more affluent socioeconomic status.

The presence of T1DM within the context of insulin pump use was also related to a relative improvement compared to non-diabetic peers on a task reflective of inhibition of habitual responses in favor of achieving a goal. These findings are suggestive that insulin pump status may reflect processes similar to stress inoculation whereby experience of a moderate stressor

such as a chronic illness that does not overwhelm capacities and resources may provide protection against the deleterious effects of future stressors.

Emerging adulthood (i.e., spanning ages 18-30, Arnett, 2000) is considered a transitional period of particular concern for patients with T1DM (Garvey et al., 2012) during which young adults with T1DM must cope with normative developmental challenges while simultaneously assuming relatively independent treatment responsibility and managing transitions to from pediatric to adult care. The current findings suggest that insulin pump therapies and/or components derived from such treatments (e.g., potential closer connection with health care services) may provide protection during this risky period of transition. If replicated, these effects support greater third-party payment or subsidization of these devices, which are currently prohibitively expensive for many individuals. Collectively, the results of this study add to an emerging literature demonstrating an exaggerated cortisol response during psychological stress within T1DM, which may exacerbate challenges faced by young adults with T1DM during this transitional period of development. However, these findings also highlight that the diagnosis of T1DM does not equate to inevitable disability.

REFERENCES

Aardal & Holm (1995). Cortisol in saliva: Reference ranges and relation to cortisol in serum. *European Journal of Clinical Chemistry and Clinical Biochemistry, 33*(12), 927-932. doi:10.1515/cclm.1995.33.12.927

Aiken, L. & West, S. G. (1991). *Multiple regression: Testing and interpreting interactions.* Thousand Oaks, CA: Sage Publications.

Al'Absi, M., Hugdahl, K., & Lovallo, & W. R., (2002). Adrenocortical stress responses and altered working memory performance. Psychophysiology, 39(1), 95-9. doi:10.1111/1469-8986.3910095

Allen, K. V., & Frier, B. M. (2003). Nocturnal hypoglycemia: Clinical manifestations and therapeutic strategies toward prevention. *Endocrine Practice, 9,* 530-543. doi:10.4158/EP.9.6.530

Allen, C., LeCaire, T., Palta, M., Daniels, K., Meredith, M., D'Alessio, D. J. (2001). Risk factors for frequent and severe hypoglycemia in type 1 diabetes. *Diabetes Care, 24*, 1878-1881. doi:10.2337/diacare.24.11.1878

Almeida, D. M. (2005). Resilience and vulnerability to daily stressors assessed via diary methods. *Current directions in Psychological Science, 14,* 64-68. doi:10.1111/j.0963-7214.2005.00336.x

American Diabetes Association (n.d.). *Hypoglycemia.* Retrieved February, 3, 2011, from http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html

Arnett, J. J. (2000). Emerging adulthood: A theory of development from the late teens through the twenties. *American Psychologist, 55*(5), 469-480. doi:http://dx.doi.org/10.1037/0003-066X.55.5.469

Army Individual Test Battery (1944). *Manual of Directions and Scoring.* Washington DC: War Department, Adjutant General's Office.

Bade-White, P. A., & Obrzut, J. E. (2009). The neurocognitive effects of type 1 diabetes mellitus in children and young adults with and without hypoglycemia. *Journal of Developmental and Physical Disabilities, 21,* 425-440. doi:10.1007/s10882-009-9151-y

Badrick, E., Kirschbaum, C., & Kumari, M. (2007). The relationship between smoking status and cortisol secretion. *Endocrinology & Metabolism, 92,* 819-824. doi:10.1210/jc.2006-2155

Benton, A. L., Hamsher, K. deS., & Sivan, A. B. (1994). Multilingual Aphasia Examination (3rd ed.). San Antonio, TX: Psychological Corporation.

Berlin, I., Bisserbe, J.-C., Eiber, R., Balssa, N., Sachon, C., Bosquet, F., Grimaldi, A. (1997). Phobic symptoms, particularly the fear of blood and injury, are associated with poor glycemic control in type 1 diabetic adults. *Diabetes Care, 20*(2), 176-178. doi:10.2337/diacare.20.2.176

Blackwell, E. M. A., de Leon, C. F., & Miller, G. E. (2006). Applying mixed regression models to the analysis of repeated-measures data in psychosomatic medicine. *Psychosomatic Medicine, 68*(6), 870-878. doi:10.1097/01.psy.0000239144.91689.ca

Bohnen, N., Houx, P., Nicolson, N., & Jolles, J. (1990). Cortisol reactivity and cognitive performance in a continuous mental task paradigm. *Biological Psychology, 31*(2), 107-16. doi:10.1016/0301-0511(90)90011-K

Boyce, W. T., & Chesterman, E. (1990). Life events, social support, and cardiovascular reactivity in adolescence. *Developmental and Behavioral Pediatrics, 11*(3), 105-111.

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271-301. doi:10.10170S0954579405050145

Boyle, P. J., & Zrebiec, J. (2007). Physiological and behavioral aspects of glycemic control and hypoglycemia in diabetes. *Southern Medical Journal, 100*(2), 175-182. doi:10.1097/01.smj.0000242866.81791.70

Brands, A. M. A., Biessels, G. J., de Haan, E. H. F., Kappelle, L. J., & Kessels, R. P. C. (2005). The effects of type 1 diabetes on cognitive performance: A meta-analysis. *Diabetes Care, 28*(3), 726-735. doi:10.2337/diacare.28.3.726

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: does cortisol play a role? *Biological Psychiatry, 55*(1), 1-9. doi:10.1016/S0006-3223(03)00473-6

Bryden, K. S., Peveler, R. C., Stein, A., Neil, A., Mayou, R. A., & Dunger, D. B. (2001). Clinical and psychological course of diabetes from adolescence to young adulthood: A longitudinal cohort study. *Diabetes Care, 24*(9), 1536-1540. doi:10.2337/diacare.24.9.1536

Bryne, D. G., Davenport, S. C., & Mazanov, J. (2007). Profiles of adolescent stress: The development of the adolescent stress questionnaire. *Journal of Adolescence,* 30(3), 393-416. doi:10.1016/j.adolescence.2006.04.004

Centers for Disease Control and Prevention (2005). *Recommended Infection-Control and Safe Injection Practices to Prevent Patient-to-Patient Transmission of Bloodborne Pathogens*. Retrieved from http://www.cdc.gov/hepatitis/Populations/PDFs/diabetes_handout.pdf

Chan, O., Chan, S., Inouye, K., Shum, K., Matthews, S. G., Vranic, M. (2002). Diabetes impairs hypothalamo-pituitary-adrenal (HPA) responses to hypoglycemia, and insulin treatment normalizes HPA but not epinephrine responses. *Diabetes, 51,*1681–1689. doi:10.2337/diabetes.51.6.1681

Chan, O., Chan, S., Inouye, K., Vranic, M., & Matthews, S. G. (2001). Molecular regulation of the hypothalamo-pituitary-adrenal (HPA) axis in streptozotocin-induced diabetes: Effects of insulin treatment. *Endocrinology, 142*, 4872-4879. doi:10.1210/en.142.11.4872

Chan, O., Inouye, K., Akirav, E., Park, E., Riddell, M. C., Vranic, M., & Matthews, S. G. (2005). Insulin alone increases hypothalamo-pituitary-adrenal activity, and diabetes lowers peak stress responses. *Endocrinology, 146*(3), 1382-1390. doi:10.1210/en.2004-0607

Chan, O., Inouye, K., Vranic, M., & Matthews, S. G. (2002) Hyperactivation of the hypothalamo-pituitary-adrenocortical axis in streptozotocin-diabetes is associated with reduced stress responsiveness and decreased pituitary and adrenal sensitivity. *Endocrinology, 143*, 1761–1768. doi:10.1210/en.143.5.1761

Charmandari, E., Kino, T., Souvatzoglou, E., & Chrousos, G. P. (2003). Pediatric stress: hormonal mediators and human development. *Hormone Research, 59*(4), 161-179. DOI: 10.1159/000069325

Chaturvedi, N., Stephenson, J. M., & Fuller, J. H. (1996). The relationship between socioeconomic status and diabetes control and complications in the EURODIAB IDDM Complications Study. *Diabetes Care, 19,* 423-430. doi:10.2337/diacare.19.5.423

Clements, A. D., & Parker, C. R. (1998). The relationship between salivary cortisol concentrations in frozen versus mailed samples, *Psychoneuroendocrinology*, *23,* 613–616. doi:10.1016/S0306-4530(98)00031-6

Crano, W. D., Brewer, M. B., & Lac, A. (2002). *Principals and methods of social research*. Mahwah, NJ: Lawrence Erlbaum Associates.

Cradock, S., & Hawthorn, J. (2002). Pain, distress, and blood glucose monitoring. *Journal of Diabetes Nursing, 6*(6), 188-191. Retrieved from http://www.thejournalofdiabetesnursing.co.uk

Crawford, J. R., & Henry, J. D. (2004). The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. *British Journal of Clinical Psychology, 43,* 245-265. doi:10.1348/0144665031752934

Cryer, P. E. (2002). Hypoglycaemia: The limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia, 45,* 937-948. doi:10.1007/s00125-002-0822-9

Cryer, P. E. (2009). Exercise-related hypoglycemia-associated autonomic failure in diabetes. *Diabetes, 58*(9), 1951-1952. doi:10.2337/db09-0834

Cryer, P. E., Davis, S. N., & Shamoon, H. (2003). Hypoglycemia in diabetes. *Diabetes* Care, 26, 1902-1912. doi:10.2337/diacare.26.6.1902

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Assoc.

Cohen, L. H., Gunthert, K. C., Butler, A. C., O'Neil, S. C., Tolpin, L. H. (2005). Daily affective reactivity as a prospective predictor of depressive symptoms. *Journal of Personality, 73*(6), 1687-1713. doi:10.1111/j.0022-3506.2005.00363.x

Cohen, S., Janicki-Deverts, D., Chen, E., & Matthews, K. A., (2010). Childhood socioeconomic status and adult health. *Annals of the New York Academy of Sciences, 1186*, 37-55. doi:10.1111/j.1749-6632.2009.05334.x

Cohen, S., Kessler, R. C., & Gordon, L. U. (1995). Strategies for measuring stress in studies of psychiatric and physical disorders. In S. Cohen, R. C., Kessler, & L. U. Gordon (Eds.), *Measuring stress: A guide for health and social scientists* (pp.3-26.). New York: Oxford University Press.

Dall, T. M., Zhang, Y., Chen, Y. J., Quick, W. W., Yang, W. G., & Fogli, J. (2009). The economic burden of diabetes. *Health Affairs, 29*(2), 297-303. doi:10.1377/hlthaff.2009.0155

De Bellis, M. D., Hooper, S. R., Spratt, E. G., & Woolley, D. P. (2009). Neuropsychological findings in childhood neglect and their relationship to pediatric PTSD. *Journal of the International Neuropsychological Society, 15,* 868-878. doi:10.1017/S1355617709990464

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The adaptive calibration model of stress responsivity. *Neuroscience & Biobehavioral Reviews, 35*(7), 1562-1592. doi:10.1016/j.neubiorev.2010.11.007

Delamater, A. M., Bubb, J., Kurtz, S. M., Kuntze, J., Smith, J. A., White, N. H., & Santiago, J. V. (1988). Physiologic responses to acute psychological stress in adolescents with Type 1 Diabetes. *Journal of Pediatric Psychology, 13*(1), 69-86.

Delamater, A. M., Kurtz, S. M., Bubb, J., White, N. H., & Santiago, J. V. (1987). Stress and coping in relation to metabolic control of adolescents with Type 1 Diabetes. *Developmental and Behavioral Pediatrics, 8*(3), 136-140.

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The Apative Calibration Model of stress responsivity. *Neuroscience & Biobehavioral Reviews, 35*(7), 1562-1592. doi:10.1016/j.neubiorev.2010.11.007

DeLongis, A., Coyne, J. C., Dakof, G., Folkman, S., Lazarus, R. S. (1982). Relationship of daily hassles, uplifts, and major life events to health status. *Health Psychology, 1,* 119-136. doi:10.1037/0278-6133.1.2.119

Denson, T. F., Spanovic, M., & Miller, N. (2009). Cognitive appraisals and emotions predict cortisol and immune responses: A meta-analysis of acute laboratory social stressors and emotion inductions. *Psychological Bulletin,135*(6), 823-53. doi:10.1037/a0016909

DesRosiers, G., & Kavanagh, D. (1987). Cognitive assessment in closed head injury: Stability, validity and parallel forms of two neuropsychological measures of recovery. *International Journal of Clinical Neuropsychology, 9*(4), 162-173.

Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes and the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine, 397, 977-986.

Diabetes Control and Complications Trial Research Group (2007). Long-term effects of diabetes and its treatment on cognitive function. *The New England Journal of Medicine, 356*(18), 1842-1852. doi:10.1056/NEJMoa066397

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*(3), 355-391. doi:10.1037/0033-2909.130.3.355

Dowd, J. B., Simanek, A. M., & Aiello, A. E. (2009). Socio-economic status, cortisol and allostatic load: a review of the literature. *International Journal of Epidemiology, 38*(5), 1297-309. doi:10.1093/ije/dyp277

Dressendörfer, R.A., Kirschbaum, C., Rohde, W., Stahl, F., & Strasburger, C.J. (1992). Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. *Journal of Steroid Biochemistry and Molecular Biology, 43*(7), 683-692. doi:10.1016/0960-0760(92)90294-S

Dutour, A., Dadoun, B. F., Feissel, A., Atlan, C., & Oliver, C. (1996). Hormonal response to stress in brittle diabetes, *Psychoneuroendocrinology, 21*(6), 525-543.

Evans, G. W., & Kim, P. (2010). Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status-health gradient. *Annals of the New York Academy of Sciences. 1186,* 174-89.

Evans, G. W., & Schamberg, M. A. (2009). Childhood poverty, chronic stress, and adult working memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*(16), 6545-6549.

Fekedulegn, D.B., Andrew, M.E., Burchfiel, C.M., Violanti, J.M., Hartley, T.A., Charles, L.E., & Miller, D.B. (2007). Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosomatic Medicine, 69, 651-659.

Flinn, M. V. (2006). Evolution and ontogeny of stress response to social challenges in the human child. *Developmental Review, 26,* 138-174.

Folkman, S., & Moskowitz, J. T. (2007). Positive affect and meaning-focused coping during significant psychological stress. In M. Hewstone, H. A. W. Schut, J. B. F. De Wit, K. Van Den Bos, & M. S. Stroebe (Eds.), *The scope of social psychology: Theory and applications* (pp. 193-208). New York: Psychology Press.

Forbes, E. E., & Dahl, R. E. (2005). Neural system of positive affect: Relevance to understanding child and adolescent depression? *Development and Psychopathology, 17*, 827-850.

Franzen, M. D., Paul, D., & Iverson, G. L. (1996). Reliability of alternative forms of the Trail Making Test. *The Clinical Neuropsychologist, 10*(2), 125-129.

Fruehwald-Schultes, B., Kern, W., Bong, W., Wellhoener, P., Kerner, W., Born, J., Fehm, H. L., & Peters, A. (1999). Supraphysiological hyperinsulinemia acutely increases hypothalamic-pituitary-adrenal secretory activity in humans. *The Journal of Clinical Endocrinology & Metabolism, 84*(9), 3041-3046.

Fulford, A. J., & Harbuz, M. S. (2005). An introduction to the HPA axis. In T. Steckler, N. H. Kalin, & J. M. H. M. Reul (Eds.), *Handbook of stress and the brain: Part 1 the neurobiology of stress* (43-66). Amsterdam, The Netherlands: Elsevier.

Garvey, K. C., Markowitz, J. T., & Laffel, L. M. B. (2012). Transition to adult care for youth with Type 1 Diabetes. *Current Diabetes Research, 12*(5), 533-541.

Gaudieri, P. A., Chen, R., Greer, T. F., & Holmes, C. S. (2008). Cognitive function in children with type 1 diabetes. *Diabetes Care, 31*(9), 1892-1897.

Ghizzoni, L., Vanelli, M., Virdis, R., Alberini, A., Volta, C., & Bernasconi, S. (1993). Adrenal steroid and adrenocortiotropin responses to human corticotrophin-releasing hormone stimulation test in adolescents with type I diabetes mellitus. *Metabolism, 42*(9), 1141-1145.

Golden, C. J. (1978). *Stroop Color and Word Test: A manual for clinical and experimental uses.* Chicago: Stoelting Co.

Golden, C., J., & Freshwater, S., M. (2002). *Stroop Color and Word Test: Revised examiner's manual.* Wood Dale, IL: Stoelting Co.

Granger, D. A., Hibel, L. C., Fortunato, C. K., & Kapelewski, C. H. (2009). Medication effects on salivary cortisol: Tactics and strategy to minimize impact in behavioral and developmental science. *Psychoneuroendocrinology, 34*(10) 1437-1448.

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Developmental and Psychopathology. Special Issue: Stress and Development: Biological and Psychological consequences, 13*(3), 515-538.

Halligan, S. L., Herbert, J., Goodyer, I. M., Murray, L. (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry, 55,* 376-381.

Hassan, K., Loar, R., Anderson, B. J., & Heptulla, R. A. (2006). The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus. *The Journal of Pediatrics, 149*(4), 526-531.

Helgeson, V. S., Reynolds, K. A., Snyder, P. R., Palladino, D. K., Becker, D. J., Siminerio, L., & Escobar, O. (2013). Characterizing the transition from paediatric to adult care among emerging adults with Type 1 diabetes. *Diabetic Medicine, 30*(5), 610-615.

Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British Journal of Clinical Psychology, 44,* 227-239.

Het, S., Ramlow, G., & Wolf, O. T. (2005). A meta-analytic review on the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology, 30,* 771-784.

Hillman, J. B., Dorn, L. D., Loucks, T. L., Berga, S. L. (2012). Obesity and the hypothalamic-pituitary-adrenal axis in adolescent girls. *Metabolism, 61*(3), 341-348. doi:10.1016/j.metabol.2011.07.009

Hirose, M., Beverly, E., & Weinger, K. (2012). Quality of life and technology: Impact on children and families with diabetes. *Current Diabetes Reports, 12*(6), 711-720.

Hoffman, R., & al'Absi, M. (2003). The effect of acute stress on subsequent neuropsychological test performance. *Archives of Clinical Neuropsychology, 19*(4), 497-506.

Hubert, W., Möller, M., & Nieschlag, E. (1989). Stress reactions in response to the procedure of LHRH tests as measured by salivary and serum cortisol and psychological variables. *Hormone Research, 32,* 198-202.

Hudson, J. I., Hudson, M. S., Rothschild, A. J., Vignati, L., Schatzberg, A. F., & Melby, J. C. (1984). Abnormal results of dexamethasone suppression tests in nondepressed patients with diabetes mellitus. *Archives of General Psychiatry,* 41, 1086-1089.

Huether, G. (1996). The central adaptation syndrome: Psychosocial stress as a trigger for adaptive modifications of brain structure and brain function. *Progress in Neurobiology, 48*, 569-612.

Huether, G. (1998). Stress and the adaptive self-organization of neuronal connectivity during early childhood. International Journal of Developmental Neuroscience, 16(3/4/), 297-306.

Johnsen, G. E., & Asbjornsen, A. E. (2008). Consistent impaired verbal memory in PTSD: A meta-analysis. *Journal of Affective Disorders, 111*(1), 74-82.

Juvenile Diabetes Research Foundation. (n.d.) *Control and management*. Retrieved from http://jdrf.org/life-with-t1d/type-1-diabetes-information/control-and-management/

Kaplan, G. A., Turrell, G., Lynch, J. W., Everson, S. A., Helkala, E-L, & Salonen, J. T. (2001). Childhood socioeconomic position and cognitive function in adulthood. *International Journal of Epidemiology, 30*(2), 256-263. doi: 10.1093/ije/30.2.256

Katz, M., Liu, C., Schaer, M., Parker, K. J., Ottet, M-C., Epps, A., … Lyons, D. M. (2009). Prefrontal Plasticity and Stress Inoculation-Induced Resilience, *Developmental Neuroscience, 31*(4), 293-299.

Kemmer, F. W. Bisping, R., Steingrüber, H. J., Baar, H. (1986). Psychological stress and metabolic control in patients with type I diabetes mellitus. *New England Journal of Medicine, 314*(17), 1078-1084.

Khoshaba, D. M., & Maddi, S. R. (1999). Early experiences in hardiness development. *Consulting Psychology Journal: Practice and Research, 51*(2), 106-116.

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., & Hellhammer, D. H. (1996). Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences, 58*(17), 1475-1483.

Kudielka, B. M., Hellhammer, D. H., & Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol response to challenge. *Psychoneuroendocrinology, 34,* 2-18.

Kuhlmann, S., Piel, M., & Wolf, O. T. (2005). Impaired memory retrieval after psychosocial stress in healthy young men. *The Journal of Neuroscience, 25*(11), 2977-2982.

LaGarde, G., Doyon, J., & Brunet, A. (2010). Memory and executive dysfunctions associated with acute posttraumatic stress disorder. *Psychiatry Research, 177,* 144-149.

Larkin, K. T., Semenchuk, E. M., Frazer, N. L., Suchday, S., & Taylor, R. L. (1998). Cardiovascular and behavioral responses to social confrontation: Measuring real-life stress in the laboratory. *Annals of Behavioral Medicine, 20*, 294–301.

Lawrence, N. S., Ross, T. J., Stein, E. A. (2002). Cognitive mechanisms of nicotine on visual attention. *Neuron, 36,* 539-548.

Lazarus, R. S. & Folkman, S. (1984). Stress, appraisal, and coping. New York: Springer.

Lezak, M.D., Howieson, D, B., & Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5 ed.). New York: Oxford University Press.

Lin, A., Northam, E. A., Rankins, D., Werther, G. A., & Cameron, F. J. (2010). Neuropsychological profiles of young people with type I diabetes 12 yr after disease onset. *Pediatric Diabetes, 11,* 235-243.

Lo, M. S. L., Ng, M. L., Azmy, B. S., & Khalid, B. A. K. (1992). Clinical applications of salivary cortisol measurements. *Singapore Medical Journal, 33*, 170-173.

LoSasso, G. L., Rapport, L. J., Axelrod, B. N., & Reeder, K. P. (1998). Intermanual and alternative for equivalence on the Trail Making Tests. *Journal of Clinical and Experimental Neuropsychology, 20*(1), 107-110.

Lovallo, W., Farag, N. H., & Vincent, A. S. (2010). Use of a resting control day in measuring the cortisol response to mental stress: Diurnal patterns, time of day, and gender effects. *Psychoneuroendocrinology, 35*(8), 1253-1258.

Lovibond, S.H. & Lovibond, P.F. (1995). *Manual for the Depression Anxiety Stress Scales*. (2 ed.). Sydney: Psychology Foundation.

Luecken, L. J. (2000). Attachment and loss experiences during childhood are associated with adult hostility, depression, and social support. *Journal of Psychosomatic Research*, 49(1), 85–91.

Luecken, L. J., Kraft, A., Appelhans, B., & Enders, C. (2009). Emotional and cardiovascular sensitization to daily stress following childhood parental loss. *Developmental Psychology, 45*(1), 296-302.

Luecken, L. J., Roubinov, D. S. & Purdom, C. (2011). Clinical Implications of Childhood Stress. In C. D. Conrad (Ed.), *The Handbook of Stress: Neuropsychological Effects on the Brain* (pp. 304-323). Oxford: Wiley-Blackwell.

Lupien, S., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose-response study in humans. *Behavioral Neuroscience, 113*(3), 420-30.

Lupien, S., Lecours, A. R., Lussier, I., Schwartz, G., Nair, N. P. V., & Meaney, M. J. (1990). Basal cortisol levels and cognitive deficits in human aging. *Journal of Neuroscience, 14*(5), 2893-2903.

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition, 65*, 209-237.

Lupien, S. J., Wilkinson, C. W., Brière, S., Ménard, C., Ng Ying Kim, N. M. K., & Nair, N. P. V. (2002). The modulatory effects of corticosteroids on cognition: studies in young human populations. *Psychoneuroendocrinology, 27,* 401-416.

Lupien, S.J., Wilkinson, C.W., Brière, S., Ng Ying Kin, N.M.K., Meaney, M.J., Nair, V., (2001). Acute modulation of aged human memory by pharmacological manipulation of glucocorticoids. *Journal of Clinical Endocrinology and Metabolism, 87*(8), 3798-807.

Luthar, S., S., & Zigler, E., (1991). Vulnerability and competence: A review of research on resilience in childhood. *American Journal of Orthopsychiatry, 61*(1), 6-22.

Lyons, D. M., Buckmaster, P. S., Lee, A. G., Wu, C., Mitra, R., Duffey, L. M., … Schatzberg, A. F. (2010). Stress coping stimulates hippocampal neurogenesis in adult monkeys. *Proceedings from the National Academy of Sciences of the United States of America, 107*(3), 14823-14827.

Lyons, D. M., & Parker, K. J. (2007). Stress inoculation-induced indications of resilience in monkeys. *Journal of Traumatic Stress, 20*(4), 423-433.

MacLeod, K. M., Hepburn, D. A., Frier, B.M. (1993). Frequency and morbidity of severe hypoglycemia in insulin-treated diabetic patients. *Diabetes Medicine, 10,* 238-245.

Marcotte, T. D., & Grant, I. (Eds.). (2009). *Neuropsychology of everyday functioning: The science and practice of neuropsychology.* New York: The Guilford Press.

Markowitz, J. T., Alleyn, C. A., Phillips, R., Muir, A., Young-Hyman, D., & Laffel, L. M. B. (2013). Disordered eating behaviors in youth with Type 1 Diabetes: Prospective pilot assessment following initiation of insulin pump therapy. *Diabetes Technology & Therapy, 15*(5), 428-433.

Mendl, M. (1999). Performing under pressure: stress and cognitive function. *Applied Animal Behaviour Science, 65,* 221-244.

McCarthy, A. M., Hanrahan, K., Kleiber, C., Zimmerman, M. B., Lutgendorf, S., & Tsalikian, E. (2009). Normative salivary cortisol values and responsivity in children. *Applied Nursing Research, 22*(1), 54-62.

McEwen, B. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33-44.

McEwen, B. (2002). Sex, stress and the hippocampus: allostatis, allostatic load and the aging process. *Neurobiology of Aging, 23*(5), 921-39.

McEwen, B. S., & Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences, 1186,* 190-222. DOI: 10.1111/j.1749-6632.2009.05331.x

Mesulam, M. M. (2000). *Principles of behavioral and cognitive neurology*. Oxford: Oxford University Press.

Miller, G. E., Chen, E., Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133*(1), 25-45.

Mitrushina, M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of normative data for neuropsychological assessment* (2 ed.). New York: Oxford University Press.

Moore, H., Craft, T., Grimaldi, L. M., Babic, B, Brunelli, S. A., & Vannucci, S. J. (2010). Moderate recurrent hypoglycemia during early development leads to persistent changes in affective behavior in the rat. *Brain, Behavior, and Immunity, 24*(5), 839-849.

Morgan, T. M., Crawford, L., Stoller, A., Toth, D., Yeo, K. J., & Baron, J. A. (2004). Acute effects of nicotine on serum glucose, insulin, growth hormone, and cortisol in healthy smokers. *Metabolism, 53,* 578-582.

Morris, M. C., Rao, U., & Garber, J. (2012). Cortisol responses to psychosocial stress predict depression trajectories: Social-evaluative threat and prior depressive episodes as moderators. *Journal of Affective Disorders, 143*, 223-230.

Morris, M. C., Rao, U., Wang, L., & Garber, J. (2013). Cortisol reactivity to experimentally manipulated psychosocial stress in young adults at varied risk for depression. *Depression and Anxiety, 00*, 1-9.

Myer, T., Smeets, T., Giesbrecht, T., Quaedflieg, C. W., & Merckelbach, H. (2013). Acute stress differentially affects spatial configuration learning in high and low cortisol-responding healthy adults. *European Journal of Psychotraumatology, 4*. doi: 10.3402/ejpt.v4i0.19854

Naguib, J. M., Kulinskaya, E., Lomax, C. L., & Garralda, M. E. (2009). Neuro-cognitive performance in children with type 1 diabetes: A meta-analysis. *Journal of Pediatric Psychology, 34*(3), 271-282.

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., & Alderson, A. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry, 56,* 527-533.

Northam, E. A., Anderson, P. J., Jacobs, R., Hughes, M., Warne, G. L., Werther, G. A. (2001). Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. *Diabetes Care, 24*, 1541-1546.

Northam, E. A., Anderson, P. J., Werther, G. A., Warne, G. L., Adler, R. G., & Andrews, D. (1998). Neuropsychological complications of IDDM in children 2 years after disease onset. *Diabetes Care, 21,* 379–384.

Oei, N. Y. L., Everaerd, W. T. A. M., Elzinga, B. M., van Weil, S., & Bermond, B. (2006). Psychosocial stress impairs working memory at high loads: An association with cortisol levels and memory retrieval. *Stress, 9*(3), 133-141.

Palladino, D. K., Helgeson, V. S., Reynolds, K. A., Becker, D. J., Siminerio, L. M., & Escobar, O. (2013). Emerging adults with type 1 diabetes: A comparison to peers without diabetes. *Journal of Pediatric Psychology, 30*(5), 610-615.

Parekh, B. (2009). Mechanisms of the blunting of the sympatho-adrenal response: A theory. *Current Diabetes Reviews, 5*(2), 79-91.

Peters, M. L., Godaert, G. L. R., Ballieux, R. E., & Heijnen, C. J. (2003). Moderation of physiological stress response by personality traits and daily hassles: less flexibility of immune system responses. *Biological Psychology, 65*(1), 21-48.

Peters, A., Laffel, L., & the American Diabetes Association Transitions Working Group (2011). Diabetes care for emerging adults: Recommendations for transition from pediatric to adult diabetes care systems. *Diabetes Care, 34*(11), 2477-2485.

Peters, J. E., Mount, E., Huggins, C. E., Rodda, C., & Silvers, M. A. (2013). Insulin pump therapy in children and adolescents: Changes in dietary habits, composition, and quality of life. *Journal of Paediatrics and Child Health, 49*(4), E300-E305.

Petrie, R. X. A., & Deary, I. J. (1989). Smoking and human information processing. *Psychopharmacology, 99,* 393-396.

Peyrot, M., McMurry, J. F., Kruger, D. F. (1999). A biopsychosocial model of glycemic control in diabetes: Stress, coping and regimen adherence. *Journal of Health and Social Behavior, 40*(2), 141-158.

Pickup, J. C. (2012). Insulin-pump therapy for Type 1 Diabetes Mellitus. *The New England Journal of Medicine, 366,* 1616-24.

Pleitez, M. A., Lieblein, T., Bauer, A., Hertzberg, O., von Lilienfeld-Toal, H., Mäntele, W. (2013). In vivo noninvasive monitoring of glucose concentration in human epidermis by mid-infrared pulsed photoacoustic spectroscopy. *Analytical Chemistry, 85*(2), 1013-20.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychneuroendocrinology, 28*(7), 916-931.

Ramchandani, N., Cantey-Kiser, j. M., Alter, C. A, Brink, S. J., Yeager, S. D., Tamborlane, W. V., & Chipkin, S. R. (2000). Self-reported factors that affect glycemic control in college students with type 1 diabetes. *The Diabetes Educator, 26*(4), 656-666.

Reagan, L. P., Grillo, C. A., & Piroli, G. G. (2008). The As and Ds of stress: metabolic, morphological and behavioral consequences. *European Journal of Pharmacology, 585*(1), 64-75.

Reisa, A., Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., …Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7(3), 280-292,

Richards, M., Hardy, R., Kuh, D., & Wadsworth, M. E. J. (2001). Birth weight and cognitive function in the British 1946 birth cohort: longitudinal population based study. *BMJ, 322,* 199-203. doi: 10.1093/ije/31.2.342

Roozendaal, B., (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning and Memory, 78*(3), 578-595.

Rosmond, R. (2003). Stress induced disturbances of the HPA axis: a pathway to Type 2 diabetes? *Medical Science Monitor, 9*(2), RA 35-9.

Roy, M. P. (2004). Patterns of cortisol reactivity to laboratory stress. *Hormones and Behavior, 46*(5), 618-627.

Roy, M., Collier, B., & Roy, A. (1990). Hypothalamic-pituitary-adrenal axis dysregulation among diabetic outpatients. *Psychiatry Review, 31,* 31-37.

Roy, M., Roy, A., Gallucci, W., Collier, B., Young, K., Kamilaris, T., & Chrousos, G. (1993). The ovine corticotropin-releasing hormone stimulation test in type I diabetic patients and controls: Suggestion of mild chronic hypercortisolism. *Metabolism, 42,* 696-700.

Roy, M. S., Roy, A., & Brown, S. (1998). Increased Urinary-free cortisol outputs in diabetic patients. *Journal of Diabetes and Its Complications, 12,* 24-27.

Rubin, R., Peyrot, M., & STAR 3 Study Group, (2012). Health-related quality of life and treatment satisfaction in sensor-augmented pump therapy for A1C reduction 3 (STAR 3) trial. *Diabetes Technology & Therapeutics, 14*(2), 143-151.

Ryan, C. M. (2006). Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatric Diabetes, 7,* 289-297.

Seeman, T., Epel, E., Gruenewald, T., Karlamangla, A., & McEwen, B. S. (2010). Socio-economic differentials in peripheral biology: Cumulative allostatic load.*Annals of the New Yok Academy of Sciences, 1186,* 223-239. DOI: 10.1111/j.1749-6632.2009.05341.x

Schady, W. J., L., Torebjörk, H. E., & Ochoa, J. L. (1983). Peripheral projections of nerve fibres in the human median nerve. *Brain Research, 277,* 249-261.

Schoofs, D., Wolf, O. T., & Smeets, T. (2009). Cold pressor stress impairs performance on working memory tasks requiring executive functions in healthy young men. *Behavioral Neuroscience, 123*(5), 1066-1075.

Schum, R. L., Sivan, A. B., & Benton, A. (1989).Multilingual Aphasia Examination: Norms for children. *The Clinical Neuropsychologist, 3,* 375–383.

Smeets, T., Cornelisse, S., Quaedflieg, C. W. E. M., Meyer, T., Jelicic, M., & Merckelbach, H. (2012). Introducing the Maastricht Acture Stress Test (MAST): A quick and non-invasive approach to elicit robust autonomic and glucocorticoid stress responses. *Psychoneuroendocrinology, 37*(12), 1998-2008.

Sontag-Padilla, L. M., Dorn, L. D., Tissot, A., Susman, E. J., Beers, S. R., & Rose, S. R. (2012). Executive functioning, cortisol reactivity, and symptoms of psychopathology in girls with premature adrenarche. *Developmental Psychopathology, 24*(1), 211-223.

Soutor, S. A., Chen, R., Streisand, R., Kaplowitz, P., Holmes, C. S. (2004). Memory matters: Developmental differences in predictors of diabetes care behaviors. Journal of Pediatric Psychology, 29(7), 493-505.

Spain, K., (2008) *Insurance matters*. Retrieved from Juvenile Diabetes Research Foundation website: http://jdrf.org/blog/2008/insurance-matters/

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3 ed.). New York: Oxford University Press.

Steckler, T. (2005). The neuropsychology of stress. In T. Steckler, N. H. Kalin, & J. M. H. M. Reul (Eds.), *Handbook of stress and the brain: Part 1 the neurobiology of stress* (25-42). Amsterdam: Elsevier.

Stroud, L. R., Foster, E., Papandonatos, G. D., Handwerger, K., Granger, D. A., Kivlighan, K. T., & Niaura, R. (2009). Stress response and the adolescent transition: Performance versus peer rejection stressors. *Development and Psychopathology, 21,* 47-68.

Sultan, S., Epel, E., Sachon, C., Vaillant, G., & Hartemann-Heurtier, A. (2008). A longitudinal study of coping, anxiety, and glycemic control in adults with type 1 diabetes. *Psychology Health, 23*(1), 73-89.

Susman, E. J., Dorn, L. D., Inoff-Germain, G., Nottelmann, E. D., & Chrousos, G. P. (1997). Cortisol reactivity, distress behavior, and behavioral and psychological problems in young adolescents: A longitudinal perspective. *Journal of Research on Adolescence, 7*(1), 81-105.

Taverniers, J., Smeets, T., Lo Bue, S., Syroit, J., Van Ruysseveldt, J.,Pattyn, N., & von Grumbkow, J. (2011). Visuo-spatial path learning, stress, and cortisol secretion following military cadets' first parachute jump: the effect of increasing task complexity. Cognitive, Affective, and Behavioral Neuroscience, 11(3), 332-43.

Tabachnick, B., G., & Fidell, L. S. (2001). *Computer-assisted research design and analysis.* Needham Heights, MA : Allyn & Bacon.

Taverniers, J., Taylor, M. K., Smeets, T. (2013). Delayed memory effects after intense stress in Special Forces candidates: exploring path processes between cortisol secretion and memory recall. Stress, 16(3), 311-20.

Taylor, R. (1998). Order effects within the Trail Making and Stroop tests in patients with neurological disorders. J*ournal of Clinical and Experimental Neuropsychology, 20,* 750–754.

Tomlinson, D. R., & Gardiner, N. J. (2008). Glucose neurotoxicity. *Nature Reviews Neuroscience, 9,* 36-45.

Vasterling, J. J., & Brailey, K. (2005). Neuropsychological findings with adults with PTSD. In Vasterling, J. J., Brewin, C. R. (Eds.). *Neuropsychology of PTSD: Biological, Cognitive, and Clinical Perspectives.* New York, NY: Guilford, 178-207.

Wagner, J., Tennen, H., Wolpert, H., (2012). Continuous glucose monitoring: A review for behavioral researchers. *Psychosomatic Medicine, 74*, 356-365.

Waldstein, S. R., Neumann, S. A., Burns, H. O., & Maier, K. J., (1998). Role-played interpersonal interaction: Ecological validity and cardiovascular reactivity. *Annals of Behavioral Medicine, 20*(4), 302-309.

Warburton, D. M., & Mancuso, G. (1998). Evaluation of the information processing and mood effects of a transdermal nicotine patch. *Psychopharmacology, 135,* 305-310.

Warren, R. E., & Frier, B. M. (2005). Hypoglycaemia and cognitive function. *Diabetes, Obesity, and Metabolism, 7,* 493-503.

Wasserman, L. I., & Trifonova, E. A. (2006). Diabetes Mellitus as a model of psychosomatic and somatopsychic interrelationships. *Spanish Journal of Psychology, 9*(1), 75-85.

Watson, D., & Clark, L.A. (1994). Manual for the Positive and Negative Affect

Schedule (Expanded Form). University of Iowa.

Weinger, K., & Jacobson, A. M. (1998). Cognitive impairment in patients with type 1 (insulin-dependent) diabetes mellitus: Incidence, mechanisms and therapeutic implications. *CNS Drugs, 9*(3), 233-252.

Weissberg-Benchell, J., Wolpert, H., & Anderson, B. J. (2007). Transitioning from pediatric to adult care: A new approach to the post-adolescent young person with type 1 diabetes. *Diabetes Care, 30*(10), 2441-2446.

Wesnes, K., & Warburton, D. M. (1984). Effects of scopolamine and nicotine on human rapid information processing performance. *Psychopharmacology, 82*, 147-150.

West, S. G., Finch, J. F., & Curran, P. J. (1995). Structural equation models with nonnormal variables: Problems and remedies. In R. H. Hoyle (Ed.). *Structural equation modeling: Concepts, issues, and applications* (pp. 56-75).

Wiesli, P., Schmid, C., Kerwer, O., Nigg-Koch, C., Klaghofer, R., Seifert, B., Spinas, G. A. & Schwegler, K. (2005). Acute psychological stress affects glucose concentrations in patients with Type 1 Diabetes following food intake but not in the fasting condition. *Diabetes Care, 28*(8), 1910-1915.

Wilkinson, R. B., Walford, W. A., & Espnes, G. A. (2011). Coping styles and psychological health in adolescents and young adults: A comparison of moderator and main effects models. *Australian Journal of Psychology, 52*(3), 155-162.

World Health Organization (2007). Health care facility recommendations for standard precautions. Retrieved from: http://www.who.int/csr/resources/publications/EPR_AM2_E7.pdf

Yeh, H-C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., Wilson, L. M., Haberl, E. B., Brick, J., Bass, E. B., & Golden, S. H. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus. *Annals of Internal Medicine, 157*(5), 336-347.

Young, A. H., Sahakian, B. J., Robbins, T. W., & Cowen, P. J. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology, 145*(3), 260-266.

Zautra, A. J. (2003). *Emotions, stress, and health.* New York, NY: Oxford University Press.

Table 1.

Order of cognitive tests used in pre- and post-stressor cognitive battery

Pre-stressor cognitive test battery	Post-stressor cognitive test battery
Sustained attention task	RVLT long-delay and recognition
COWAT	Sustained attention task
Stroop	COWAT
Trail Making Test	Stroop
RVLT- trials 1-5 through short delay recall	Trail Making Test

Table 2

Display of study design for one-way related measures ANOVA

Cluster	Cortisol AUC_i			Within Cluster Total
	Diabetic	Control 1	Control 2	
C_1				$\sum C_1$
C_2				$\sum C_2$
...				...
C_{21}				$\sum C_{21}$
Diabetic Membership Totals	∑Diabetic	∑Control 1	∑Control2	

Note. C_j refers to a cluster of cases containing one diabetic participant and two yoked control participants. Yoked controls were randomly assigned to position "Control 1" or position "Control 2." Study design for one-way related measures used for examining within-cluster equivalence on matching variables and cortisol outcomes. The planned contrast compares the effect of diabetic membership versus the average of the two control participants across levels of clusters (as reflected by the shading).

Table 3

Display of study design for two-way related measures ANOVA

Cluster	Pre-Stressor Cognitive Score			Post-Stressor Cognitive Score			Within Cluster Total
	Diabetic	Control1	Control2	Diabetic	Control1	Control2	
C_1							$\sum C_1$
C_2							$\sum C_2$
...							...
C_{21}							$\sum C_{21}$
Diabetic Membership Totals	∑Diabetic	∑Control1	∑Control2	∑Diabetic	∑Control 1	∑Control2	

Note. C_j refers to a cluster of cases containing one diabetic participant and two yoked control participants. Yoked controls were randomly assigned to position "Control 1" or position "Control 2." Study design for two-way related measures used for examining within-cluster equivalence pre-post cognitive change. The planned contrast compares the effect of diabetic membership versus the average of the two control participants across levels of clusters (as reflected by the shading) within each cognitive score factor (e.g., pre and post-stressor cognitive task score). An interaction between the pre-post factor and the planned contrast provides tests the hypothesis that diabetic participants cognitively respond to the stress task in a different manner than yoked controls.

Table 4

Descriptive statistics and t-tests on matching variables for the two matched control groups.

	Control 1 (n = 23) *M* (*SD*)	Control 2 (n = 23) *M(SD)*	t	*p*
Gender (%male)	39.13%	39.13%	0.00	1.00
Age	22.48 (3.87)	22.43 (3.67)	-0.56	0.58
Highest Education	3.74 (1.21)	3.43 (1.24)	-0.22	0.83
Maternal Education	3.96 (1.36)	3.65 (1.72)	0.38	0.71
Paternal Education	4.43 (1.50)	4.13 (1.69)	1.19	0.24
			χ^2	*p*
Ethnicity(%):			0.36	0.84
Non-Hispanic White	91.3%	87.0%		
Hispanic or Latino/a	4.35%	8.70%		
Black	4.35%	4.35%		

Note. For each cluster of participants (e.g., diabetic, yoked control 1, and yoked control 2), the two control participants were randomly assigned to position of “Control 1” and “Control 2.”

Table 5

Descriptive statistics and t-tests on matching variables between diabetic member and pooled controls. Statistics for the control cases are calculated across the 23 x 2 = 46 control cases; n= 23 diabetic cases.

	Diabetic (n = 23) *M*(*SD*)	Control (n = 46) *M(SD)*	t	*p*
Gender (%male)	39.13%	39.13%	0.00	1.00
Age	23.00 (4.02)	22.46 (3.73)	-0.56	0.58
Highest Education	3.65 (1.11)	3.59 (1.22)	-0.22	0.83
Maternal Education	3.65 (1.61)	3.80 (1.54)	0.38	0.71
Paternal Education	3.78 (1.76)	4.28 (1.59)	1.19	0.24
			χ^2	*p*
Ethnicity(%):			4.20	0.24
Non-Hispanic White	82.61%	89.13%		
Hispanic or Latino/a	4.35%	6.52%		
Black	4.35%	4.35%		
More than one race	8.69%	0.00%		

Table 6

Related-measures ANOVA among diabetic, yoked control 1 and yoked control 2 on continuous matching variables.

Variable	Diabetic (n=23) *EMM*(*SE*)	Control 1 (n = 23) *EMM*(*SE*)	Control 2 (n = 23) *EMM*(*SE*)	*F*	*p*	η_p^2
Age (in years)	23.00 (0.84)	22.48 (0.81)	22.44 (0.76)	2.63	.08	.11

Note. EMM = Estimated Marginal Mean, SE = Standard Error. For each cluster of participants (e.g., diabetic, yoked control 1, and yoked control 2), the two control participants were randomly assigned to position of “Control 1” and “Control 2.”

Table 7

Planned contrast between the diabetic participant and average of the two yoked controls on continuous matching variable age.

Variable	Diabetic (n=23), *EMM*(*SE*)	Control (n=46) *EMM*(*SE*)	*F*	*p*	η_p^2
Age	23.00 (.84)	22.46 (.79)	6.37	.02*	.23

Note. EMM = Estimated Marginal Mean, SE = Standard Error. Planned contrast from related measures ANOVA to compare difference between the diabetic and the average of participant's two yoked controls. Differences between the two matched controls did not reach statistical significance and effect sizes were below.

Table 8

Related measures ANOVA among diabetic (n = 23), yoked control 1 (n = 23) and yoked control 2 (n = 23) *on ordinal categorical matching variables*

Variable	Frequency Distribution							*F*	*p*	η_p^2
	Did not complete high school	High School diploma	Some College	Jr. College or Technical School	College Degree	M.A./M.S, Ph.D., J.D., or M.D.				
Participants' education level								1.16	0.32	0.05
Diabetic	0.00%	8.70%	52.17%	8.70%	26.09%	4.35%				
Control 1	0.00%	8.70%	52.17%	4.35%	26.09%	8.70%				
Control 2	0.00%	17.39%	56.52%	0.00%	17.39%	8.70%				
Maternal education level								0.47	0.61	0.02
Diabetic	8.69%	13.04%	39.13%	0.00%	21.74%	17.39%				
Control 1	4.35%	4.35%	39.13%	8.70%	30.43%	13.04%				
Control 2	8.70%	26.09%	17.39%	4.35%	26.09%	17.39%				
Paternal education level								2.35	0.14	0.05†
Diabetic	17.39%	4.35%	26.09%	4.35%	30.43%	17.39%				
Control 1	0.00%	13.04%	21.74%	8.70%	21.74%	34.78%				
Control 2	8.70%	13.04%	13.04%	13.04%	26.09%	26.09%				
	<$14,999	$15,000-$29,000	$30,000-$44,999	$45,000-$59,999	$60,000-$79,999	$80,000-$99,999	$100,000-$150,000	>$150,000		
Family income during childhood									1.37	0.26	0.06
Diabetic	13.04%	8.70%	13.04%	17.39%	26.09%	8.70%	8.70%	4.35%			
Control 1	0.00%	17.39%	4.35%	21.74%	13.04%	13.04%	21.74%	8.70%			
Control 2	8.70%	21.74%	8.70%	13.04%	13.04%	4.35%	17.39%	13.04%			

**significant at p<0.05*

†sphericity violated, lower limit of partial eta squared (η_L^2) provided

Note. For each cluster of participants (e.g., diabetic, yoked control 1, and yoked control 2), the two control participants were randomly assigned to position of "Control 1" and "Control 2."

Table 9

Planned contrast between the diabetic participant (n = 23) and average of the two yoked controls (n = 46) on ordinal categorical matching variables.

Variable	Frequency Distribution							*F*	*p*	η_p^2
	Did not complete high school	High School diploma	Some College	Jr. College or Technical School	College Degree	M.A./M.S, Ph.D., J.D., or M.D.				
Participants' education level								0.10	0.75	0.01
Diabetic	0.00%	8.69%	52.17%	8.69%	26.09%	4.35%				
Control	0.00%	13.04%	54.35%	2.18%	21.74%	8.70%				
Maternal education level								0.29	0.60	0.01
Diabetic	8.69%	13.04%	39.13%	0.00%	21.74%	17.39%				
Control	6.52%	15.21%	28.26%	6.52%	28.26%	15.22%				
Paternal education level								4.87	0.04*	0.08†
Diabetic	17.39%	4.35%	26.09%	4.35%	30.43%	17.39%				
Control	4.35%	13.04%	17.39%	10.87%	23.91%	30.43%				
	<$14,999	$15,000-$29,000	$30,000-$44,999	$45,000-$59,999	$60,000-$79,999	$80,000-$99,999	$100,000-$150,000	>$150,000		
Family income during childhood								1.66	0.21	0.07
Diabetic	13.04%	8.70%	13.04%	17.39%	26.09%	8.70%	8.70%	4.35%		
Control	4.35%	19.57%	6.52%	17.39%	13.04%	8.70%	19.57%	10.87%		

**significant at p<0.05*

†sphericity violated, η_L^2 provided

Note. Planned contrast from related measures ANOVA comparing the difference between the diabetic participant and the average of his/her two yoked control participants (Diabetic n = 23; Control n = 46). There were no differences observed between the two matched controls (e.g., contrasts did not reach statistical significance or result in a large effect size for any variable; $\eta_p^2 < .05$ for all contrasts between the two control groups).

Table 10

Descriptive information for cortisol variables and possible cortisol covariates.

Variable	*n*	*M*	*SD*	*Mdn*	Min	Max	Skew	Kurtosis
Cortisol AUCi								
Diabetic	21	2790.46	8616.98	1253.10	-19537.65	25980.60	0.12	3.33
Control	42	-2476.74	10240.26	-1821.68	-28766.70	26730.75	0.03	2.00
Cortisol AUCg								
Diabetic	21	24006.73	11494.11	20749.50	9899.70	48370.20	0.66	-0.66
Control	42	23154.53	11351.09	21261.08	5629.05	51779.55	0.68	0.01
Daily servings of caffeine								
Diabetic	21	2.52	2.38	2.00	0.00	8.00	0.73	-0.40
Control	42	1.17	1.34	1.00	0.00	7.00	2.03	7.38
Weekly servings of alcohol								
Diabetic	21	1.86	3.04	0.00	0.00	10.00	2.05	3.65
Control	41	4.02	4.59	3.00	0.00	16.00	0.96	0.12
Blood Glucose AUCi								
Diabetic	21	-81324.33	123548.81	-85290.00	-300181.00	179820.00	-0.12	-0.01
Control	42	-16840.00	56214.83	-14160.00	-196620.00	152790.00	-0.90	5.34
Blood Glucose AUCg								
Diabetic	21	684592.86	209375.83	643230.00	430800.00	1260000.00	1.41	1.84
Control	42	500627.14	59123.88	493245.00	383820.00	699780.00	0.75	2.00
Body Mass Index								
Diabetic	21	25.90	5.08	25.18	19.54	38.61	1.33	1.77
Control	42	24.31	4.99	23.24	16.93	38.19	1.19	1.22

Note. Descriptives derived from variables after winsorizing and prior to transformations.

Table 11

Descriptive information for possible cortisol covariates

Variable	*n*	*M*	*SD*	*Mdn*	Min	Max	Skew	Kurtosis
Waist to Hip Ratio								
Diabetic	21	0.85	0.08	0.84	0.73	0.99	0.15	-1.17
Control	42	0.86	0.08	0.86	0.72	0.98	-0.18	-0.93
Days since menstrual cycle								
Diabetic	12	20.83	23.41	12.50	0.00	77.00	1.83	2.63
Control	26	18.81	14.25	15.50	2.00	63.00	1.68	3.33
Time from waking								
Diabetic	19	5.77	2.26	5.78	1.53	11.25	0.42	0.61
Control	42	6.32	2.61	6.44	1.43	11.10	-0.10	-1.23
Hours slept in previous night								
Diabetic	19	7.45	1.77	8.00	2.50	10.00	-1.16	1.91
Control	42	7.66	1.99	8.00	3.00	11.50	-0.29	-0.24
Baseline Positive Affect								
Diabetic	21	5.18	2.32	4.60	1.40	9.60	0.22	-0.78
Control	42	5.20	1.81	5.10	1.00	9.60	-0.05	0.05
Baseline Negative Affect								
Diabetic	21	1.75	0.96	1.50	1.00	5.00	2.19	5.93
Control	42	1.74	0.80	1.42	1.00	4.17	1.24	0.97
Number of Medications								
Diabetic	21	0.24	0.54	0.00	0.00	2.00	2.32	5.06
Control	42	0.17	0.38	0.00	0.00	1.00	1.86	1.51
DASS-Stress								
Diabetic	21	6.10	3.82	6.00	1.00	14.00	0.60	-0.47
Control	42	4.62	3.28	4.50	0.00	12.00	0.34	-0.52

Note. Descriptives derived from variables after winsorizing and prior to transformations.

Table 12

Frequency information for potential cortisol binary covariates

Variable	N	Yes (%)	No (%)
Current smoker			
Diabetic	21	4 (19.04%)	17 (80.95%)
Control	42	4 (9.52%)	38 (90.48%)
Oral contraception			
Diabetic	13	6 (46.15%)	7 (53.85%)
Control	42	11 (42.31%)	15 (57.69%)
Insulin Pump Use			
Diabetic	21	11 (52.38%)	10 (47.62%)

Table 13

Correlations between cortisol outcomes and possible covariates collapsed across diabetic and non-diabetic participants

Variable		1	2	3	4	5	6	7	8	9	10
1. Cortisol AUCi		1									
	n	63									
2. Cortisol AUCG		0.22	1								
	n	63	63								
3. Smoking		-0.23	-0.01	1							
	n	63	63	63							
4. Gender		-0.24	0.19	0.19	1						
	n	63	63	63	63						
5. Diabetes		0.25*	0.04	0.13	0.00	1					
	n	63	63	63	63	63					
6. WHR		-0.08	0.23*	0.15	0.72**	-0.07	1				
	n	63	63	63	63	63	63				
7. Menstrual Cycle		0.25	-0.12	-0.06	.	0.05	0.33*	1			
	n	38	38	38	38	38	38	38			
8. Positive Affect		-0.07	-0.07	0.00	0.01	0.00	-0.08	-0.17	1		
	n	63	63	63	63	63	63	38	63		
9. Medications		0.05	-0.34**	0.05	-0.04	0.08	-0.03	-0.05	-0.08	1	
	n	63	63	63	63	63	63	38	63	63	
10. DASS-Stress		-0.12	-0.04	0.25	0.00	0.20	0.03	-0.11	-0.07	0.34**	1
	n	63	63	63	63	63	63	38	63	63	63

*Correlation is significant at p<0.05

**Correlation is significant at p<0.01

Note. Gender (0=female, 1=male), Diabetes (0=control, 1=T1DM), WHR= Waist to Hip Ratio, Menstrual cycle=days since last cycle, Positive affect= baseline positive affect, DASS-Stress = perceived stress subscale from DASS

Table 14

Correlations between cortisol outcomes and possible covariates for control participants

Variable		1	2	3	4	5	6	7	8	9
1. Cortisol AUCi		1								
	n	42								
2. Cortisol AUCg		0.11	1							
	n	42	42							
3. Smoking		-0.19	0.02	1						
	n	42	42	42						
4. Gender		-0.32*	0.24	0.08	1					
	n	42	42	42	42					
5. WHR		-0.15	0.20	0.06	0.70**	1				
	n	42	42	42	42	42				
6. Menstrual cycle		0.16	-0.41*	-0.02	.	0.24	1			
	n	26	26	26	26	26	26			
7. Positive affect		-0.31*	-0.11	0.22	-0.07	-0.13	-0.26	1		
	n	42	42	42	42	42	26	42		
8. Medications		0.10	-0.43**	-0.15	-0.09	-0.07	0.08	0.12	1	
	n	42	42	42	42	42	26	42	42	
9. DASS-Stress		0.00	0.05	0.14	-0.01	0.08	-0.14	0.21	0.21	1
	n	42	42	42	42	42	26	42	42	42

*Correlation is significant at p<0.05

**Correlation is significant at p<0.01

Note. Gender (0=female, 1=male), WHR= Waist to Hip Ratio, Menstrual cycle=days since last cycle Positive affect= baseline positive affect, DASS-Stress = perceived stress subscale from DASS

Table 15

Correlations between cortisol outcomes and possible covariates for diabetic participants

Variable		1	2	3	4	5	6	7	8	9	10
1. Cortisol AUCi		1									
	n	21									
2. Cortisol AUCg		0.49*	1								
	n	21	21								
3. Smoking		-0.46*	-0.06	1							
	n	21	21	21							
4. Gender		-0.08	0.09	0.37	1						
	n	21	21	21	21						
5. Insulin Pump		-0.40	-0.15	-0.02	-0.23	1					
	n	21	21	21	21	21					
6. WHR		0.11	0.34	0.30	0.77**	-0.11	1				
	n	21	21	21	21	21	21				
7. Menstrual cycle		0.39	0.19	-0.12	.	0.08	0.51	1			
	n	12	12	12	12	12	12	12			
8. Positive affect		0.38	-0.01	-0.26	0.13	-0.30	-0.02	-0.06	1		
	n	21	21	21	21	21	21	12	21		
9. Medications		-0.08	-0.23	0.24	0.02	0.07	0.03	-0.22	-0.32	1	
	n	21	21	21	21	21	21	12	21	21	
10. DASS-Stress		-0.54*	-0.23	0.35	0.03	0.49*	-0.02	-0.11	-0.47*	0.47*	1
	n	21	21	21	21	21	21	12	21	21	21

*Correlation is significant at p<0.05

**Correlation is significant at p<0.01

Note. Gender (0=female, 1=male), WHR= Waist to Hip Ratio, Menstrual cycle=days since last cycle Positive affect= baseline positive affect, DASS-Stress = perceived stress subscale from DASS

Table 16
Descriptive information for cognitive variables

Variable	*n*	*M*	*SD*	*Mdn*	Min	Max	Skew	Kurtosis
Pre-stressor Stroop								
Diabetic	23	-26.00	10.22	-25.00	-41.00	0.00	0.47	0.42
Control	46	-27.02	8.04	-26.50	-44.00	-11.00	-0.12	-0.29
Post-stressor Stroop								
Diabetic	23	-25.04	9.01	-24.00	-45.00	-10.00	-0.38	-0.25
Control	46	-28.17	8.48	-28.00	-46.00	-4.00	0.21	0.51
Pre-stressor SAAT								
Diabetic	22	4.05	9.36	3.50	-12.00	26.00	0.38	-0.17
Control	44	3.70	8.46	4.00	-19.00	21.00	-0.32	1.10
Post-stressor SAAT								
Diabetic	22	10.09	7.84	9.00	-1.00	27.00	0.68	-0.08
Control	44	9.36	9.24	9.00	-17.00	28.00	-0.69	1.50
Trails B								
Diabetic	23	55.30	25.83	48.00	27.00	134.00	1.88	3.55
Control	46	47.72	23.24	44.00	19.00	166.00	3.16	14.44
Trails D								
Diabetic	23	60.83	13.90	58.00	40.00	84.00	0.33	-1.24
Control	46	66.11	22.89	62.50	32.00	120.00	0.59	-0.64
COWAT (CFL)								
Diabetic	23	41.22	12.00	40.00	21.00	65.00	0.34	-0.58
Control	46	39.74	11.05	39.50	20.00	61.00	0.10	-0.94
COWAT (PRW)								
Diabetic	23	42.22	9.33	43.00	20.00	58.00	-0.67	0.59
Control	46	42.13	8.93	44.00	27.00	61.00	-0.06	-1.12

Note. Descriptives derived from variables after winsorizing and prior to transformations. SAAT=Sustained Attention Allocation Task, COWAT=Controlled Oral Word Association Task

Table 17

Descriptive information for cognitive variables and possible cognitive covariates

Variable	*n*	*M*	*SD*	*Mdn*	Min	Max	Skew	Kurtosis
RVLT trial 5								
Diabetic	23	13.13	1.66	13.00	9.00	15.00	-0.95	0.45
Control	46	13.26	2.12	14.00	5.00	15.00	-2.14	5.32
RVLT recall								
Diabetic	23	11.61	2.73	13.00	5.00	15.00	-0.83	-0.03
Control	46	11.52	2.77	12.00	3.00	15.00	-1.21	1.43
Blood Glucose AUCi								
Diabetic	22	-74007.32	125360.64	-83325.00	-300181.00	179820.00	-0.19	-0.18
Control	46	-13918.70	55696.88	-11190.00	-196620.00	152790.00	-0.88	5.20
Blood Glucose AUCg								
Diabetic	22	675684.55	208558.34	641655.00	430800.00	1260000.00	1.45	1.96
Control	46	500817.39	63575.53	493245.00	369150.00	699780.00	0.53	1.21
Hours slept in previous night								
Diabetic	21	7.48	1.73	8.00	2.50	10.00	-1.14	1.89
Control	46	7.68	1.90	8.00	3.00	11.50	-0.34	0.04
Baseline Positive Affect								
Diabetic	23	5.10	2.25	4.60	1.40	9.60	0.31	-0.65
Control	46	5.04	1.82	5.00	1.00	9.60	0.09	-0.12
Baseline Negative Affect								
Diabetic	23	1.81	0.97	1.67	1.00	5.00	1.88	4.21
Control	46	1.74	0.79	1.42	1.00	4.17	1.19	0.90

Note. Descriptives derived from variables after winsorizing and prior to transformations. RVLT = Rey Verbal Learning Test.

Table 18

Descriptive information for possible cognitive covariates

Variable	*n*	*M*	*SD*	*Mdn*	Min	Max	Skew	Kurtosis
Number of Medications								
Diabetic	23	0.30	0.63	0.00	0.00	2.00	1.99	2.94
Control	46	0.17	0.38	0.00	0.00	1.00	1.78	1.22
Cortisol AUCi								
Diabetic	21	2790.46	8616.98	1253.10	-19537.65	25980.60	0.12	3.33
Control	42	-2476.74	10240.26	-1821.68	-28766.70	26730.75	0.03	2.00
Cortisol AUCg								
Diabetic	21	24006.73	11494.11	20749.50	9899.70	48370.20	0.66	-0.66
Control	42	23154.53	11351.09	21261.08	5629.05	51779.55	0.68	0.01

Note. Descriptives derived from variables after winsorizing and prior to transformations.

Table 19

Correlations between cognitive outcomes and possible covariates collapsed across diabetic and non-diabetic participants

Variable		1	2	3	4	5	6	7	8
1. Stroop		1							
	n	69							
2. SAAT		0.01	1						
	n	66	66						
3. Trails B		0.17	-0.50**	1					
	n	69	66	69					
4. COWAT		-0.13	0.24*	-0.29*	1				
	n	69	66	69	69				
5. RVLT Trial 5		-0.12	0.15	-0.43**	0.17	1			
	n	69	66	69	69	69			
6. Hours Slept		-0.16	-0.02	0.11	-0.20	-0.09	1		
	n	67	64	67	67	67	67		
7. Negative Affect		0.00	0.05	-0.12	-0.05	-0.12	-0.07	1	
	n	69	66	69	69	69	67	69	
8. Medications		-0.17	0.19	-0.09	0.07	-0.04	-0.03	0.10	1
	n	69	66	69	69	69	67	69	69

*Correlation is significant at $p<0.05$

**Correlation is significant at $p<0.01$

Note. All cognitive measures are from pre-stressor battery. Hours slept=hours slept in previous night, Negative affect=baseline negative affect, Medications = number of medications, SAAT= Sustained Attention Allocation Task, COWAT= Controlled Oral Word Association Task, RVLT= Rey Verbal Learning Test

Table 20

Correlations between cognitive outcomes and possible covariates for control participants

Variables		1	2	3	4	5	6	7	8
1. Stroop		1							
	n	46							
2. SAAT		0.15	1						
	n	44	44						
3. Trails B		0.08	-0.04**	1					
	n	46	44	46					
4. COWAT		-0.13	0.38*	-0.33*	1				
	n	46	44	46	46				
5. RVLT Trial 5		-0.01	0.07	-0.44**	0.23	1			
	n	46	44	46	46	46			
6. Hours slept		-0.01	-0.11	0.12	-0.22	-0.20	1		
	n	46	44	46	46	46	46		
7. Negative Affect		0.05	0.05	-0.04	-0.14	0.06	-0.08	1	
	n	46	44	46	46	46	46	46	
8. Medications		-0.17	-0.04	0.02	-0.08	-0.23	-0.04	0.05	1
	n	46	44	46	46	46	46	46	46

*Correlation is significant at p<0.05

**Correlation is significant at p<0.01

Note. All cognitive measures are from pre-stressor battery. Hours slept=hours slept in previous night, Negative affect=baseline negative affect, Medications = number of medications, SAAT= Sustained Attention Allocation Task, COWAT= Controlled Oral Word Association Task, RVLT= Rey Verbal Learning Test

Table 21

Correlations between cognitive outcomes and possible covariates for diabetic participants

Variable		1	2	3	4	5	6	7	8	9
1. Stroop		1								
	n	23								
2. SAAT		-0.19	1							
	n	22	22							
3. Trails B		0.29	-0.66**	1						
	n	23	22	23						
4. COWAT		-0.15	0.02	-0.27	1					
	n	23	22	23	23					
5. RVLT Trial 5		-0.30	0.29	-0.40	0.07	1				
	n	23	22	23	23	23				
6. Hours Slept		-0.43	0.16	0.13	-0.14	0.19	1			
	n	21	20	21	21	21	21			
7. Negative Affect		-0.07	0.04	-0.29	0.09	-0.43*	-0.05	1		
	n	23	22	23	23	23	21	23		
8. Medications		-0.19	0.46*	-0.29	0.22	0.24	0.01	0.15	1	
	n	23	22	23	23	23	21	23	23	
9. Insulin Pump		-0.37	0.19	-0.45*	0.25	0.30	0.41	0.21	0.15	1
	n	23	22	23	23	23	21	23	23	23

*Correlation is significant at $p<0.05$

**Correlation is significant at $p<0.01$

Note. All cognitive measures are from pre-stressor battery. Hours slept=hours slept in previous night, Negative affect=baseline negative affect, Medications = number of medications, SAAT= Sustained Attention Allocation Task, COWAT= Controlled Oral Word Association Task, RVLT= Rey Verbal Learning Test

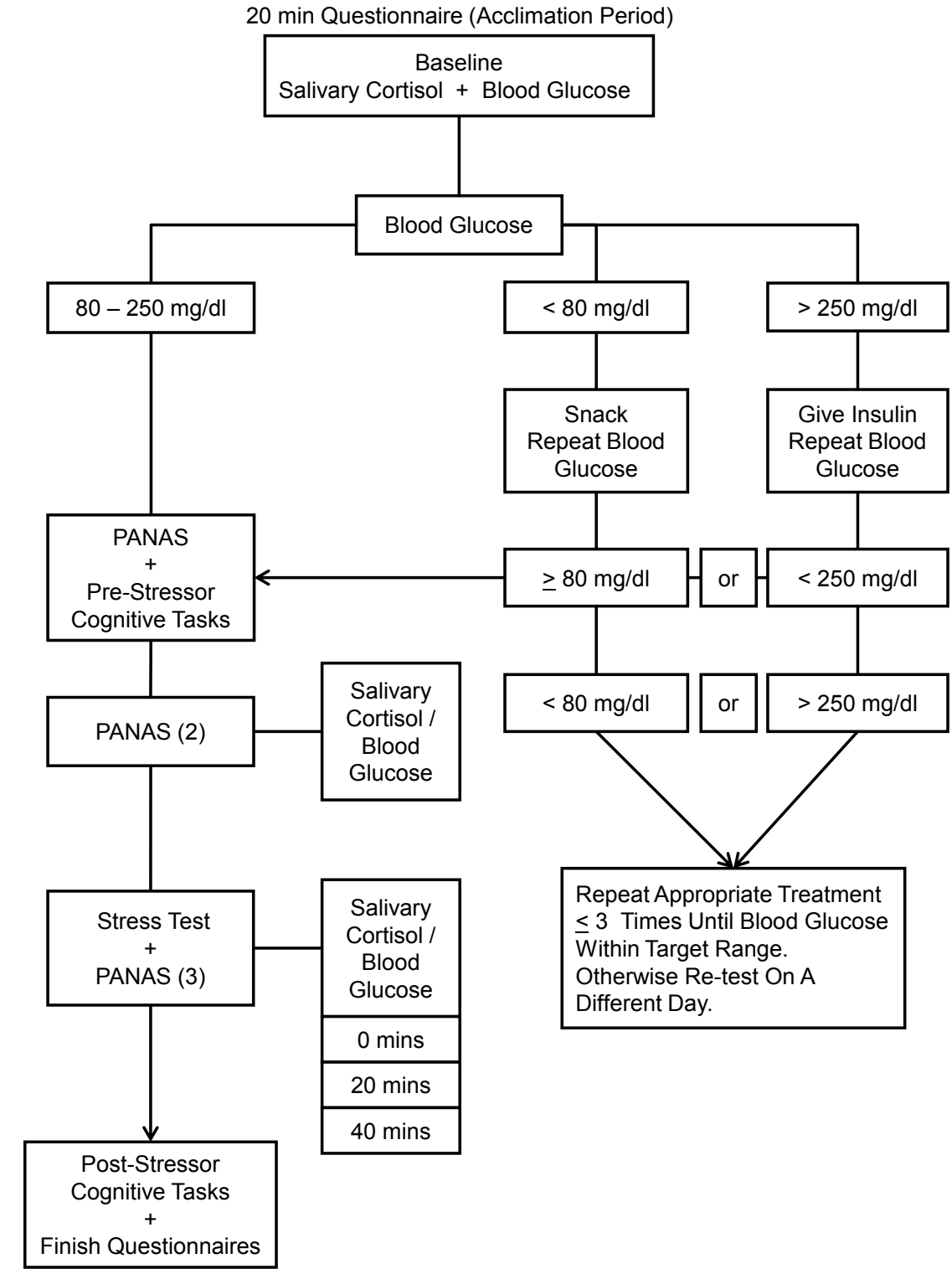


Figure 1. Study Protocol

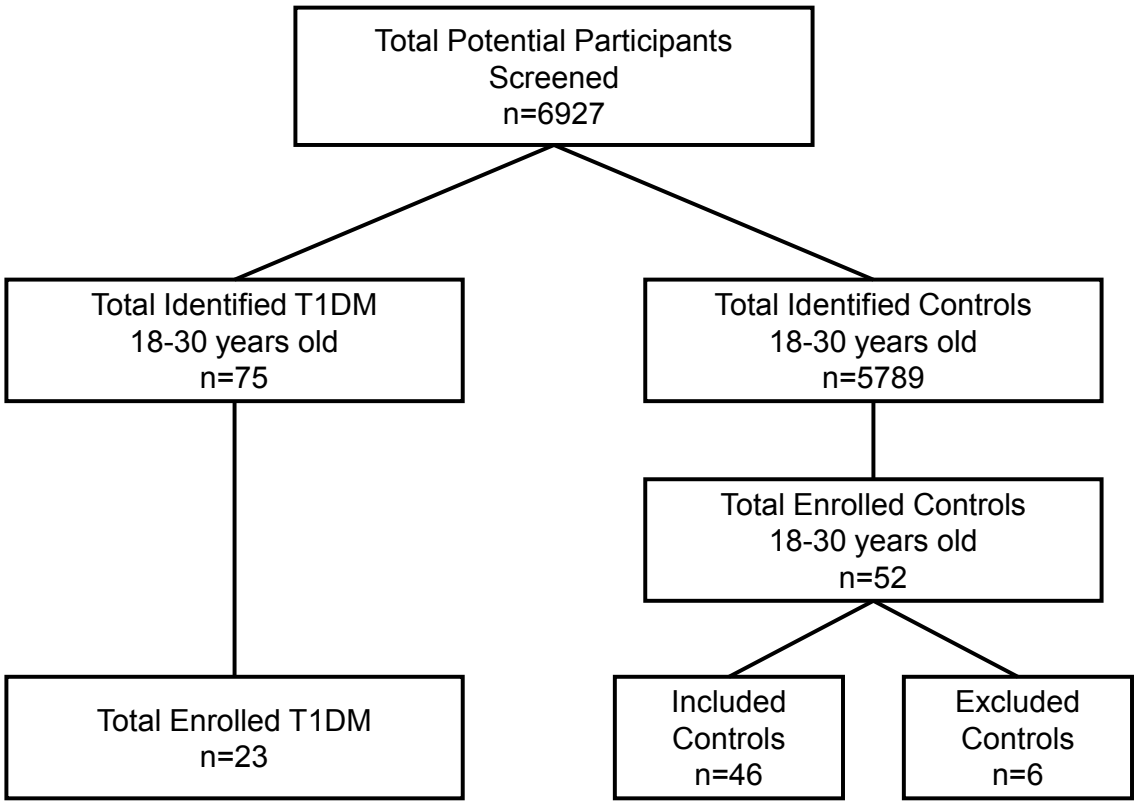


Figure 2. Consort Flow Chart

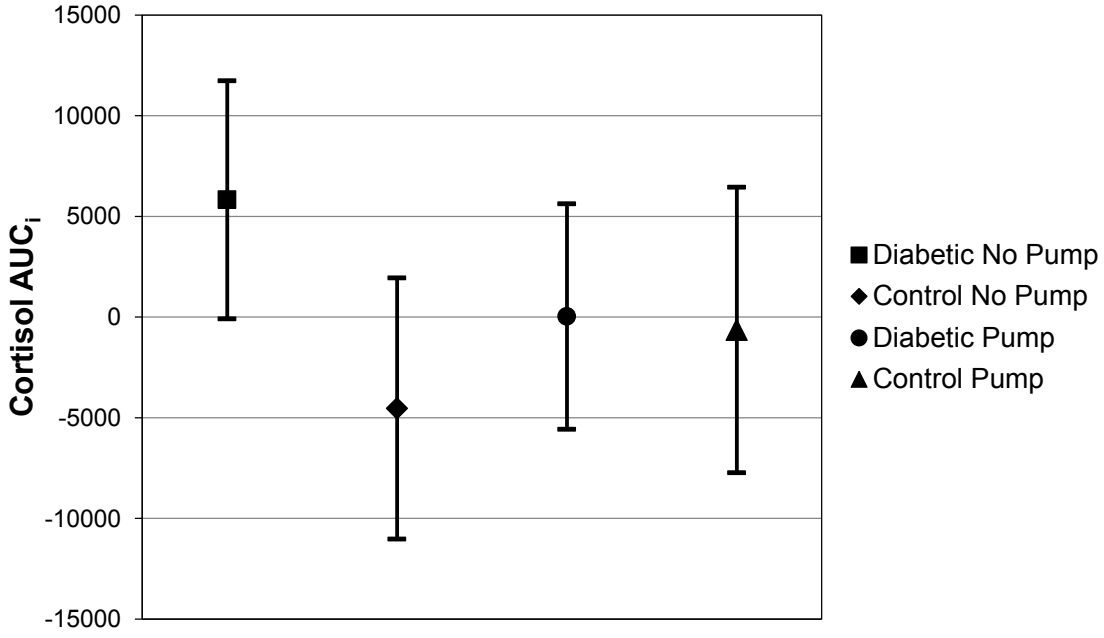


Figure 3. Interaction between T1DM status and insulin pump status (i.e., clusters with and without diabetics on insulin pump) on cortisol AUC_i.

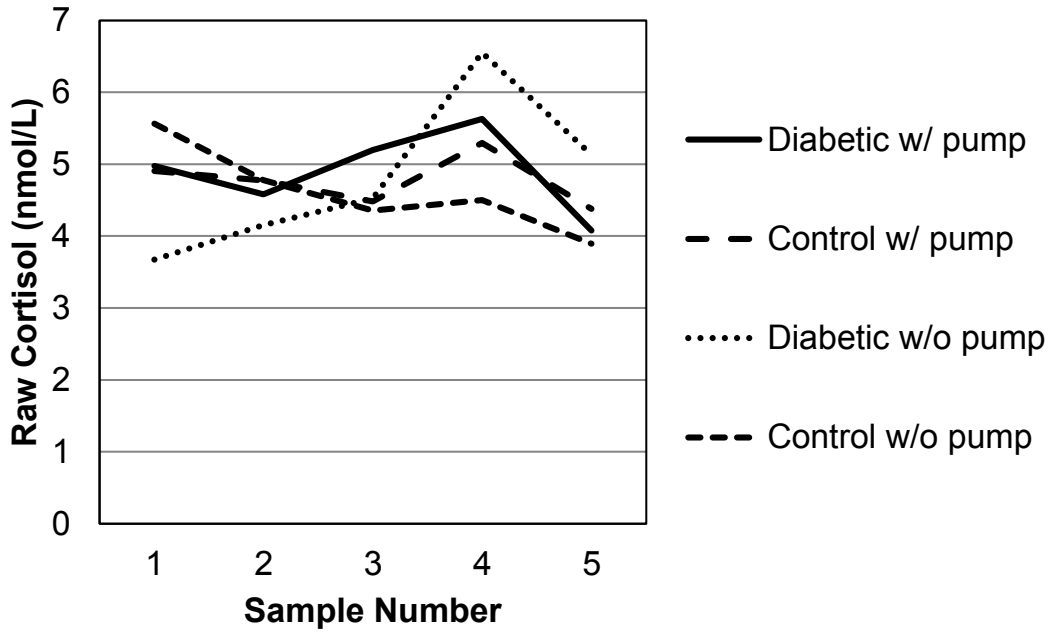


Figure 4. Plots of average raw cortisol levels for each group (i.e., Diabetics with insulin pump, controls matched to diabetics with insulin pumps, diabetics without insulin pumps, controls matched to diabetics without insulin pump) across samples collected over the course of participation.

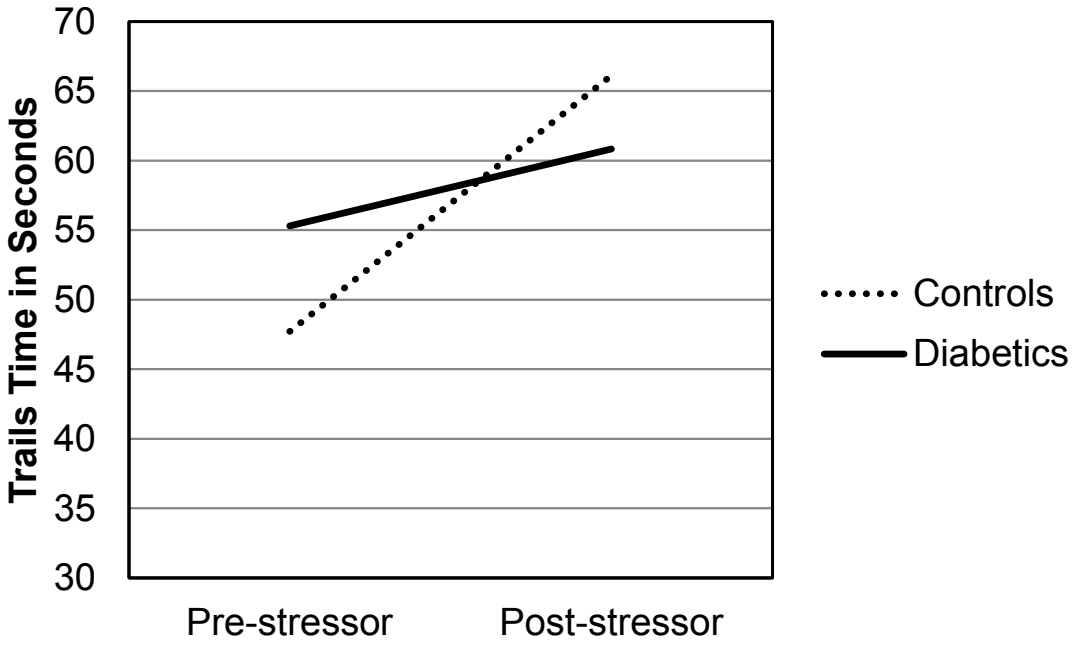
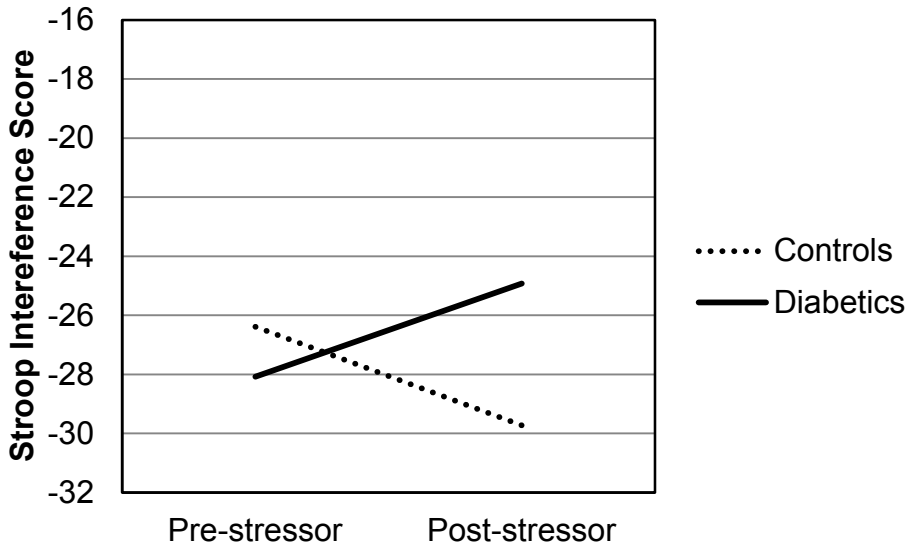
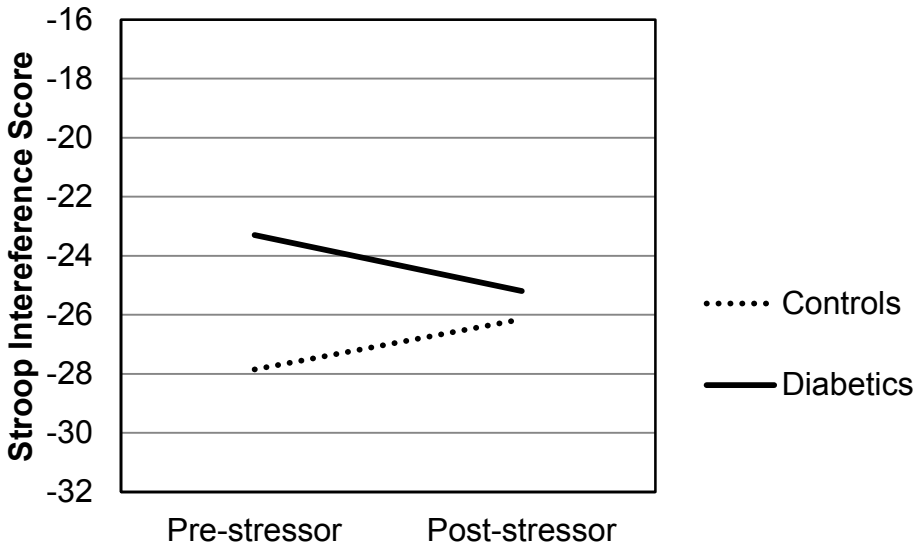


Figure 5. Interaction between T1DM status and performance on Trail Making Test from pre- to post-stressor task. Higher scores reflect longer time to complete task and poorer performance.



a) Significant interaction between T1DM diagnosis and change in performance across pre to post-stressor Stroop interference task within clusters in which the T1DM participant was on an insulin pump.



b) non-significant interaction between T1DM diagnosis and change in performance across pre to post-stressor Stroop interference task within clusters in which the T1DM participant was not on an insulin pump.

Figure 6. Significant interaction between insulin pump status, T1DM diagnosis and pre to post-stressor changes on Stroop interference task. Higher scores (closer to zero) indicate lower interference and better performance.

APPENDIX A

QUESTIONNAIRES

10-ITEM PANAS

Question: Describe how you feel right now on a scale of 1 to 10, where 1 is “not at all,” and 10 is “extremely”:

Items in order:

upset

nervous

interested

hostile

enthusiastic

strong

irritable

excited

ashamed

determined

DEPRESSION AND ANXIETY STRESS SCALE (DASS)

STRESS SUBSCALE

ITEMS:

I found it hard to wind down.
I tended to over-react to situations.
I felt that I was using a lot of nervous energy.
I found myself getting agitated.
I found it difficult to relax.
I was intolerant of anything that kept me from getting on with what I was doing.
I felt that I was rather touchy.

SCALE:

Value	Description
0	did not apply to me at all
1	applied to me to some degree or some of the time
2	applied to me to a considerable degree, or a good part of the time
3	applied to me very much, or most of the time

APPENDIX B

IRB APPROVAL DOCUMENTATION

ASU Knowledge Enterprise Development

Office of Research Integrity and Assurance

To:	Linda Luecken PSY
From:	Carol Johnston, Chair Biosci IRB
Date:	07/27/2011
Committee Action:	**Expedited Approval**
Approval Date:	07/27/2011
Review Type:	Expedited F3 F7
IRB Protocol #:	1107006648
Study Title:	Cognition and stress reactivity in young adults with and without type 1 Diabetes Mellitus
Expiration Date:	07/26/2012

The above-referenced protocol was approved following expedited review by the Institutional Review Board.

It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date. You may not continue any research activity beyond the expiration date without approval by the Institutional Review Board.

Adverse Reactions: If any untoward incidents or severe reactions should develop as a result of this study, you are required to notify the Biosci IRB immediately. If necessary a member of the IRB will be assigned to look into the matter. If the problem is serious, approval may be withdrawn pending IRB review.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, or the investigators, please communicate your requested changes to the Biosci IRB. The new procedure is not to be initiated until the IRB approval has been given.

Please retain a copy of this letter with your approved protocol.