THE NEUROPSYCHOLOGICAL EFFECTS OF TYPE 1 DIABETES AND DEPRESSIVE SYMPTOMS IN ADOLESCENTS

by

Lauren Elizabeth Wheeler

Copyright © Lauren Elizabeth Wheeler 2010

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF DISABILITY AND PSYCHOEDUCATIONAL STUDIES

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY
WITH A MAJOR IN SCHOOL PSYCHOLOGY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2010
As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Lauren Elizabeth Wheeler entitled The Neuropsychological Effects of Type 1 Diabetes and Depressive Symptoms in Adolescents and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Date: 4/5/2010

John Obrzut

Date: 4/5/2010

Michelle Perfect

Date: 4/5/2010

Lawrence Aleamoni

Date: 4/5/2010

Lee Ryan

Final approval and acceptance of this dissertation is contingent upon the candidate’s submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Date: 4/5/2010

Dissertation Director: John Obrzut
STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this dissertation are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the copyright holder.

SIGNED: Lauren Elizabeth Wheeler
ACKNOWLEDGEMENTS

There are many people I would like to acknowledge who provided me with encouragement, support, and technical assistance for this project. Firstly, thank you to the many participants who gave of their time and made this research possible.

At the University of Arizona, thank you to my advisor and dissertation chairperson, John Obrzut, Ph.D., for ongoing supervision of dissertation activities, manuscript editing, and clarification of the process for reaching a finished product. Many thanks to Michelle Perfect, Ph.D. who provided me with inspiration for research topics, experience in the recruitment process and research design, and a plethora of thoughtful supervision throughout the project. I also thank the other two committee members, Lee Ryan, Ph.D., and Lawrence Aleamoni, Ph.D., for their support and guidance in the planning, analysis, and completion of this research. Thank you to Mark Borgstrom, Ph.D., for helping with the statistical analyses and interpretation of the data.

In addition, I would like to acknowledge and thank Drs. Chetan Patel, M.D., Priti Patel, M.D., and Mark Wheeler, M.D., and their staff for assisting with recruitment, literature updates, and constant encouragement.

Finally, thank you to all my friends and family who encouraged and supported me throughout my graduate studies, especially Mom, Dad, Garrett, Joe, & Christina.
DEDICATION

It is an honor to have such a wonderful family to whom I can dedicate this work.

Mom, Dad, & Garrett– the love and support that I have received both during my graduate studies and throughout my entire life has been exceptional, unconditional, and boundless.

Thank you.
TABLE OF CONTENTS

LIST OF TABLES ................................................................................. 8

LIST OF FIGURES ............................................................................... 9

ABSTRACT .......................................................................................... 10

CHAPTER 1 INTRODUCTION .............................................................. 12
  Neurological Impact of Diabetes ......................................................... 13
    Neuroanatomical effects of diabetes .............................................. 13
    Neurocognitive effects of diabetes ................................................. 14
  Neurological Impact of Depression .................................................. 16
    Neuroanatomical effects of depression ........................................... 16
    Neurocognitive effects of depression ............................................. 17
  Diabetes and Depression .................................................................. 17
  Statement of Problem ....................................................................... 19
  Purpose of Study ............................................................................ 20
  Research Questions .......................................................................... 20
  Definition of Terms ......................................................................... 21
  Summary .......................................................................................... 22

CHAPTER 2 REVIEW OF THE LITERATURE ....................................... 24
  Neurological Impact of Diabetes ......................................................... 24
    Neuroanatomical effects of diabetes .............................................. 24
    Neurophysiological effects of diabetes .......................................... 28
    Neuropsychological effects of diabetes ........................................ 30
      Memory and learning ................................................................. 33
      Attention ..................................................................................... 40
    Factors related to the neuropsychological effects of diabetes ...... 42
      Age of onset and disease duration ............................................. 42
      Gender differences ................................................................... 45
      Effects of hypoglycemia ........................................................... 46
  Neurological Impact of Depression .................................................. 50
    Neuroanatomical effects of depression ........................................... 50
    Neuropsychological effects of depression .................................... 54
      Memory performance in depressed individuals ....................... 54
      Attention and inhibition in depressed individuals ................... 58
  Effect of Depressive Symptoms on Cognitive Functioning in Individuals with Diabetes .................................................. 66
  General Summary ........................................................................... 68

CHAPTER 3 METHODOLOGY ............................................................... 70
  Participants ....................................................................................... 70
  Materials ........................................................................................ 71
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS - Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent measures:.............71</td>
</tr>
<tr>
<td>Wide Range Assessment of Memory and Learning- Second Edition (WRAML2):............71</td>
</tr>
<tr>
<td>Stroop Color and Word Test Adult and Children's Versions Revised:.............73</td>
</tr>
<tr>
<td>Independent measures:...........74</td>
</tr>
<tr>
<td>Demographic questionnaire:.......75</td>
</tr>
<tr>
<td>The Beck Depression Inventory for Youth, Second Edition (BDI-Y II):...........75</td>
</tr>
<tr>
<td>The Kaufman Brief Intelligence Test, Second Edition (KBIT-2):..............76</td>
</tr>
<tr>
<td>Procedure:.........................78</td>
</tr>
<tr>
<td>Data Analysis:.....................80</td>
</tr>
<tr>
<td>Summary:............................83</td>
</tr>
</tbody>
</table>

CHAPTER 4 ANALYSIS AND RESULTS OF DATA..............84
| Participant Characteristics:........84 |
| Relationship between Diabetes, Depressive Symptoms, and Memory:........87 |
| Relationship between Diabetes, Depressive Symptoms, and Learning:.......92 |
| Relationship between Diabetes, Depressive Symptoms, and Attention:......95 |
| Relationship between Diabetes-related Variables and Depressive Symptoms:97 |
| Summary:................................98 |

CHAPTER 5 DISCUSSION.................................99
| Purpose of Study:.........................99 |
| Relationship among Diabetes, Depressive Symptoms, and Neuropsychological Functioning:........99 |
| Relationship between diabetes, depressive symptoms, memory and learning:........99 |
| Relationship between diabetes, depressive symptoms, and attention:.......102 |
| Relationship between Diabetes-related Factors and Depressive Symptoms:........105 |
| Limitations of the Study:.................107 |
| Future Directions:.........................109 |

APPENDIX A: DEMOGRAPHIC QUESTIONNAIRE.............111
APPENDIX B: FLYER POSTER.............................112
APPENDIX C: FLYER HANDOUT.........................113
APPENDIX D: ADOLESCENT ASSENT FORM...............114
APPENDIX E: PARENT CONSENT FORM....................117
APPENDIX F: IRB APPROVAL FORMS.....................121

REFERENCES........................................124
LIST OF TABLES

Table 1. Description of Participant Demographic Variables ........................................85
Table 2. Means and Standard Deviations of Diabetes-related Variables ..................86
Table 3. Number and Percentage of Diabetic Participants for Diabetes-related
Variables ..................................................................................................................86
Table 4. Analysis of Variance for Neuropsychological Test Performance by Diabetes x
Depressive Symptoms Interaction ..............................................................................88
Table 5. Means and Standard Deviations for Neuropsychological Test Performance ....93
Table 6. Summary of Regression Analysis for Variables Predicting Depressive
Symptoms in Adolescents with Diabetes .................................................................98
LIST OF FIGURES

Figure 1. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal memory scores .........................................................89

Figure 2. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal recognition scores ........................................90

Figure 3. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal memory delayed scores ........................................91

Figure 4. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal learning scores ...........................................94

Figure 5. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on attention/concentration scores ................................. 96
ABSTRACT

This study investigated the relationship between the interaction of diabetes and depressive symptoms and neuropsychological functioning in a sample of adolescents. It also addressed whether disease-related variables such as age of onset of diabetes and presence of severe hypoglycemic episodes were predictive of severity of depressive symptoms. Depressive symptoms were assessed using the Beck Depression Inventory for Youth, Second Edition (BDI-Y II). The neuropsychological domains of memory, attention, and overall cognitive abilities were assessed using a cross-battery approach with subtests from the Wide Range Assessment of Memory and Learning – Second Edition (WRAML2), the Stroop Test, and the Kaufman Brief Intelligence Test – Second Edition (KBIT-2), respectively.

The total sample consisted of 62 youth between the ages of 13 and 17 years: 31 adolescents diagnosed with Type 1 diabetes and 31 adolescents without diabetes. Adolescents were recruited from an outpatient pediatric diabetes clinic and an outpatient general medicine pediatric clinic located in Tuscon, AZ as well as by referral from word of mouth. The mean age of participants was 15.26 (SD= 1.33) years. Of the 62 participants, 29 (46.8%) were female and 33 were male (53.2%). The mean and standard deviation for participants’ BDI-Y II T-scores was 50.68 (8.65). In terms of ethnic distribution, the sample was comprised of Caucasian (54.8%), Hispanic (38.7%), African American (4.8%), and Asian (1.6%) adolescents. Approximately 39% of participants qualified for free (n=18) or reduced price (n=6) lunch at school. For the group with
diabetes, the mean age at onset was 8.77 years (SD = 4.74) and the mean duration was 6.90 years (SD = 4.84).

Significant findings included that the interaction effect of diabetes and depressive symptoms scores was statistically significant for verbal memory, verbal recognition, verbal memory delayed, verbal list learning, and attention/concentration. No significant differences were found for verbal working memory, visual memory, visual recognition, or attention/inhibition. Regression analyses showed that none of the diabetes-related variables included in the study variables (age of diabetes onset, duration of diabetes, presence of severe hypoglycemic episodes, type of insulin therapy) were predictive of depressive symptoms scores that adolescents reported.
CHAPTER 1
INTRODUCTION

This chapter will provide an overview of the issues associated with having diabetes including the effects of diabetes on the brain and the increased risk of depression. This chapter also includes a statement of the problem, the purpose of the study, specific research questions addressed in the study, and definitions of significant terms.

Diabetes is one of the most common chronic diseases in school-aged children and has been steadily increasing in prevalence since 1980 with more than 13,000 children diagnosed each year. About one in every 400 to 600 children and adolescents has Type 1 diabetes (Centers for Disease Control and Prevention, 2005), and the percentage of children with newly diagnosed diabetes classified as Type 2 has increased from less than 5 percent before 1994 to 30 to 50 percent in subsequent years (Fagot-Campagna et al., 2000; Kaufman, 2002).

Type 1 diabetes is a serious metabolic disorder in which the pancreas ceases to produce the insulin necessary to metabolize glucose resulting in the accumulation of glucose in the bloodstream and urine while organs requiring glucose, such as the brain, starve. Type 2 diabetes is characterized by high blood glucose levels due to resistance to insulin and inadequate compensation in the secretion of insulin (National Diabetes Education Program, 2006). An intricate and persistent regimen of diet, exercise, and insulin by injection is necessary to approximate the normal metabolic state of the non-
diabetic individual. Insulin requirements must be continuously adjusted to avoid hyperglycemia and hypoglycemia.

In both types of diabetes, individuals experience marked fluctuation in levels of glucose due to deficiencies in insulin production and regulation and the subsequent insulin injections. Exposure to the resulting hyperglycemic and hypoglycemic conditions has been linked to both transient and permanent impairment in neuropsychological functioning in the areas of visual-motor, memory, attention, processing speed, and executive functioning (Awad, Gagnon, & Messier, 2004; Gonder-Frederick et al., 2009; Rovet, 2000). Furthermore, because of difficulties in balancing insulin injections with activity and diet in children, an estimated 31% of all children with Type 1 diabetes experience one or more episodes of severe hypoglycemia (Daneman, Frank, Perlman, Tamm, & Ehrlich, 1989). Hypoglycemia has been linked to deficits in attention, memory, visuospatial skills, and motor skills (Desrocher & Rovet, 2004; Bade-White & Obrzut, 2009).

**Neurological Impact of Diabetes**

**Neuroanatomical effects of diabetes.** Research substantiates that both Type 1 and Type 2 diabetes are associated with neuroanatomical changes (den Heijer et al., 2003; Lunetta et al., 1994; Lobnig, Kromeke, Optenhostert-Porst & Wolf, 2005) and that these changes are differentially affected by disease-related factors such as presence of hypoglycemic episodes, hyperglycemia exposure, and age of onset (Manschot et al., 2006; Musen et al., 2006; Perantie et al., 2007; Salem, Matta, Tantawy, Hussein, & Gad, 2002). For example, compared to healthy young adults, young adults with Type 1
diabetes have significantly larger lateral ventricles and dilated subarachnoid spaces in the cerebral vault and cerebellum due to atrophy (Lunetta et al., 1994). A later study confirmed the increased amount of cerebrospinal fluid (CSF) and found that amount of CSF was associated with declines in psychomotor speed and selective attention (Lobnig et al., 2005).

Type 2 diabetes in older adults aged 60-90 years old has been associated with deep white matter lesions (DWMLs), cortical atrophy, periventricular white matter lesions (PWMLs), subcortical atrophy (Manschot et al., 2006) and hippocampal and amygdalar atrophy compared to healthy adults, with a positive relationship between insulin resistance and amygdalar atrophy (den Heijer et al., 2003). This suggests that the regions associated with memory and emotional abilities are damaged by insulin resistance.

In regards to long-term effects of diabetes and recurrent severe hypoglycemia on the brain and cognitive abilities of adults with Type 1 diabetes lasting at least ten years, high-intensity periventricular white matter lesions, particularly SPWMLs, were common whereas deep white matter lesions were infrequent (Ferguson et al., 2003). The presence of background retinopathy was associated with more frequent SPWMLs in the basal ganglia as well as poorer performance on cognitive tests of fluid intelligence, information processing speed, and the ability to maintain attention and concentration.

**Neurocognitive effects of diabetes.** Different variables have been found to affect the implication of diabetes on neuropsychological functioning such as age of onset, frequency and severity of hypoglycemic episodes, presence of hyperglycemic episodes,
gender, and treatment regimens. Previous research has addressed a variety of combinations of these variables in order to elucidate the relationship between diabetes and neuropsychological functioning in the domains of motor speed and efficiency, visuospatial abilities, nonverbal abilities, verbal abilities, memory, attention and inhibition, executive functioning, and processing speed (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). Four key relationships that have been identified are between attention and memory deficits and hypoglycemia, verbal and executive functioning deficits and hyperglycemia, executive functioning and puberty, and motor and visuospatial deficits and early age of onset (Desrocher & Rovet, 2004). In fact, in terms of early onset, the ages of five to seven years old have been identified as one of the critical periods in which diabetes most severely impacts cognition (Biessels, Kerssen, de Haan, & Kappelle, 2007).

Cognitive functioning of children and adolescents with diabetes has been documented as being in the normal range and comparable to healthy children at the time of diabetes onset and tends to decline in particular domains over a period of years (Kovacs, Goldston, & Iyengar, 1992; Northam, Anderson, Werther, Adler, & Andrewes, 1995; Northam et al., 1998; Northam, et al., 2001), suggesting that differences in cognitive functioning between diabetics and non-diabetics cannot be explained by prior abilities. One of the earliest studies on cognitive functioning in diabetic children found that age of diabetes onset was predictive of performance on tasks of visual memory, incidental memory, visuoconstructional abilities, visuospatial abilities, vocabulary, symbol digit learning, and Trails B (Ryan, Vega, and Drash, 1985). These measures are
typically associated with right hemisphere functioning with the exception of the vocabulary subtest. On the other hand, disease duration was related to attention and short term auditory memory, similarities, spelling, and reading, measures usually associated with left hemisphere functioning.

Research linking structural and neurophysiological abnormalities to cognitive abilities has been inconclusive with findings of little correlation (Salem et al., 2002; Tupola et al., 2004) and findings of significant correlation (Manschot et al., 2006; Watari et al., 2008). For example, Manschot et al. (2006) found that DWMLs, cortical atrophy, and infarcts were related to impairment in processing speed. Subcortical atrophy was related to problems of attention and executive function.

**Neurological Impact of Depression**

**Neuroanatomical effects of depression.** Depressive disorders in adults have been associated with brain abnormalities such as reduced hippocampal volumes (Bremner, et al., 2000; Frodl et al., 2002; Sheline, Sanghavi, Mintun, & Gado, 1999) and abnormal patterns of brain activity in the anterior cingulate cortex (Alexopoulos, Gunning-Dixon, Latoussakis, Kanellopoulos, & Murphy, 2008; Brody, Barsom, Bota, & Saxena; 2001). Fewer studies have been conducted with children and adolescents, but those that exist also support differences between depressed youth and nondepressed youth. For example, non-medicated depressed youth have been shown to have smaller left hippocampal volumes compared to medicated and healthy participants in one study (Caetano et al., 2007) and smaller left and right hippocampal volumes compared to the healthy participants in another study (MacMaster et al., 2008). Other studies have found
differences in the frontal lobes of depressed adolescents (Steingard et al., 2002) and in prefrontal cortex volume of children and adolescents with major depression (Nolan et al., 2002).

**Neurocognitive effects of depression.** Numerous studies have found that depression is related to neurocognitive deficits in children and adolescents. Specifically, youth with depression have been shown to experience poorer memory performance than their non-depressed counterparts in the areas of auditory working memory, long delayed recall and recognition of word lists, and spatial and visual memory (Gunther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004, Matthews, Coghill, & Rhodes, 2008; Porter et al., 2003). Severity of depression in terms of number of depressive symptoms endorsed was linked to increased difficulties in immediate recall of word lists.

Attention performance has also been noted as an area of deficit for youth with depression compared to healthy individuals. Specific areas of deficit include decreased ability to inhibit distractors or increased attentional distractibility, slower responses during sustained, selective, and switching attention tasks, and less accuracy during sustained and switching attention tasks (Cataldo, Nobile, Lorusso, Battaglia, & Molteni, 2005; Killgore, Gruber, & Yurgelun-Todd, 2007; Kyte, Goodyer, & Sahakian, 2005; Lepisto et al., 2004; Porter et al., 2003; Wilkinson & Goodyer, 2006; Zakzanis et al., 1998).

**Diabetes and Depression**

In addition to the health risks and neurocognitive deficits associated with diabetes, adolescents with diabetes are also more susceptible to developing depression. Several
studies suggest that diabetes doubles the risk of depression compared to those without the disorder (Anderson, Lustman, Clouse, De Groot, & Freedland, 2000; Hood et al., 2006), and an estimated 18% of adolescents with diabetes also have depression (Kokkonen & Kokkonen, 1995). Furthermore, diabetes comorbid with depression is associated with an increase in the number of depressive symptoms compared to depressed non-diabetics (Petersen, Iosifescu, Papakostas, Shear, & Fava, 2006). Depression in and of itself has been associated with negative impact on neuropsychological functioning, specifically declines in memory, attention, and psychomotor speed (Lauer et al., 1994; Kizilbash, Vanderploeg, & Curtiss, 2002; Zakzanis, Leach, & Kaplan, 1998) and inconclusively with executive functioning (Smitherman, Huerkamp, Miller, Houle, & O’Jile, 2007). Furthermore, depressive symptoms have been linked to deterioration in adolescents’ ability to manage their diabetes, which can lead to further brain insult (Helgeson, Siminerio, Escobar, & Becker, 2009; McGrady, Laffel, Drotar, Repaske, & Hood; 2009). A landmark study of 2,672 diabetic youth found that depressed mood was associated with poor glycemic control and increased emergency room visits (Lawrence et al., 2006).

Both diabetes and depression are independently linked to increased hypothalamus-pituitary-adrenal axis (HPA) activity, one of the peripheral components of the stress system (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). Chronic activation of this stress system leads to increased and prolonged secretion of corticotropin-releasing hormone (CRH) and glucocorticoids, which lead to insulin resistance and suppression of growth hormones, respectively. Changes to the HPA may be accompanied by depression, excessive fear, addictive behaviors, and gradual
development of metabolic disorders. Thus damage to the HPA could underlie both diabetes and depression, and perhaps the severity and nature of HPA damage are related to the development of one or both conditions. In support of the link between insulin resistance and depression, impaired insulin sensitivity has been found in depressed adults and has been resolved with successful treatment of the depression (Okamura et al., 2000).

**Statement of Problem**

The need is to investigate the effects of Type 1 diabetes and depressive symptoms on adolescents’ neuropsychological functioning in important domains of memory, learning, attention/concentration, and attention/inhibition. In spite of the prevalence and potential detrimental outcomes of diabetes comorbid with depression, there is a gap in the literature about how the interaction between diabetes and depressive symptoms impacts adolescents’ neuropsychological functioning.

One similar study examined the cognitive function of depressed adults with Type 2 diabetes and found that this population tended to have lower overall cognitive functioning than non-depressed diabetics specifically in areas of attention and processing speed (Watari et al., 2006). However, analogous research regarding neuropsychological functioning in adolescents does not exist. Adolescents may have different sequelae and outcomes than adults due to the fact that neural connections are still forming in their brain over the course of development. Further, this study addresses limitations in the previous study by assessing the number and frequency of depressive symptoms in both the experimental and control groups in order to differentiate effects due to the interaction
between diabetes and depressive symptoms from the effects of depressive symptoms only.

**Purpose of Study**

The purpose of this study was to examine the relationship between the interaction of diabetes and depressive symptoms and neuropsychological functioning in a sample of adolescents. This research is an imperative step towards the development of better interventions and strategies for improving the overall cognitive functioning and learning in this high incidence disability group.

Given that children with diabetes are more likely to receive lower marks in school than healthy children (Dahlquist & Kallen, 2007) and that particular subgroups experience a variety of academic difficulties (Rovet, Ehrlich, Czuchta, & Akler, 1993), studies that examine the underlying deficits in neuropsychological functioning are necessary to develop evidence based interventions for improving school performance.

**Research Questions**

This study has four research questions. The first three questions pertain to neuropsychological functioning that is associated with the interaction between diabetes and depressive symptoms in adolescents. First, which aspects of memory are affected by the interaction between diabetes and depressive symptoms in adolescents? Second, is learning affected by the interaction between diabetes and depressive symptoms in adolescents? Third, which aspects of attention are affected by the interaction between diabetes and depressive symptoms in adolescents? Lastly, this study addressed whether
there is a relationship between number of depressive symptoms and disease-related variables such as age of onset of diabetes and presence of severe hypoglycemic episodes.

**Definition of Terms**

Several specific terms were used throughout this research. Each term will be defined for the purposes of the present study.

- **Early onset diabetes.** Type 1 diabetes diagnosed before or at five years of age
- **ERPs.** Event related potentials
- **Hyperglycemia.** When blood sugar levels rise because there is not enough insulin to metabolize glucose.
- **Hypoglycemia.** When blood sugar levels decrease because of an excess of insulin in the body. Hypoglycemia is defined when blood sugar levels are low enough that physical symptoms appear such as light-headedness, weakness, or mental confusion.
- **Later onset diabetes.** Type 1 diabetes diagnosed after five years of age
- **Metabolic control.** Maintenance of blood sugar levels
- **P300.** Late cortical neurophysiological event
- **Selective attention.** This refers to the ability to filter information to detect relevant and ignore irrelevant stimuli.
- **Sustained attention.** This refers to the ability to maintain performance in a task that is inherently uninteresting and unrewarding
- **Severe hypoglycemic episodes.** Episodes in which glucose level is below 50 mg/dL and which require help from an outside party to recover, that is, which cannot be self-treated.
**Type 1 diabetes.** Beta cell destruction usually leading to absolute insulin deficiency.

**Summary**

Diabetes is one of the most common chronic diseases in school-aged children and has been steadily increasing in prevalence since 1980 with more than 13,000 children diagnosed each year. About one in every 400 to 600 children and adolescents has Type 1 diabetes (Centers for Disease Control and Prevention, 2005), and the percentage of children with newly diagnosed diabetes classified as Type 2 has increased from less than 5 percent before 1994 to 30 to 50 percent in subsequent years (Fagot-Campagna et al., 2000; Kaufman, 2002). In both types of diabetes, individuals experience marked fluctuation in levels of glucose due to deficiencies in insulin production and regulation and the subsequent insulin injections. Exposure to the resulting hyperglycemic and hypoglycemic conditions has been linked to both transient and permanent impairment in neuropsychological functioning in the areas of visual-motor, memory, attention, processing speed, and executive functioning (Awad, Gagnon, & Messier, 2004; Gonder-Frederick et al., 2009; Rovet, 2000).

In addition to the health risks associated with diabetes, adolescents with diabetes are also more susceptible to developing depression. Several studies suggest that diabetes doubles the risk of depression compared to those without the disorder (Anderson et al., 2000; Hood et al., 2006), and an estimated 18% of adolescents with diabetes also have depression (Kokkonen & Kokkonen, 1995). Depression has been associated with decline
in memory, attention, and psychomotor speed (Lauer et al., 1994; Kizilbash et al., 2002; Zakzanis et al., 1998).

This study examined the effects of the interaction between diabetes and depressive symptoms on neuropsychological functioning in a sample of adolescents. This research is an imperative step towards the development of better interventions and strategies for improving the overall cognitive functioning and learning in this high incidence disability group.

The following chapter presents a review of the literature pertinent to this study. The third chapter presents the methodology and procedures that were used in this research project. The fourth chapter offers analysis of the results. Finally, the fifth chapter gives a discussion of conclusions from this research project and offers implications for future research.
CHAPTER 2
REVIEW OF THE LITERATURE

This chapter contains a review of the literature relevant to the present study. It is divided into two sections. The first section provides literature pertaining to the neurological impact of Type 1 diabetes on learning and behavior. This section presents the neuroanatomical, neurophysiological, and neuropsychological differences in individuals who experience Type 1 diabetes compared to healthy individuals. The second section reviews the literature pertaining to the neurological and neuropsychological differences in individuals who experience depression compared to healthy individuals. It also considers the interrelationship among depressive symptoms, diabetes, and various domains of neuropsychological functioning including memory, learning, and attention.

Neurological Impact of Diabetes

**Neuroanatomical effects of diabetes.** Research substantiates that diabetes is associated with neuroanatomical differences compared to healthy individuals and that these differences are differentially affected by disease-related factors such as presence of hypoglycemic episodes and age of onset. For example, Perantie et al. (2007) measured brain volumes of youth with Type 1 diabetes and compared them to healthy children as well as analyzed the data in relation to the variables of history of hypoglycemia, hyperglycemia, and age of onset. They found that the group with diabetes compared to the healthy group did not have a significant difference in amount of gray or white matter volume. However, youth with diabetes who had experienced severe hypoglycemia had significantly less gray matter volume in the superior temporal/occipital cortex compared
to youth with diabetes who had not experienced severe hypoglycemic episodes. This brain region has been linked to the episodic memory system. Hyperglycemia exposure was associated with differences in both gray and white matter volumes, smaller gray matter in the posterior cortical areas and smaller white matter volume in the right superior parietal area, areas which are associated with higher-order visuospatial function and episodic memory. Hyperglycemia exposure was also associated with larger gray matter volume in the right middle frontal gyrus suggesting either an abnormal developmental trajectory or compensation for the lower gray matter volume found in the right cuneus and precuneus. Brain activation in this area has been linked to spatial working memory functions. Earlier age of onset was not associated with any differences in gray matter volume but was associated with larger white matter volume near the left precuneus, an area also associated with episodic memory.

A study by Ferguson et al. (2005) compared MRI brain scans of young adults with early onset diabetes to young adults with later onset diabetes to see if structural differences existed which would support an organic contribution to differences in neuropsychological functioning rather than or in addition to psychosocial consequences. In their study, early onset diabetes (EOD) was defined as onset before the age of 7 years. Results showed that mild-to-moderate ventricular atrophy was common and significantly more prevalent in individuals with EOD (61% versus 20% of scans). Small punctate white matter lesions (SPWMLs) in the hippocampus were more frequent in the EOD group although the number of SPWMLs in other brain regions was comparable across groups. Ferguson et al. cautioned against concluding from the evidence of more frequent
SPWMLs in the EOD group that white matter changes are associated with EOD because of the small number of cases included in the analysis (n=26). Early onset diabetics also had 37% greater lateral ventricular volume. The enlarged ventricular volumes suggest either that EOD is detrimental to brain development or that EOD leads to an advanced state of brain ageing relative to chronological age if these regions atrophied rather than failed to develop. The differences in brain structure between EOD and LOD groups offer support that a neuroanatomical component may contribute to the differences in cognitive abilities in these groups, such as the observed differences in nonverbal intelligence and information processing speed.

In order to examine the long-term effects of diabetes on the brain after intellectual development has been reached, Ferguson et al. (2003) examined cognitive function and brain structure in individuals with Type 1 diabetes who were diagnosed before the age of 18 years and were between the ages of 20 and 45 years at the time of the study. High-intensity periventricular white matter lesions, particularly SPWMLs, were common and present in one-third of the scans whereas deep white matter lesions were observed infrequently. This type of lesion signifies an area of increased water content, gliosis, and demyelination within white matter. The presence of background retinopathy was associated with more frequent SPWMLs in the basal ganglia as well as poorer performance on cognitive tests of fluid intelligence, information processing speed, and the ability to maintain attention and concentration. Researchers also found that no measure of severe hypoglycemia was correlated with MRI neuroimaging abnormalities or neuropsychological performance.
A study that compared the regional cerebral blood flow (CBF) using single photon emission tomography (SPECT) in children and adolescents with Type 1 diabetes and healthy youth found significantly lower cerebral perfusion in the left basal ganglia and left inferior frontal regions of the participants with diabetes (Salem et al., 2002). Hypoperfusion was also apparent to a lesser degree in parietal and temporal regions. Salem et al. found differences between diabetics and non-diabetics on perceptual reasoning tasks. In another study, SPECT also revealed that children with diabetes had greater right hemisphere perfusion than left hemisphere perfusion, which is the opposite of healthy children (Tupola et al., 2004). No correlation was found between perfusion patterns and scores on neurocognitive testing in either study. This could be explained by the finding that functional neuro-imaging studies have found activation primarily in the parietal lobes to be associated with perceptual reasoning whereas the studies using SPECT found differences in the frontal and temporal lobes (Salem et al., 2002). Therefore, SPECT cerebral perfusion changes may not currently be able to be directly related to measurable changes in cognitive function given current measurable constructs and instruments.

These studies provide support that neuroanatomical differences exist for individuals with Type 1 diabetes compared to healthy individuals. Specific differences include decreased gray matter volume for individuals who experience hypoglycemia, changes in gray and white matter volumes for individuals who experience hyperglycemia, increased atrophy and SPWMLs linked to EOD, and hypoperfusion in some areas of the brain.
Neurophysiological effects of diabetes. The underlying mechanisms causing brain damage in diabetics are not clear but a variety of findings from human and animal studies reveal specific physiological differences between brains exposed to diabetes and those not exposed to diabetes. One study used magnetic resonance spectroscopy (MRS) to monitor chemical and metabolic changes in the pons, left basal ganglion, and posterior parietal white matter (PPWM) in youth aged 8-19 years old who have poorly controlled Type 1 diabetes (Sarac et al., 2005). This study compared ratios of metabolites, which included N-acetylaspartate (NAA), the most sensitive central nervous system metabolite whose levels reflect neuronal density and viability. Results showed that the group with diabetes had lower NAA to creatine (Cr) and choline (Cho) to Cr ratios in the pons and a lower NAA to Cr ratio in the PPWM compared to healthy controls. These metabolic abnormalities may indicate neuronal loss or functional impairment in individuals with diabetes when the diabetes is poorly controlled.

Another study used electroencephalograms (EEGs) to compare differences in the patterns of brain waves found in children with diabetes and healthy children (Solstesz & Acsadi, 1989). The mean age of participants was 11.2 years and the duration of diabetes was a mean of 5 years. Results showed that children with diabetes had significantly higher rates of abnormalities (i.e. irregular rhythm or spiked waves) than healthy children, 49% compared to 24%. This rate is similar to more recent work by Tupola et al. in which approximately 50% of children with diabetes had abnormal EEGs (2004). The children with diabetes who had abnormal EEGs had earlier onset of diabetes and were more likely to have had previous severe episodes of hypoglycemia but there were no
differences in duration of diabetes or mean HbA1 concentrations. Given that 80% of the diabetics who had experienced severe hypoglycemia had abnormal EEGs, these findings suggest a relationship between hypoglycemia and abnormal EEG patterns.

Using brainstem auditory evoked potentials (BAEPs) and visually evoked potentials (VEPs), Seidl et al. (1996) examined the latency in response of children aged 4 to 18 years old when presented with auditory stimuli and visual stimuli. They found that children who had diabetes for at least two years had prolonged latency response patterns for both types of stimuli. These prolonged latencies were highly correlated with the duration of diabetes. Further, BAEP abnormalities are usually associated with white matter damage. These results are similar to a study using rats in which BAEP and VEP latencies of diabetic rats were initially comparable to those of non-diabetic rats (Biessels et al., 1999). However, 3-4 months after having been induced with diabetes, latencies increased and then continued to gradually increase with duration of diabetes. Axonal conduction velocity was measured in the spinal cord pathways and found to be significantly decreased at six months after the diabetes inoculation. Insulin treatment tended to improve both conduction velocity and evoked potentials but most latencies were not significantly improved compared to untreated diabetic rats. These results show that diabetes is associated with slower CNS response to visual and auditory information.

One region of interest has been the hippocampus (Chabot, Massicotte, Milot, Trudeau, & Gagne, 1997; Trudeau, Gagnon, & Massicotte, 2004; Klein & Waxman, 2003). Studies of rats with induced diabetes have shown that damage to both presynaptic and postsynaptic structures in the hippocampus is associated with hyperglycemia (Klein
& Waxman, 2003). These hippocampal synaptic changes may also be related to neuronal loss because the resulting dysregulated neuronal calcium homeostasis would be expected to contribute to neuronal loss especially given that the neuroprotection of insulin-like growth factor is diminished in diabetics. Further, studies with rats have also shown that impairment in generating long term potentiation in the hippocampus is associated with diabetes (Biessels et al., 1999) and specifically with abnormal glutamate receptors such as those found in individuals with diabetes (Trudeau et al., 2004). Long term potentiation is the increase in synaptic transmission induced by high-frequency stimulation and is an important mechanism of learning and memory, particularly in spatial learning.

Taken together, the findings from these studies support that there are neurophysiological differences in metabolite ratios, brain wave patterns, slowed CNS responses, and possible neuronal loss in individuals with diabetes compared to healthy individuals. Factors that appeared to influence these differences included quality of metabolic control, presence of hypoglycemic episodes, and duration of diabetes.

**Neuropsychological effects of diabetes.** Cognitive functioning of children and adolescents with diabetes has been documented as being in the normal range and comparable to healthy children at the time of diabetes onset and tends to decline in particular domains over a period of years (Kovacs et al., 1992; Northam et al., 1995; Northam et al., 1998; Northam, et al., 2001), suggesting that differences in cognitive functioning between diabetics and non-diabetics cannot be explained by abilities prior to diabetes onset.
One of the earliest studies on cognitive functioning in diabetic adolescents assessed youths who were between 12 and 18 years old and who had a history of at least three years with Type 1 diabetes on a wide range of neuropsychological tests including the Wechsler Intelligence Scales for Children Revised (WISC-R) for participants aged 12 to 15 years old and the Wechsler Adult Intelligence Scale (WAIS) for participants aged 16 to 18 years old (Ryan, Vega, Longstreet, & Drash, 1984). Although the adolescents with diabetes performed in the normal limits on all tests, they performed significantly poorer than matched healthy controls on measures of verbal intelligence, visuomotor coordination, and critical flicker threshold, which is the fastest frequency at which a flickering light is perceived as flickering rather than constant. Adolescents with diabetes also tended to perform worse than healthy adolescents on Trails B which measures processing speed, visuomotor integration, and the executive functioning abilities including attention and set-shifting. Further, diabetic adolescents aged 16-18 years performed more poorly on digit span, a short term memory task, than healthy adolescents. This early study revealed that adolescents with Type 1 diabetes had difficulties compared to healthy adolescents on measures sensitive to brain damage thereby implicating a need for further investigation.

As research with diabetic populations has progressed, different variables have been found to affect the implication of diabetes on neurocognitive functioning. The diabetes-related variables include age of onset, frequency and severity of hypoglycemic episodes, presence of hyperglycemic episodes, and treatment regimens. For example, Ryan et al. (1985) used multiple regression to investigate the relationship between
diabetes-related variables and scores on neuropsychological tests that measured learning and memory, visuospatial processes, attention, and mental and motor speed. It was found that age of onset was predictive of performance on tasks of visual memory, incidental memory, visuoconstructional abilities, visuospatial abilities, vocabulary, symbol digit learning, and processing speed. On the other hand, disease duration was related to attention and short term auditory memory, similarities, spelling, and reading. Both age of onset and disease duration were related to fine motor skills of the non-dominant hand with disease duration being more highly correlated.

Another more recent study reviewed the literature pertaining to the cognitive effects associated with Type 1 diabetes in childhood and identified four key relationships (Desrocher & Rovet, 2004). First, motor and visuospatial deficits were related to early age of onset, second, attention and memory deficits were associated with hypoglycemia, third, verbal and executive functioning deficits were related to hyperglycemia, and fourth, executive functioning varied with puberty.

In order to add to the knowledge gained from cross-sectional and relatively short term longitudinal studies, a study by Schoenle, Schoenle, Molinari, and Largo (2002) followed a group of children with diabetes for over a decade, testing them multiple times until they reached 16 years old. Participants were 64 children with diabetes who were diagnosed prior to the age of ten years old. Researchers tested them at ages 2, 3, 4, 5, 7, 9, and 14 years using the German versions of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the WISC-R, and at 11, 13, and 16 years old using the Adaptives Intelligenz Diagnostikum. They found that overall IQ did not depend on
presence of hypoglycemic episodes, gender, or age of onset. However, for boys who were diagnosed before the age of six years, the higher the HbA1c, the more likely a decline in verbal IQ over time. Boys were also found to have early age of onset and poor metabolic control before the age of 7 years as risk factors for lower performance IQ. Although these results indicate that the course of diabetes in the early years for males may be a risk factor for normal brain development, interpretation of more specific processing deficits is limited in this study because the only independent variables that were analyzed were verbal IQ and performance IQ.

These studies provide evidence that diabetes and diabetes-related factors such as diabetes duration, age of onset, and presence of hypoglycemic episodes are related to deficits in a number of neuropsychological domains. Specifically, visuospatial abilities, motor skills, verbal comprehension abilities, short term memory, and executive functioning appear to be affected. The next section describes the neuropsychological functioning in youth with diabetes in the specific domains of memory and learning, and attention.

**Memory and learning.** Many studies have found an increased difficulty in the domains of memory and learning for individuals with diabetes including adolescents (Kovacs, Ryan, & Obrosky, 1994; Northam et al., 1995, Northam et al., 1998, Northam et al., 2001; Ryan, 1999; Fox, Chen, & Holmes, 2003; Hershey, Craft, Bhargava, & White, 1997; Hershey, Lillie, Sadler, & White, 2003; Manschot et al., 2006; Desrocher & Rovet, 2004; Ryan, Vega, & Drash, 1985; Wolters, Yu, Hagen, & Kail, 1996).
Work by Northam and colleagues (1995; 1998; 2001) examined the neuropsychological functioning including memory and learning in children and adolescents with Type 1 diabetes at the time of diagnosis as well as at 2 years and 6 years after disease onset. Their samples of 124, 123, and 90 youth, respectively were between the ages of 3 and 14 years of age during the first assessment period. During the first assessment, the researchers examined immediate memory for a list of 15 words presented orally using the Rey Auditory Verbal Learning Test (RAVLT), for digits presented orally (Digit Span subtest from the Wechsler Preschool and Primary Scale of Intelligence, Revised and Wechsler Intelligence Scale for Children, Revised), and for spatial location of blocks presented visually (Corsi Block Span). They also assessed long term memory for visual information in a delayed condition of the Rey-Osterrieth Complex Figure Test (CFT) which requires drawing a figure from memory. Learning was measured by the total number of words learned on the Rey Auditory Verbal Learning Test (RAVLT) as well as total number of words recalled after an interference list and total words recognized. Learning of spatial location of visual information was measured by the L’Hermitte Board (LHB). Results showed that children assessed soon after diagnosis performed comparably to healthy children on all memory and learning tasks. When tested again two years later on the RAVLT, CFT, LHB, and Digit Span subtest, differences between the first and second assessments for diabetic children were not significantly different from the differences found in healthy children on measures of immediate or delayed memory. However, children with diabetes had a poorer learning rate on the learning tasks in that they showed less positive change in their scores than healthy
children. Learning of auditory word lists and spatial location was also impaired at two years after diagnosis. At six years after initial diagnosis, children with diabetes did not differ in their performance on any of the immediate memory tasks comprised of memory for stories, designs, word lists, and spatial location. However, at this third assessment, children with diabetes performed significantly worse than healthy children on delayed recall of the Rey design and in overall long term memory when all long term memory task scores were combined. Taken together, these findings support the assertion that diabetic children are normal in terms of neuropsychological functioning in the domains of memory and learning at time of disease onset and that later differences cannot be explained by some pre-morbid vulnerability. Over time, long term memory for visual information becomes worse when compared to changes in time for healthy children. The finding that learning of word lists and spatial location was impaired at two years after diagnosis, but not at six years, could be explained by the differences in measurement sensitivity. That is, at the second assessment, learning was assessed more in depth by including the following additional measures: total words recalled over five trials, total words recalled after interference, number of times a child recalled fewer words than on the previous trial, total score minus words recalled on trial 1 to control for immediate memory, total cards correctly placed over five trials, trials to criterion, number of times a child placed fewer cards correctly than on previous trial, and total cards correctly placed minus score for trial 1 to control for immediate memory. In contrast, the third assessment only included total scores summed over five trials for words learned and total scores summed over four trials for visual cards learned.
Another study by Hershey et al. (1997) examined memory and frontal dysfunction in 38 adolescents and adults with Type 1 diabetes who were diagnosed before the age of 14 years. Participants were between the ages of 15 and 42 and were grouped by presence or absence of experienced severe hypoglycemic episodes. Measures of declarative memory included a paragraph recall task in which the paragraph was presented orally, the California Verbal Learning Test (CVLT), and a checkerboard patterns recall task presented visually. Each of these tests had an immediate and delayed condition. Measures of nondeclarative memory included a picture priming task for memory of visual information, a word-stem priming task for verbal information presented visually, a serial reaction time task for implicit motor memory, and tactile mazes for motor and spatial memory. Results showed that on the story recall task there was an interaction effect of condition, meaning that the pattern of immediate and delayed performance was different for each group. Post hoc analyses revealed that the group of diabetics who experienced hypoglycemic episodes performed significantly poorer than either of the other groups. Diabetics in both hypoglycemic and non-hypoglycemic groups performed worse than healthy controls on tasks requiring the identification of degraded pictures after priming, thus supporting a deficit in visual memory. Further deficits were observed for diabetics who experienced severe hypoglycemic episodes including poorer performance in delayed recall of verbal information. One limitation of this study was that separate analyses for adolescent data and adult data were not conducted and therefore vulnerabilities unique to adolescents could have been masked by aggregate data. Furthermore, age of onset was defined as before the age of 14 years while other literature has supported a difference in
cognitive functioning between early onset before the age of 5 years and late onset after the age of 5 years. Therefore, defining early onset as before the age of 14 years old may limit the detection of some effects.

Wolters et al. (1996) examined short term memory and strategy use with 61 youth with Type 1 diabetes who were between the ages of 9 and 16 years old. The diabetic group was divided into subgroups by age of onset in which the early onset diabetes group (EOD) was defined as having been diagnosed for at least seven years and the group with late onset diabetes (LOD) had been diagnosed for between two and seven years. Parents were asked to rate their child’s general metabolic control on a scale of 1-5. The dependent measure was a pause time memory task in which the participants were told to learn words that appeared one at a time on a computer screen for a given amount of time. The participants could self-pace the interstimulus interval which allowed them to rehearse any or all of the previous words before continuing. Results showed that all groups were in the normal range however disease-related variables were associated with differences in performance. For example, children with EOD used similar rehearsal strategies as healthy children and children with LOD but recalled fewer total words. Also, children who had poor control of their diabetes did not use strategies designed to increase recall as often or as effectively as children who had better control of their diabetes.

Fox et al. (2003) conducted a longitudinal study to examine learning and memory and performance strategies in children with Type 1 diabetes over a four year period. The study included 95 participants who were between the ages of 7 and 16 years old and had been diagnosed for at least 6 months thus ruling out residual insulin as an effect. Verbal
memory and learning was assessed using the RAVLT. Results showed a developmental trend in which memory for words on the first trial of the RAVLT improved over time with no effect of diabetes status or gender. That is, from the first assessment to four years later, all groups increased in the percentage of words they recalled at comparable rates with no differences in pattern due to gender or having diabetes. However, learning as measured by the percentage of words learned on trials two to five of the RAVLT differed depending on both diabetes and gender. Gender differences are described later in this chapter. Multiple regression analysis revealed that gender, socioeconomic status, disease duration, hypoglycemic episodes, age of onset, and average HbA1 combined were not predictive of memory performance. However, gender, duration of disease and age of onset predicted learning performance over time. The best predictor of learning performance over time was disease duration with longest duration related to poorest performance. Given that age of onset was found to be related to the variability in learning performance and that other literature has supported a difference in cognitive functioning between early onset and late onset, grouping all diabetics together was a limitation of this study. That is, participants had an average age of onset of 7.9 years with a standard deviation of approximately 3 years, so some of the sample had EOD and other participants had LOD. A design more sensitive to differences in learning patterns would have differentiated between diabetics diagnosed before or at five years of age versus those diagnosed after five years of age.

Examining verbal memory and its effect on verbal intelligence, Kovacs et al. (1994) tested 57 adolescents with Type 1 diabetes whom they had been following for
eight years. They used the Four-Word Short-Term Memory Test to measure the ability to hold small amounts of verbal information in memory for several seconds while completing interference tasks, the Logical Memory Test to measure the ability to remember a story presented orally, and the Verbal Associative Learning Test to measure learning efficiency of words presented orally. Results showed that after having diabetes for eight years, verbal memory for stories was in the average range while verbal memory for word associations tended to be poorer than for healthy controls. Working memory was mildly impaired. Long term metabolic control, blood glucose level at memory testing, and demographic factors were not related to memory performance. One of the few studies to include a depression-anxiety measure, this study also found that depression-anxiety scores on a nine item clinical interview were not related to memory performance. However, the brevity of the depression measure may have limited its accuracy in measurement of depressive symptoms. The impact of depressive symptoms on cognition will be discussed further in another section of this chapter.

Overall, differences can be seen for children and adolescents with diabetes compared to healthy children and adolescents in a variety of memory and learning conditions ranging from slower verbal learning growth rate two years after diagnosis to poorer long term memory six years after diagnosis. Use of strategies to aid short term word memory was not as effective for children with diabetes as for healthy children and may explain the poorer performance by children with diabetes for eight years on a word association learning task. Disease duration was the best predictor of verbal learning
performance with longest duration related to poorest performance. Hypoglycemia was shown to impact verbal memory in both immediate and delayed conditions.

**Attention.** Another domain which has been studied in terms of the effects of Type 1 diabetes on learning and cognition is that of attentional processes (Anderson, Anderson, & Anderson, 2006; Brands, Biessels, de Haan, Kappelle, & Kessels, 2005; Bjorgaas, Gimse, Vik, & Sand, 1997; Hershey et al., 1997; Manschot et al., 2006; Northam et al., 2001; Northam et al., 1995; Desrocher & Rovet, 2004). Overall, there are mixed findings which may be due to differences in measurement instruments and sample characteristics.

As previously mentioned, Northam et al. (1995; 1998; 2001) examined the effect of Type 1 diabetes on children and adolescents over a period of six years. At time of diabetes diagnosis, they compared performance of youth with diabetes to healthy control subjects on tasks of attention that included the Digit Span forward subtest from the WISC-IV and the Corsi Block Span test, which measure the ability to attend to and register sequentially auditory information and visual information, respectively. Performance on these two tasks was comparable for diabetic and non-diabetic adolescents. Six years later, diabetic adolescents were compared to healthy adolescents using Digit Span forward, Code Transmission in which the participant identifies a target stimulus from stimuli presented via audiotape every two seconds for 12 minutes, and Sky Search in which participants identify a target visual stimulus against background distraction. These latter tasks measure sustained attention for auditory information and selective attention for visual information, respectively. Children with diabetes performed significantly poorer in accuracy on Code Transmission than healthy controls with a
particular deficit for children with onset of diabetes before the age of four years old. The diabetic group also had a significantly poorer overall attention index compared to healthy children when all three attention measures were combined, although when Digit Span performance was analyzed separately, the diabetic group performed comparably to non-diabetic group both at time of diagnosis and six years later. These findings suggest that sustained attention for auditory stimuli and overall attention decline over time in diabetics. Alternatively, these results could be explained as an ongoing attentional deficit that was not detected previously because earlier studies used only measures of attention that were shorter in length and not sensitive to the differences in sustained attention performance (Digit Span and Coding subtests of WISC-R).

Hershey et al. (1997) used the Stroop Color-Word Interference task to measure inhibition of automatic responses and a serial addition task to measure attention and mental control. Participants were between the ages of 15 and 42 years old and had been diagnosed with Type 1 diabetes before they were 14 years of age. Performance in the three Stroop conditions was assessed: word reading of names of colors, naming of color blocks, and naming of the ink color that color words were printed in that did not correspond to the word. They also used a serial addition task in which numbers were presented orally and the participants had to produce a sum at the end of the number string. Whereas diabetics overall did not perform more poorly than healthy controls on either the Stroop task or the serial addition task, diabetics who experienced severe hypoglycemic episodes demonstrated a slowed performance on the Stroop Color-Word Interference task compared to healthy children. This may be explained by a decline in
attention or by slowed processing speed. However, as previously stated, this study was limited in regards to the sensitivity of analysis of adolescents’ neuropsychological functioning given that the EOD cutoff was 14 years of age. Although there is evidence for differences in performance on attention tasks for diabetics compared to healthy individuals, factors such as age of onset and presence of hypoglycemic episodes may contribute to these differences and are presented in the next section of this chapter.

**Factors related to the neuropsychological effects of diabetes.**

*Age of onset and disease duration.* Other factors that have been considered in relation to the scores on cognitive testing were metabolic control and age of disease onset (Northam et al., 2001). In general, Northam et al. found that children with diabetes performed more poorly than healthy children on measures of intelligence, attention, processing speed, long-term memory, and executive skills. When age of onset was defined as early onset before the age of four years and late onset after the age of four years, the areas differentially affected by diabetes were attention, processing speed, and executive skills in which the early onset group was more impaired. Specific to attention, children with diabetes onset before the age of four years identified fewer correct targets on Code Transmission.

Another earlier study differentiated between age of onset effects and disease duration effects (Ryan et al., 1985). Ryan et al. defined early onset of disease as onset before the age of five and later onset as occurring at or after five years of age. Their sample of 125 adolescents who were between the ages of 10 and 19 years had had diabetes for at least three years at the time of the study and had no psychiatric disorders.
They used a symbol-digit learning test and the short form of Ryan’s Verbal Learning Test to measure associative learning, a modified version of the Visual Reproduction from the Wechsler Memory Scale (WMS) to measure immediate and delayed visual memory, and recall of symbols from the digit-symbol task to measure incidental memory. They also measured attention and short term auditory memory using the Digit Span subtest of the Wechsler scales. Results showed that youth with early onset diabetes performed significantly poorer than those with later onset diabetes and the healthy children on tasks of visual memory in both immediate and delayed conditions. They also performed more poorly on the incidental memory task than those with later onset diabetes. In terms of attention, the early onset diabetes group performed significantly poorer on the Digit Span subtest than the healthy children, however there was no significant difference between the early and the late onset diabetes groups. Using multiple regression to elucidate the relationship between diabetes-related variables and scores on the neuropsychological tests, it was found that age of onset was predictive of performance on tasks of immediate and delayed visual memory as well as incidental memory whereas disease duration was related to performance on tasks of attention and short term auditory memory.

A study by Bjorgaas et al. (1997) examined psychomotor efficiency, attention, and memory in diabetic children who had experienced severe hypoglycemic episodes and those who had not. Psychomotor efficiency was assessed using Trails A and B, a verbal fluency task, and the Digit Symbol subtest of the WISC-R. Attention and impulsivity were measured by the Children’s Checking Task Test in which the child listens to numbers being presented and circles a number on a page when that number presented
auditorily does not match the one presented visually. Memory was assessed by the RAVLT and the visual reproduction subtests of the Wechsler Memory Scale-Revised (WMS-R). Participants were 28 children with Type 1 diabetes, ages 8 to 16 years old that were grouped by presence or absence of severe hypoglycemic episodes. Within the group that had experienced severe hypoglycemic episodes there were five children with EOD diagnosed before five years of age and ten children with LOD. Although the group of children with diabetes in general did not differ significantly from healthy children on any of the cognitive measures, differences existed within the diabetic group. They found that psychomotor efficiency was poorer in participants who experienced severe hypoglycemic episodes and EOD compared to those with LOD. Attention was also poorer for children with EOD who experienced severe hypoglycemic episodes compared to those with LOD and to those without severe hypoglycemic episodes. Performance on memory tasks was not found to differ within the diabetic group. One limitation in interpreting these results stems from EOD being highly correlated with disease duration for the children with diabetes who experienced severe hypoglycemic episodes. For this population, it is impossible to discern whether differences in performance were due to the age at which diabetes developed or the long term effects of the disease. Also, performance on some of the psychomotor efficiency tests such as Digit Symbol may have been affected by attention and therefore attentional deficits may underlie or contribute to the assertion that there are psychomotor deficits. These studies show that age of onset and disease duration may influence the relationship between diabetes and neuropsychological functioning in the areas of processing speed, attention, executive functioning, immediate and delayed
visual memory, and psychomotor efficiency. The next section describes how gender is also a factor in determining the neuropsychological effects of diabetes.

**Gender differences.** As mentioned previously, Fox et al. (2003) examined memory and learning in children with diabetes using the Rey Auditory Verbal Learning Test (RAVLT). They differentiated between performance patterns by diabetes status as well as gender. They found that healthy girls had significantly higher learning scores than any other group at the first assessment while the other groups showed non-significant differences. Four years later, the only significant difference was between healthy girls’ learning performance and diabetic boys’ learning performance. Boys with diabetes did not improve in word list learning over the four years while the other three groups did. Effects of serial position of words in the word list on learning were also examined. Primacy position was defined as the first five words on the list, medial position was defined as the middle five words, and recency position was defined as the last five words. At the first assessment, healthy girls learned more words in the primacy position than all other groups, but at the second assessment healthy girls only learned significantly more words in the primacy position than boys with diabetes. That is, the primacy effect increased over time for girls with diabetes while it actually declined over time for boys with diabetes. Words in medial and recency positions were learned more easily at the second assessment than the initial assessment for all groups revealing no gender differences in medial and recency effects. Overall, these results suggest that among children with diabetes, boys are particularly vulnerable as they do not make the same developmental gains during adolescence that healthy children and girls with diabetes
make in verbal learning over time. Thus, diabetes appears to impact learning in boys more significantly than in girls.

**Effects of hypoglycemia.** Severe cases of hypoglycemia have been linked to severe impairment in memory. For example, Chalmers et al. (1991) used magnetic resonance imaging (MRI) to determine the relationship between brain abnormalities following a severe hypoglycemic episode and subsequent cognitive functioning. A 34-year-old man with Type 1 diabetes went into hypoglycemic coma after which he experienced marked impairment in immediate recall and short term memory with a retention span of one to two minutes and retrograde amnesia of several weeks. Ten months later his immediate memory for stories had improved but his long term memory for the stories in the delay condition of 30 minutes was non-existent. Also, a deficit in verbal learning of paired associate words presented orally persisted at the ten month assessment. MRI showed a lesion in the hippocampal area after the hypoglycemic episode and again six months later. These results indicate that temporal lobe damage can occur secondary to severe hypoglycemic episodes that lead to coma and that this damage is linked to persistent memory impairment.

A study by Hershey et al. (2003) examined hypoglycemia using frequency of episodes as a variable related to performance on different types of memory tasks and attention. Their sample consisted of 51 youth with Type 1 diabetes who were between the ages of 6 and 16 years and excluded youth with other major illnesses including depression. Spatial memory was measured by a spatial delayed response task in which participants had to remember the location of dots on a computer screen after a distractor
task. Verbal memory was measured using a paragraph recall task in which the paragraph was presented orally and using the word list learning task from the CVLT-Children’s version. Object memory was measured using the Delayed Match to Sample, List Presentation in which participants had to recognize abstract patterns presented on a computer screen after completing different types of distractor tasks. Attention was measured using a sustained and selective attention task in which participants watched a computer screen for 8 minutes responding to a target stimulus. The researchers used parent report to determine the frequency of hypoglycemic episodes and assessed three levels on this variable: 0 episodes, 1-2 episodes, 3+ episodes. They found that in children with Type 1 diabetes, the frequency of hypoglycemic episodes accounted for a significant portion of the variance on long delay spatial memory tasks but not on short term memory, object memory, verbal memory, or attention, which confirms the findings of impaired visual spatial memory in previous research (Ryan et al., 1985). Although Hershey’s study (2003) was sensitive to differences in cognitive functioning related to frequency of hypoglycemic episodes, caution must be used in concluding the true effects because the number of hypoglycemic episodes was confounded with age of onset. That is, children who had three or more severe hypoglycemic episodes were more likely to have developed diabetes before the age of five years than children in the other two groups. This study by Hershey et al. (2003) illustrates the difficulty in teasing apart the effects of age of onset from number of hypoglycemic episodes experienced. A similar study (Hershey et al. 1997) found that in their sample, age of onset was not related to history of hypoglycemia. Although they found that their sample of adolescents and adults that had
experienced hypoglycemic episodes were slower on the Stroop task, it is unknown whether these results can be extended downward to children and adolescents.

One study compared children with diabetes who experienced hypoglycemic seizures and those who did not on neuropsychological measures seven years after diagnosis (Rovet & Ehrlich, 1999). A sample of 16 children with a mean age of 12 years was examined seven years after diagnosis. Also used were data gathered from previous data sets regarding this sample’s neuropsychological functioning at one and three years after diagnosis (Rovet, Ehrlich, & Czuchta, 1990). In the last assessment period, attention was measured using the Continuous Performance Test (CPT) and matching familiar figures test (MFFT). Memory was assessed using the WPPSI sentences and the Digit Span subtest from the WISC-R. It was found that memory declined over time primarily between the third and seventh year. At the seventh year assessment, the group with EOD performed significantly poorer on the CPT in terms of total errors. However, when grouped by seizure history, the group with seizures performed significantly poorer on both attention tasks as characterized by more impulsive responses as well as lower scores on visual memory and verbal learning tasks. They also performed more poorly on the executive processing task as measured by the number of perseverative errors made on the Wisconsin Card Sorting Test (WCST). These findings indicate that hypoglycemic seizures may negatively impact cognitive functioning. However, one limitation to this study was that the researchers did not analyze the data in terms of gender. The EOD and LOD non-seizure groups were comprised of 50% and 25% males, respectively, whereas the EOD and LOD seizure groups had 83% and 67% males, respectively. As mentioned
in the previous section of this chapter, there is evidence to suggest that males are more vulnerable to cognitive deficits than females, and therefore, gender differences may underlie or contribute to the apparent hypoglycemic seizure effects.

In addition to the previous studies, a multi-site study by the Diabetes Control and Complications Trial (DCCT, 2007) research group enrolled 1,441 individuals with Type 1 diabetes between the ages of 13 and 39 years and followed them for 18 years to determine the effects of intensive treatment (three or more insulin injections or external pump infusions per day) compared to conventional treatment (one to two insulin injections per day). The purpose of the study was to determine if treatment that increases risk of hypoglycemic episodes would negatively affect neuropsychological functioning. Tests administered were WAIS subtests for participants ages 16 years and older, WISC-R subtests for children younger than 16 years (Similarities, Digit Span, Digit Symbol, Block Design, and Object Assembly), Halstead-Reitan Neuropsychological Test Battery subtests (Category, Tactual Performance, Trail Making, and Finger Tapping), Wechsler Memory Scale subtests (Logical Memory and Visual Reproduction), the Digit Vigilance Test, the Grooved Pegboard Test, the Verbal Fluency Test, the Four-Word Short-Term Memory test, the Symbol-Digit Learning Test, and the Embedded Figures Test. Analysis of the data collected from participants at baseline and then at years 2, 5, 7, and 9 of the study on four cognitive factors (spatial ability, processing speed, memory, and verbal ability) emerged showing that neither repeated episodes of hypoglycemia nor treatment type was associated with cognitive decline on these four domains (Austin & Deary, 1999). At the conclusion of the study, consistent findings of nonsignificant differences
were found in all eight subdomains (problem solving, learning, immediate memory, delayed recall, spatial information, attention, psychomotor and mental efficiency, and motor speed; DCCT, 2007). These findings indicate that neither intensive therapy nor episodes of severe hypoglycemia are related to cognitive decline in adults. However, because the adolescents’ data were not analyzed separately, it is not possible to conclude that these neuropsychological domains were not negatively affected in the adolescents. In fact, given past findings of hypoglycemic effects in children and adolescents, these findings support the idea that children and adolescents have increased vulnerability of cognitive impairment compared to adults with Type 1 diabetes. Also, very strong practice effects are associated with repeated reassessment and could have reduced the sensitivity of these tests in detecting subtle learning and memory impairments (Ryan, 1999).

To summarize these findings, hypoglycemic episodes have been shown to contribute to the deficits of children and adolescents in the areas of spatial memory, visual memory, verbal learning, attention, and memory decline over time. A recent review of the aforementioned and other studies also found that hypoglycemia was associated with cognitive deficits in the domains of memory and attention, in addition to visuospatial skills, motor skills, and executive functioning (Bade-White & Obrzut, 2009).

**Neurological Impact of Depression**

**Neuroanatomical effects of depression.** Depressive disorders have been associated with brain abnormalities although the majority of studies have been conducted in adults. For example, reduced hippocampal volumes have been found among depressed adults (Bremner, et al., 2000; Frodl et al., 2002; Sheline, Sanghavi, Mintun, & Gado,
as well as abnormal patterns of brain activity in the anterior cingulate cortex (Alexopoulos, Gunning-Dixon, Latoussakis, Kanellopoulos, & Murphy, 2008; Brody, Barsom, Bota, & Saxena; 2001). Due to the maturation of the brain that happens during adolescence, which includes pruning of gray matter and proliferation of white matter, studies with adults have limited generalizability to depressed adolescents.

One study that investigated neuroanatomical differences in children and adolescents with and without unipolar depression focused on medial temporal lobe structures (Caetano et al., 2007). Their sample consisted of 19 depressed children and 24 healthy children between the ages of 8 and 17 years. Participants underwent a magnetic resonance imaging (MRI) scan of the entire brain with regions of interest in the hippocampus and amygdala. Total brain volume was used as a covariate in the statistical analyses. Results showed that the depressed participants had significantly smaller left hippocampal gray matter volumes compared to the healthy participants. Non-medicated depressed participants showed a trend towards smaller left hippocampal volumes compared to medicated and healthy participants. There were no statistically significant differences in mean volumes for the left or right amygdala.

Another study yielded similar results when it examined hippocampal and amygdala volumes in a slightly larger sample with a wider range of ages (MacMaster et al., 2008). Their sample consisted of 32 depressed participants and 35 healthy participants between the ages of 8 and 21 years. The depressed participants were non-medicated and had at least one first-degree relative who was also depressed. Results from the MRI scans revealed that both left and right hippocampal volumes were significantly
smaller for the depressed participants compared to the healthy participants. Neither left nor right amygdala volumes were significantly different between groups.

In contrast to the above studies, Rosso et al. (2005) found significant reductions of left and right amygdala volumes but not in hippocampal volumes. Their sample consisted of 20 children and adolescents with recent onset of major depressive disorder and 24 healthy controls. Sixteen of the depressed participants had one or more first-degree relatives with depression. All participants were non-medicated for at least three months prior to participation in the study. The difference in amygdala volumes between groups was approximately 12% and was not related to group differences in age or whole brain volume. The researchers hypothesized that the finding that depressed children did not have altered hippocampal volumes could be due to their relatively short duration of depression. They also stated that their findings regarding amygdala volumes could differ from other studies due to differences in region of interest (ROI) parameters used to separate the hippocampus from the amygdala and possible gender effects given that their sample was predominantly female.

Another study examined white matter hyperintensities (WMH) in children admitted to hospital inpatient treatment units (Lyoo, Lee, Jung, Noam, & Renshaw, 2002). The Diagnostic Interview Schedule for Children (DISC) was used to identify psychiatric disorders. Ninety-four youth with unipolar depression in the age range of 7 to 17 years old and 83 youth without any severe levels of diagnosis on the DISC in the age range of 6 to 15 years participated in the study. After completing brain MRI scans, results showed that the group with depression was significantly more likely to have severe levels
of WMH than the control group and that the frontal lobes were the predominant locations of these WMH.

Other studies supported differences in the frontal lobes of depressed adolescents (Steingard et al., 2002) and in prefrontal cortex volume of children and adolescents with major depression (Nolan et al., 2002). Steingard et al. found that significantly smaller frontal white matter volumes and significantly larger frontal gray matter volumes were present in a sample of 19 depressed adolescents with a mean age of 15.4 years when compared to 38 healthy adolescents with a mean age of 14.6 years after controlling for age and whole brain volume. Depressed adolescents had been non-medicated for at least three months prior to the study.

Nolan et al. investigated prefrontal cortex volume and included family history of major depression as a variable (2002). Their sample consisted of 22 drug-naïve youth with major depressive disorder (MDD) between the ages of 9 and 17 years and 22 case-matched healthy participants. Participants with MDD who also had a first-degree relative with MDD (familial MDD) did not differ from healthy controls in terms of either left or right prefrontal cortical volumes. However, participants with no family history of MDD (nonfamilial MDD) had significantly larger left-sided prefrontal cortical volumes when compared to participants with familial MDD and controls. Further, significant inverse correlations were found between number of depressive symptoms and total left-sided prefrontal cortical volume and left-sided prefrontal gray matter for participants with familial MDD. These results support the notion that depression may have familial and nonfamilial subtypes that are related to different brain abnormalities. These findings that
individuals with depression have differences compared to healthy individuals in hippocampal volumes, amygdala volumes, frontal lobe volumes, and prevalence of WMH in the frontal lobe support a neuroanatomical basis for the neuropsychological differences observed in individuals with depression that are described in the next section.

**Neuropsychological effects of depression.** It has been well documented that adults with depression have deficits in some neuropsychological domains compared to healthy controls. In fact, symptoms for major depressive disorder include difficulty concentrating and difficulty remembering details (NIMH, 2008). Research has suggested similar patterns in children and will be described in the following subsections.

**Memory performance in depressed individuals.** Memory is one domain which has been associated with deficit in depressed individuals (Biringer et al., 2007; Freedman, 1994; Henry & Crawford, 2005; Porter et al., 2003; Gunther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004; Zakzanis et al., 1998). One study using adolescents examined cognitive functioning including memory in children between the ages of 8 and 17 years who were depressed (Gunther et al., 2004). The study had 31 non-medicated participants with depressive disorder, 33 healthy controls, and 34 non-medicated children with anxiety disorder. It was found that the depressed children performed significantly poorer than both healthy controls and the children with anxiety disorders on the interference, long delay recall, and recognition memory tasks on the RAVLT. These tasks require individuals to recall words that have been presented orally after presentation of an interference list, after a 30 minute delay, and to recognize words, respectively. Because the depressed children did not differ in their ability to immediately recall the words
compared to healthy children, their deficit in memory was not thought to be due to an encoding problem but instead to retention or retrieval problems. The authors explain that these results may be due to dysregulation in the hypothalamus-pituitary-adrenal axis, which has previously been linked to depressive disorders in both adolescents and adults (Brooks-Gunn, Auth, Petersen, & Compas, 2001) and leads to abnormal levels of cortisol secretion. Abnormal levels of cortisol secretion have been previously linked to decreased memory functioning (Charmandari et al., 2003).

Another study that used a similar verbal learning paradigm for children, the Children’s Auditory Verbal Learning Test, had a sample that consisted of 21 non-medicated depressed children and 21 non-depressed controls between 9 and 12 years of age (Lauer et al., 1994). They had two subgroups of depressed children that were classified as high depressed and low depressed based on Children’s Depression Inventory (CDI) scores where 14-19 was low depressed and 20-29 depressed. They found that high depressed children performed significantly poorer on immediate recall than low depressed and non-depressed children but not on delayed recall. This discrepancy between findings across the two studies is likely due to methodological differences such as a narrower age range (9-12 years vs. 8-17 years) and differences in severity of depression as Gunther et al.’s study (2004) had a mean CDI score of 13.3 for the group with diagnosed depression.

Gunther et al.’s (2004) findings are similar to research with adults that has linked depressive symptoms to declines in short delayed free recall, short delayed cued recall, long delayed cued recall of list words, and to a lesser extent long delayed free recall on
the CVLT (Biringer et al., 2007; Henry & Crawford, 2005). In the study by Biringer et al. (2007), 30 adults with major depressive disorder (MDD) between the ages of 20 and 50 years were tested and then re-tested two years later when they were partially or fully recovered from MDD. Measures included the CVLT, Paced Auditory Serial Addition Task (PASAT), the Digit Span subtest of the WAIS-R, and the Rey Complex Figure Test (RCFT). At follow up, performance on the above tasks was significantly improved with the exception of the RCFT. The improvement in depression explained 12% of the variance in increasing verbal memory. However, improvement in depressive symptomatology from baseline to follow-up was not correlated with changes in attention or visual memory function.

Earlier studies that used the Arithmetic, Digit Span, and Coding subtests of the WISC-R as measures found deficits in depressed children’s short term and working memory compared to other cognitive domains (Livingston, Stark, Haak, & Jennings, 1996; Kaslow, Rehm, & Siegel, 1984; McGee, Anderson, Williams, & Silva, 1986). Livingston et al. (1996) assessed the neuropsychological functioning of a sample of 17 depressed children between the ages of 9 and 14 years of age in which treatment status was not reported. Participants’ scores on the subtests of the WISC-R and subtests from the Halstead-Reitan Neuropsychological Battery for Children revealed a profile pattern in which depressed children’s lowest performance scores were on the Freedom from Distractibility factor, tactual performance test time scores, and auditory processing tasks. These results are in accordance with an earlier finding (Kaslow et al., 1984) that number of depressive symptoms as measured by the CDI was significantly negatively correlated
with performance on the Block Design, Coding, and Digit Span subtests from the WISC-R, which are subtests that also require attentional resources and tactile performance, found for children not in psychotherapy nor taking psychotropic medication. Similarly, McGee et al. (1986) found that in a sample of eleven-year-olds, depressive symptoms as measured by the Diagnostic Interview Schedule for Children (DISC-C) were significantly negatively correlated with performance on the Arithmetic and Block Design subtests, which require memory, attention, auditory processing, and tactile performance.

Spatial memory and visual memory have also been found to be detrimentally affected by depression. For example, Matthews, Coghill, and Rhodes (2008) examined spatial and visual memory performance in a sample of 12-16 year-old, non-medicated, depressed females. Compared to a healthy control group, the depressed girls made more errors and demonstrated poorer use of strategy on a spatial working memory task in which mnemonic strategies were used to search for spatial stimuli. The depressed girls scored significantly lower than the healthy girls on a pattern recognition task and on a visual recognition task. Additionally, the depressed girls made significantly more errors on a paired associate word learning task. These results suggest that for girls, depression is correlated with lower scores on spatial memory and visual memory tasks.

Although to this author’s knowledge spatial memory has not been studied with depressed boys, research with adults suggests that depression has a negative impact which could be similar for younger populations. A sample of 16 depressed adults performed significantly more poorly than healthy controls on a delayed alternation task, which involved remembering where objects were placed, but not on the object alternation
without delay task (Freedman, 1994). They also did poorer on tactile learning of the placement of objects. Another study found that a sample of 44 depressed men and women who were not on medication performed significantly poorer than healthy controls on tasks of pattern and spatial recognition and spatial working memory from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Porter et al., 2003). Thus, these results indicate that spatial memory was impaired in depressed individuals compared to non-depressed individuals.

Adult research also offers a hypothesis for the impact of depression on memory relative to all neuropsychological domains (Zakzanis et al., 1998). In their review of 22 adult studies, Zakzanis et al. found that for depressed adults, depression had the largest effect on declarative episodic memory (d=−1.93 for RAVLT list A trial 5). It also had an effect size above the median on tests of verbal fluency and tests of attention. The fact that effect size was higher for memory than for attention supports the assertion that the observed memory deficit in depressed adults may not be secondary to an attention deficit.

Overall, children and adolescents with depression have been shown to experience deficits in auditory working memory, long delayed recall and recognition of word lists, and spatial and visual memory. Severity of depression in terms of number of depressive symptoms endorsed was linked to increased difficulties in immediate recall of word lists.

Attention and inhibition in depressed individuals. Literature has shown varied results in regards to attention performance of depressed individuals. Findings vary depending on the type of attention being measured and how well the measure partials out the effects of memory. For example, while performance on tests measuring basic
attention, such as the Digit Span and Letter Number Sequence subtests of the Wechsler scales, has not been found to be decreased, as indicated by a meta-analysis of studies (Veiel, 1997), more sensitive measures have indicated a deficit in the ability to switch attention as well as to inhibit attention to stimuli, which results in increased distractibility (Cataldo, Nobile, Lorusso, Battaglia, & Molteni, 2005; Killgore, Gruber, & Yurgelun-Todd, 2007; Kyte, Goodyer, & Sahakian, 2005; Lepisto et al., 2004; Porter et al., 2003; Wilkinson & Goodyer, 2006; Zakzanis et al., 1998).

For example, a study by Lepisto et al. (2004) focused on auditory distractibility. They had their sample of ten non-medicated, depressed children and ten healthy children between the 10 and 12 years of age watch soundless videos and ignore sounds that were intermittently presented. Recorded event-related potentials (ERPs) showed that children with depression had shorter latencies in discriminating between novel and repetitive sounds and quicker involuntary attention switching towards salient stimuli and stimulus changes. These results indicate that children with depression have enhanced sensory sensitivity and attentional distractibility compared to healthy children.

One study that differentiated between the ability to sustain attention, ability to switch attention, and ability to selectively attend, examined performance accuracy as well as latency (Wilkinson & Goodyer, 2006). Sustained attention was measured by a task during which participants listened to ten short audiotape sequences with irregularly-spaced tones that they had to count in their head. After each sequence, participants reported the number of tones that they counted, and their score on the task was the number of sequences for which they gave the correct answer. Tasks measuring ability to
switch attention included counting the number of creatures on a path while switching the
direction of counting upon reaching “up” or “down” arrows and reading the numbers “1”
and “2” from a number page while saying aloud the opposite number. Selective attention
was assessed by two tasks. The first task required participants to circle pairs of identical
starships that were in an array of identical and non-identical pairs of starships. The
second task required participants to scan a map and circle target symbols. Wilkinson and
Goodyer found that depressed youth between 11 and 17 years of age who were not taking
medication were significantly slower than healthy participants on tasks of attention
switching and tended to be less accurate. Regarding performance on tasks of selective
attention, depressed youth who were on medication tended to be slower than healthy
controls; however, depressed and non-depressed youth performed comparably in terms of
accuracy. Sustained attention was measured by a relatively short task (6 minutes) which
may account for the lack of group effect on latency. However, when comparing accuracy
on this task, depressed youth on medication performed significantly poorer than healthy
controls.

In another study, Cataldo et al. (2005) used a vigil continuous performance test
that lasted 14 minutes. Results revealed that depressed adolescents were more
inconsistent in their reaction times compared to healthy adolescents, tended to make more
omission errors, and displayed slower reaction times. This study used a sample of 21
patients with depression versus 21 healthy controls between 9 and 17 years of age. These
findings indicate that depressed children and adolescents had difficulty in sustaining
attention that was not due to increased impulsivity.
Taken together, the results from these two previous studies indicate that depressed youth have difficulty both sustaining attention and switching attentional resources. Further, the difficulty with switching attention remained significant when processing speed was controlled for. Although decreases in the ability to sustain attention may have been due to side effects of medication in the study by Wilkinson and Goodyer (2006), the study by Cataldo et al. (2005) showed that non-medicated depressed adolescents had difficulties in sustaining attention. Furthermore, a study of non-medicated depressed adults found a deficit in sustained attention (Porter et al., 2003).

Favre et al. (2009) investigated attention and executive functioning in children and adolescents with major depressive disorder using a sample of 39 participants between the ages of 8 and 17 years with MDD and 24 healthy controls. The participants with MDD were recruited from an outpatient clinic of a medical center and were non-medicated for at least two weeks prior to testing. Attention and executive functioning were measured by performance on the Wisconsin Card Sorting Task (WCST), the Controlled Oral Word Association Test (COWAT), the Stroop Color Word Test, the Trail Making Test (TMT), and the Freedom from Distractibility Index of the Wechsler Intelligence Scale for Children, Third Edition (WISC-III). Independent t-tests comparing the experimental and control groups revealed no significant differences in performance on any of the measures. However, qualitative differences in performance on the switching condition of the TMT and on the COWAT suggest that subtle differences exist. The researchers performed a post-hoc power analyses to determine that they would have needed between 4,000 and 43,000 subjects for adequate power to detect differences.
between groups. Given the contrast between these findings and parallel research with adults, this study supports the need for future studies to be conducted to elucidate the effects of MDD on neurocognitive functioning in adolescents.

Kyte et al. (2005) used a paradigm similar to the WCST to measure attention switching and sustaining abilities in 30 adolescents who experienced a first episode of depression in the past year and 49 healthy controls with a mean of 15.25 years of age. Three participants were on antidepressant medication and five had a past history of antidepressant medication. These authors found that depressed adolescents performed comparably to healthy controls not only in sustaining attention but also in attention shifting when neutral stimuli were presented. These contradictory findings could be due to differences in the types of measurement and differences between depressed samples. In addition, Kyte et al. also employed in their study a condition of emotionally charged stimuli. They found that for depressed adolescents, target valence affected accuracy; depressed children made more errors for happy targets than sad targets. Furthermore, they found that healthy children deliberated more in their decision-making than depressed children. Taken together, these findings indicate that depressed children are more impulsive as well as selectively more attentive to stimuli with a negative valence.

Cataldo et al. (2005) also found support for impaired inhibition being associated with depression in adolescents. Cataldo et al. used the Stroop test to measure attention/inhibition in the sample previously mentioned and found that for depressed adolescents, the difference in performance time between the color naming and mismatched word-and-color conditions was significantly greater than the difference for
non-depressed adolescents. This finding signifies a difficulty with counteracting interference and inhibiting irrelevant information.

In terms of explaining the mechanism that underlies this deficit in inhibition, research with adults has tested two possible theories (Lemelin, Baruch, Vincent, Everett, & Vincent, 1997). Lemelin et al. proposed that impaired performance on the interference condition of the Stroop test is due to either a decreased total amount of processing resources leading to poor performance on tasks that require more resource than is available, or a disturbance in the allocation of processing resources when a task requires inhibiting of distractors. In order to assess this theory they conducted a study in which 33 non-medicated, depressed adults and 30 healthy adults, ages 18 to 65 years, completed the three conditions of the Stroop test as well as a fourth condition in which the page contained nonconflictual words such as “Table” printed in red. Similar to the interference condition of the Stroop, participants had to say the color of the word and not read the word. This task was considered to be less resource demanding than the color word distractors of the traditional interference condition because it did not involve the resolution of a conflict. If the depressed group’s performance on the nonconflictual distractor interference condition and traditional interference condition was impaired, it was likely due to a distractor inhibition disturbance, whereas if performance on the nonconflictual distractor interference condition remained intact then difficulty on the traditional interference condition was likely due to a general reduction of processing resources that is more salient on tasks requiring a high level of processing resources. The results showed that the depressed group performed significantly poorer than the control
group on the traditional interference task but not on the nonconflictual distractor interference task. Therefore, the hypothesis that attention and inhibition difficulties are due to a distractor inhibition disturbance was supported.

Attentional problems and ability to inhibit responses may also be affected in individuals with depression who are on medication. Langenecker et al. (2005) found that depressed women on antidepressant medication gave significantly fewer correct responses than non-depressed women on the difficult condition of a Go/No-Go inhibition task. However, Cataldo et al. (2005) found contradictory results for depressed adolescents on a similar Walk-Don’t Walk-test, but it is unclear whether this difference can be attributed to the differences in tasks. In the Walk-Don’t Walk-test, depressed patients can compensate for their inattention with slow reaction times which would allow them enough time to listen to the stimulus and control their motor response.

In terms of regions of the brain that are activated during tasks requiring inhibition, Killgore et al. (2007) examined the correlation between severity of depressive symptoms and lateralization of brain activations in the superior, middle, and inferior frontal gyri, anterior cingulate gyrus, and the left and right amygdala during cognitive tasks. They used the Stroop task, which has been shown to activate the anterior cingulate gyrus and prefrontal cortex, and found that scores on the Beck Depression Inventory (BDI) were positively correlated with increased right lateralized activity during the color naming task. During the Stroop interference task, which is the more challenging of the tasks, the opposite pattern of lateralization was found in which BDI scores were negatively correlated with increased right lateralized activity thereby suggesting that higher
depression scores were associated with increased left lateralization of activity. These results suggest that depressed individuals have reduced activation in the left frontal lobe during baseline, and when tasks are cognitively demanding, the left prefrontal cortex and anterior cingulate gyrus compensate by recruiting more resources in order to sustain performance thereby showing more activation than the right frontal lobe. In addition, these results are relevant to the present study because the participants had non-clinical BDI scores similar to those in the present study.

Lastly, Gunther et al. (2004) examined cognitive functioning in children 8-17 years of age who were depressed, including 31 non-medicated participants with depressive disorder, 34 non-medicated children with anxiety disorder and 33 healthy controls. They used a simple reaction time task, an optic and acoustic discrimination task, a Go/No Go paradigm task, and a sustained attention task to measure different components of attention. Contradictory to previously mentioned findings, results showed that depressed children performed with comparable reaction time, number of misses, and number of false alarms, similar to healthy children on tasks of alertness, sustained attention, divided attention, and inhibition. This discrepancy could be due to differences between samples in severity of depressive symptoms and other methodological differences such as instrumentation.

In summary, depressed individuals compared to healthy individuals have been found to have decreased ability to inhibit distractors or increased attentional distractibility, slower responses during sustained, selective, and switching attention tasks, and less accuracy during sustained and switching attention tasks.
Effect of Depressive Symptoms on Cognitive Functioning in Individuals with Diabetes

One limitation of many of the previously mentioned studies is that they excluded participants with psychiatric disorders and did not include measures of depressive symptoms (Anderson et al., 2006; Bjorgaas et al., 1997; Fox et al., 2003; Hershey et al., 2003; Northam et al., 2001; Rovet & Alvarez, 1997; Rovet et al., 1990; Rovet, Ehrlich, & Hoppe, 1988; Ryan et al., 1984; Schoenle et al., 2002). Therefore, participants with undiagnosed depression may have been unintentionally included in the sample and it was assumed that the proportion with depressive symptoms in both diabetic and control groups were comparable. However, given that diabetes is a risk factor for developing depressive symptoms, this assumption may be faulty and compromise the validity of the explanation for cognitive differences between groups. In addition, the interaction between diabetes and depressive symptoms may impact neuropsychological functioning thereby contributing to differences between diabetic and control groups that were observed in previous studies.

However, one study that did measure depressive symptoms (Northam et al., 1995), found that their sample of children with Type 1 diabetes did not differ from the sample of healthy controls based on maternal ratings from the Child Behavior Checklist (CBCL). However, teacher ratings indicated significantly higher scores for children with diabetes in the categories of Internalizing Behaviors, Withdrawn, Somatic Complaints, Anxious/Depressed, and Attention Problems. Even after the Internalizing Scale was modified by deleting items pertaining to somatic symptoms and behavior that could be
attributed to the diabetes, teachers classified 20% of children with diabetes in the clinical range on the Internalizing Scale, which was significantly more than the 12% of healthy children classified as such. The relationship between psychosocial factors and neuropsychological functioning was examined by conducting correlational analyses using CBCL and cognitive test performance scores. The findings indicated that there were no significant correlations for children with diabetes when maternal behavior ratings were used but there were differences found when the teacher report form was used. The Social Problems scale was associated with poorer performance on the Freedom from Distractibility index, reading, and spelling for children with diabetes but only with spelling for the non-diabetics. This finding suggests that the implications of psychosocial factors may be different for children with diabetes than children without diabetes in terms of test performance. Research thus far is limited in the area of psychosocial factors including depressive symptoms and their contribution to neuropsychological effects of diabetes in children and adolescents.

One study examined whether the effects of diabetes on cognitive functioning were more severe for individuals with comorbid depression (Watari et al., 2006). They compared a sample of depressed adults with Type 2 diabetes to adults with Type 2 diabetes without depression and to a healthy control group. Participants were assessed on a variety of measures including the Stroop Test, the Trail Making Test, the Digit Symbol and Letter-Number Sequencing subtests from the WAIS-III, the Rey-Osterrieth Complex Figure Test, and the California Verbal Learning Test. Results showed that the adults with Type 2 diabetes and depression tended to have lower overall cognitive functioning than
non-depressed adults with Type 2 diabetes, specifically in areas of attention, executive
functioning, and processing speed. However, the study did not assess the number of
depressive symptoms in both the experimental and control groups and therefore could not
differentiate between effects due to the interaction between diabetes and depressive
symptoms and the effects of depressive symptoms only. The present study utilized a
similar design to examine interactions between Type 1 diabetes and depressive symptoms
in adolescents, who may have different sequelae and outcomes than adults due to the fact
that neural connections are still forming in their brain over the course of development.
However, depressive symptoms were assessed in the non-diabetic group in order to
address the limitations inherent in Watari et al.’s study.

**General Summary**

This review of the literature has addressed the neurological impact of Type 1
diabetes by considering the neuroanatomical, the neurophysiological, and the
neuropsychological effects of the diabetic condition on overall learning and behavior. It
has also reviewed the literature pertaining to the effect of depression on
neuropsychological functioning and specifically considers the relationship between
depressive symptoms and various domains of neuropsychological functioning including
memory, learning, and attention. In general, previous research has shown that both
depression and diabetes negatively impact neuropsychological functioning. Thus, the
present study was conducted in order to examine the effects of diabetes interacting with
depressive symptoms on neuropsychological functioning in the domains of memory,
learning, and attention in a sample of adolescents. This study extends beyond current
literature by examining memory and attention and depressive symptoms in greater depth than previous studies of adolescents with diabetes.
CHAPTER 3
METHODOLOGY

This chapter describes the method utilized in the study, including a description of the participants, materials used, and the procedures followed for data collection. Also included is a description of specific hypotheses that were tested and the manner in which the data were analyzed.

Participants

The present study was based on a representative sample of adolescents diagnosed with Type 1 diabetes (N=31) and healthy adolescents (N=31) ranging in age from 13 to 17 years. A total of 62 participants were enrolled in the study. An a priori power analysis determined that 76 participants were needed to yield power at .8 with an effect size of .3. However, this sample size was modified to 62 participants due to the fact that many potential participants met the study’s strict exclusionary criteria.

Potential participants were excluded if they had a significant history of psychiatric or neurologic illness other than depression, a history of dependence on alcohol or illicit drugs, a diagnosed developmental or learning disability that could impact neuropsychological functioning, or were not fluent in English. These exclusionary criteria were chosen as any of them could be related to outcomes on neuropsychological testing, thereby introducing error to the results. Specific reasons for exclusion were not tracked so that confidentiality would be maintained for non-participants; potential participants were told that they need not identify which specific exclusionary criteria applied to them.
Adolescents were recruited from an outpatient pediatric diabetes clinic and an outpatient general medicine pediatric clinic in the same medical center as the diabetes clinic. These sites were located in Tucson, AZ. Adolescents were also referred to the study by friends and family of participants via word of mouth. This particular pediatric diabetes clinic is the largest specialized clinic serving adolescents with diabetes in Tucson and Southern Arizona. Therefore, recruitment from this clinic was thought to yield a representative sample of the population of adolescents with diabetes in Southern Arizona who receive medical treatment. The outpatient general medicine pediatric clinic at the same medical center was chosen as a recruitment site in order to obtain a sample of adolescents without diabetes who were similar to the adolescents with diabetes in terms of demographic characteristics such as ethnicity and lunch status.

Materials

**Dependent measures.** The following measures were used as dependent variables in this study.

*Wide Range Assessment of Memory and Learning- Second Edition (WRAML2).* The WRAML2 was designed to assess memory ability and for use in both clinical and research contexts (Sheslow & Adams, 2003). It contains six core subtests: Story Memory (recall of a story paragraph presented auditorily), Verbal Learning (list learning of 16 words presented auditorily), Design Memory (reproduction from memory of designs shown on cards), Picture Memory (recall of details in pictures), Finger Windows (recall of spatial sequences presented visually), and Number-Letter (recall of numbers and letters presented auditorily).
Three index scores were derived from the six core subtests: Verbal Memory, Visual Memory, and Attention-Concentration. The additional subtests that measure delayed memory and recognition (Story Memory Delay Recall, Verbal Learning Delay Recall, Story Memory Recognition, Verbal Learning Recognition, Design Memory Recognition, and Picture Memory Recognition) were also administered. These delayed memory and recognition subtests were used to compute scores on the Verbal Recognition and Visual Recognition indexes. Another supplemental subtest, Verbal Working Memory, was given to measure an individual’s ability to remember and manipulate information that was presented auditorily. For each subtest, the scaled scores have a mean of 10 and a standard deviation of 3. For each memory index, the standard scores have a mean of 100 and a standard deviation of 15.

The WRAML2 has norms for ages 5 to 90 years old. The standardization sample consisted of 1,200 children and adults and was matched as closely as possible to the March, 2001 U.S. Census in terms of gender, race/ethnicity, educational attainment, and geographic region.

Reliability data from the WRAML2 indicate person separation reliabilities from Rasch statistics ranging from .85 to .94 on the core subtests (Sheslow & Adams, 2003). Internal consistency using Cronbach’s alpha coefficients ranges from .82 to .96 on the core index scores, and from .71 to .95 across the six core subtests. External validity was examined by comparing scores on the instrument with several other memory and learning measures including the Wechsler Memory Scale-III (WMS-III) and the California Verbal Learning Test-II (CVLT-II). Correlations between the WRAML2 subtests and those of
the WMS-III range from .36-.66 for indexes that are proposed to be measuring similar constructs. Specifically, there was a .60 correlation between the WRAML2 General Memory index score and the WMS-III General Memory index score, and a .60 correlation between the WRAML2 Working Memory index score and the WMS-III Working Memory index. Similar findings are noted on the CVLT-II with non-clinical samples; a correlation of .68 was found between the WRAML2 Verbal Memory and CVLT-II Trial 1-5 Total. In delayed conditions, a correlation of .60 and .65 was found between the WRAML2 Verbal Recognition and CVLT-II Short Delay Cued Recall and CVLT-II Long Delay Free Recall, respectively.

**Stroop Color and Word Test Adult and Children's Versions Revised.** The Stroop Color and Word Test measures speed and accuracy when individuals are presented with interference stimuli; when presented with color-word stimuli patients must name colors but not read the words. In other words, it assesses the inhibition of a more automatic verbal response (reading) in order to generate a conflicting response of naming the dissonant ink colors. This test has been used to differentiate normal, non-brain-damaged subjects from brain-damaged subjects, identifies good flexibility, and evaluates stress, cognition, and psychopathology.

The Stroop Color and Word Test consists of three subtests. Each subtest is composed of a 5 x 20 matrix of items and is offered on a separate page: The Word test contains the names of colors printed in black ink; the Color test is presented with semantically meaningless symbols (XXXX) printed in colored ink; and the Color-Word test is composed of words from the first page, printed in the colors from the second page,
with the restriction that the words and colors do not match (the word "RED" is presented in green or blue).

Comparison scores across the three subtests render a Color-Word Interference Effect score that reportedly identifies individual differences within and among specifically defined populations. The scoring method used was the number of items completed in 45 seconds. New norms are included in both the children (ages 5-14 years) and adult (ages 15-90 years) manuals (Golden, Freshwater, & Golden, 2003; Golden & Freshwater, 2002). The children's version uses T-scores, drawn from means and standard deviations, by age, whereas the adult T-scores are tabled, based on multiple regression equations, utilizing education and age.

Limited data are offered related to test-retest reliability and alternate forms reliability. The test-retest coefficients were reported in 1965 and 1975, covering periods from 1 minute to 10 days (Soares, 2007). The coefficients ranged from .69 to .89 with different forms of the test. There is a lack of evidence supporting validity of the Stroop Color and Word Test; no validity data are offered in either manual. However, this test is widely used in published research and has been used in several studies with diabetic populations (Hershey et al., 1997; Manschot et al., 2006; Watari et al., 2006) and depressed populations (Cataldo et al., 2005; Killgore et al., 2007). Findings from this study were compared to previous results.

**Independent measures.** The following measures were used as independent variables in this study.
**Demographic questionnaire.** A questionnaire (see Appendix A) was designed by the researcher to be used by adolescents with the help of their parent/guardian. The questions pertained to variables that have been found in the literature to influence neuropsychological and cognitive functioning, such as ethnicity, socioeconomic status, and age. Socioeconomic status was defined as a three level variable measured by the item on the demographic questionnaire asking for school lunch status: free, reduced price, full price.

**The Beck Depression Inventory for Youth, Second Edition (BDI-Y II).** The Beck Depression Inventory for Youth, Second Edition (BDI-Y II) is designed to identify symptoms of depression in children and adolescents including negative thoughts about self or life, and future; feelings of sadness; and physiological indications of depression (Beck, Beck, Jolly, & Steer, 2005). The BDI-Y II contains 20 statements about thoughts, feelings, or behaviors associated with emotional and social impairment in children and adolescents and as stated in the manual can be used with youth ages 7-18 years. The items are written at a second grade reading level.

The standardization sample for the norming of the BDI-Y II consisted of 1,000 children, who were between the ages of 7 and 18 years old. The sample was stratified on the variables of age, ethnicity, parent education level, and gender.

The BDI-Y II provides a raw score for the depression scale which is then converted to a standardized T score. Scores are reported as standardized T-scores ranging from 34 to 100 with a mean of 50 and standard deviation of 10.
The BDI-Y II technical manual provides psychometric properties (Beck et al., 2005). Internal consistency was measured using Cronbach’s alpha coefficients which ranged from .86 to .96 across ages and gender. Test-retest was calculated using a subsample of 105 children and 65 adolescents across a median retest interval of seven days. Corrected correlations for the children ages 11 to 14 ranged from .84 to .93 and for adolescents ages 15 to 18 ranged from .83 to .93. In terms of concurrent validity, the BDI-Y II has been shown to be highly correlated to the Children’s Depression Inventory, the Revised Children’s Manifest Anxiety Scale, and to the Piers-Harris Children’s Self-Concept Scale.

*The Kaufman Brief Intelligence Test, Second Edition (KBIT-2).* The KBIT-2 is a brief intelligence test for individuals from 4 to 90 years of age. It is designed for traditional brief assessment purposes such as screening, conducting periodic cognitive reevaluations, and assessing cognitive functioning when it is a secondary consideration (Kaufman & Kaufman, 2004). The standardization sample consisted of 2,120 individuals and was stratified on race-ethnicity, geographic region, and educational level using the March 2001 Current Population Survey.

The KBIT-2 yields an IQ Composite as well as Verbal and Nonverbal subscales. The Verbal scale is composed of two combined subtests that assess receptive vocabulary and general information (Verbal Knowledge) as well as comprehension, reasoning, and vocabulary knowledge (Riddles). The Nonverbal scale uses a Matrices subtest to assess the ability to complete visual analogies and understand relationships. All standard scores
have a mean of 100 and standard deviation of 15, with the average range being defined as scores between 85 and 115. Subsequent descriptors are at 15-point intervals.

The KBIT-2's IQ Composite internal consistency is high as measured by Cronbach’s alpha coefficient of .93 across ages (.89 to .96) (Kaufman & Kaufman, 2004). The Verbal (.91) and Nonverbal (.88) coefficients are also within acceptable ranges. Composite test-retest stability was .90 over mean intervals of 22.5 to 30.8 days, with a mean performance increase of 4 points, with the Verbal (r = .91) and Nonverbal (r = .83) scales each showing similar increases on retesting. Coefficients at different ages are adequate (.83 or higher) except for the Nonverbal scale for the 4- through 12-year age groups (.76).

In terms of validity, evidence supporting construct validity is presented in the KBIT-2 Manual and subsequent research (Kaufman & Kaufman, 2004; Madle, 2007). For example, increases in raw scores across age groups were found whereas no meaningful differences were found across gender. In older examinees, the expected lifespan declines in performance (Baltes, Staudinger and Lindenberger, 1999) were noted. Matrices, a measure of fluid ability, peaked during early adulthood and then began a gradual decline, whereas the Crystallized-Verbal scales increased or remained stable until old age. Furthermore, studies of clinical groups that involved intelligence as a key part of their definition had expected mean scores as follows: (Intellectually Gifted = 115.0; Mentally Retarded = 61.1), as did other groups with likely intellectual deficits (Traumatic Brain Injury = 73.4; Dementia = 74.1) or slightly decreased cognitive scores.
(Learning Disability = 88.0; Speech and Language Impaired = 85.3; Attention-Deficit-Hyperactivity Disorder = 90.5) (Madle, 2007).

Concurrent validity has been established by comparing the KBIT-2 to several other measures of intelligence. KBIT-2 scores were lower than the K-BIT by about 2 points, which is consistent with expected declines due to the Flynn Effect (Flynn, 1987). Comparisons showed Full Scale and Performance IQs about 4.5 points and 7 points higher, respectively, on the Wechsler Abbreviated Scale of Intelligence (WASI) than on the corresponding KBIT-2 scales, even though the correlations were strong. The KBIT-2 Full Scale-IQ Composite correlations with the WISC-III and WISC-IV were .76 and .77, respectively. The WAIS-III correlation was .89. Mean Full Scale IQs, however, ranged from 1.3 points lower (WISC-IV) to 5 to 7 points higher (WAIS-III) than the KBIT-2 IQ Composite.

Procedure

Flyers (see Appendix B and C) were posted and distributed at the previously mentioned medical clinics. Potential participants were also asked by medical clinic staff members if they would like to hear about a research study taking place. Those who expressed interest when approached or who later contacted the researcher were told the purpose of the study, the eligibility criteria for participation, and what participation would entail in terms of time, risks, and benefits. Potential participants who were eligible and wished to participate and their legal guardian were given an explanation of procedures and potential risks and were provided the opportunity to have any questions answered.
regarding the study. Assent (see Appendix D) was obtained from all youth and parents provided written informed consent (see Appendix E) prior to enrollment in the study.

At the assessment appointment, each adolescent, with the help of his/her parent/guardian, was asked to fill out a demographic questionnaire asking questions regarding the participant’s age, gender, ethnicity, grade in school, free or reduced lunch status, and medical conditions. Participants with diabetes were asked additional questions related to their diabetes such as age of onset, length of time the participant has had diabetes, methods of insulin therapy used, and whether or not the participant has ever experienced a severe hypoglycemic episode in which he or she needed emergency response treatment or help to recover. At the end of the consent process, the researcher began the neuropsychological assessment procedures or scheduled a future appointment for the assessment.

Each adolescent was tested using a battery of psychometric tests and questionnaires assessing neuropsychological functioning and social and emotional functioning. Specifically, participants completed the BDI-Y II to assess depressive symptoms and the KBIT-2 to obtain an estimated intelligence quotient. Then participants were assessed using subtests from the WRAML2 and the Stroop Color and Word Test to assess memory, learning, attention/concentration, and attention/inhibition. The tests were administered to the participants individually and in the same order by the researcher in one session. The order of tests was as follows: BDI-Y II, Stroop Test, WRAML 2, KBIT2. This order was the same for each participant and was chosen to minimize fatigue effects. The Stroop Test was the only timed task and so it was given towards the
beginning of the session. The KBIT2 measures general intelligence including crystallized intelligence, which are relatively stable constructs, and thus administered last. At the end of the assessment, participants were thanked for their time and hard work and were given the choice of a $15 gift card or cash. All procedures were approved by the Institutional Review Board (IRB) of the University of Arizona prior to their use in the study (see Appendix F).

**Data Analysis**

The purpose of this study was to investigate the relationship between diabetes, depressive symptoms, and neuropsychological functioning in adolescents in the domains of memory, learning, attention/concentration, and attention/inhibition. Memory, learning, and attention abilities were defined as scores on the WRAML2 and the Stroop Test. Specifically, this research examined whether the effects of diabetes on neuropsychological functioning were related to or depended on depressive symptoms scores. The following null hypotheses were tested:

**Null hypothesis 1.** There will be no significant interaction effect between diabetes and depressive symptoms scores on memory performance.

**Null hypothesis 2.** There will be no significant interaction effect between diabetes and depressive symptoms scores on verbal learning performance.

**Null hypothesis 3.** There will be no significant interaction effect between diabetes and depressive symptoms scores on attention performance.
**Null hypothesis 4.** There will be no significant relationship between depressive symptoms scores and disease-related variables such as age of onset of diabetes and presence of severe hypoglycemic episodes.

The test results for the dependent variables (memory, learning, attention/concentration, attention/inhibition) as measured by the WRAML2 and the Stroop Test, respectively, and the intelligence scores (KBIT-2) were converted to standard scores to facilitate direct comparison among measures. Scores on the BDI-Y II were converted to T-scores based on age and gender norms. All score conversions were based on the data provided in each of the respective manuals. To address examiner reliability, a trained school psychology graduate student scored the WRAML2 responses of 15 (24%) randomly selected participants. Scoring agreement between the examiner and observer was calculated to be 99.38%.

Data were analyzed using Predictive Analytics Software (PASW) version 18.0. Descriptive statistics on demographic variables were obtained for all participants and on diabetes-related variables for participants with diabetes. Statistical analyses for Null Hypotheses 1-3 were conducted using General Linear Modeling (GLM). The GLM method was chosen because it permits the study of relationships between multiple predictors and dependent variables and it permits analysis of both categorical and continuous variables. The GLM method is also advantageous because it retains the power associated with linear regressions. Analyses examined the relative contribution of each predictor variable while controlling for the effects of all other independent variables, the interaction effect between specific predictor variables while controlling for the effects of
all other independent variables, and the validity of all independent variables combined. Specifically, the interaction effects of diabetes and depressive symptoms were examined in relation to differences in memory, learning, and attention performance. No cases had missing data. P-plots were checked to verify that assumptions of normality were not violated. Null hypothesis 4 was tested using standard multiple regression to determine whether diabetes disease-related variables were predictive of depressive symptoms scores.

In addition, further analyses were conducted in which the independent variable for depressive symptoms, BDI-Y II T-score, was used as a grouping variable to compare neuropsychological functioning in depressed and non-depressed adolescents. The manual for the BDI-Y II considers T-scores of 70 or higher to fall in clinically significant range for depression and BDI-Y II T-scores of 60-69 to fall in the at-risk range for depression. However, only a few participants in the current study fell within the clinically significant or at-risk ranges (3.2% and 14.5%, respectively). Therefore, using the procedure described in Leonard, Jang, Savik, Plumbo, and Christensen (2002), two groups were created using the median of the scores (T=50.68): adolescents with above the median depressive symptoms scores and adolescents with below the median depressive symptoms scores. A multivariate analysis of variance (MANOVA) was used to determine if the relationship between diabetes and neuropsychological performance was the same for adolescents with above average depressive symptoms scores as for adolescents with below average depressive symptoms scores. The MANOVA was a 2 (diabetes and no diabetes) x 2 (below median depressive symptoms scores and above median depressive
symptoms scores) x 10 (neuropsychological measures) factorial design with gender, ethnicity, lunch status, and IQ as covariates. An alpha level of .05 was used for all statistical tests of significance. Eta² will be reported as a measure of effect size for all statistical procedures using analysis of variance.

Summary

A total of 62 adolescents were enrolled in this study. They were assessed using a demographic questionnaire, the BDI-Y II to assess depressive symptoms, the KBIT2 to obtain an estimate of adolescents’ intelligence quotient, the WRAML2 to assess memory, learning, and attention/concentration, and the Stroop Color and Word Test to assess attention/inhibition.

Three null hypotheses concerning the effect of the interaction between diabetes and depressive symptoms on adolescents’ performance on memory, learning, and attention tasks were tested using GLM procedures. A fourth null hypothesis concerning the relationship between depressive symptoms and diabetes disease-related variables was tested using multiple regression. Additional analyses were conducted using above and below median BDI-Y II T-scores to form groups. The results of these analyses are presented next in chapter 4.
CHAPTER 4
ANALYSIS AND RESULTS OF DATA

This chapter presents an analysis and the results of the data collected. First, the characteristics of the participants will be described. Then the findings for each hypothesis will be reported. The first three hypotheses address neuropsychological functioning and the fourth hypothesis addresses the relations between diabetes disease-related factors and depressive symptoms.

Participant Characteristics

The demographic characteristics of the sample of 62 adolescents are found in Table 1. The mean age of participants was 15.26 (SD= 1.33) years. Of the 62 participants, 29 (46.8%) were female and 33 were male (53.2%). The mean and standard deviation for participants’ BDI-Y II T-scores was 50.68 (8.65); 51.52 (9.726) for non-diabetics and 49.84 (7.493) for diabetics. An independent samples t-test showed that the two groups’ BDI-Y II T-scores did not differ significantly (t(60) =.761, p= .450). In terms of ethnic distribution, the sample was comprised of Caucasian (54.8%), Hispanic (38.7%), African American (4.8%), and Asian (1.6%) adolescents. Approximately 39% of participants qualified for free (n=18) or reduced price (n=6) lunch at school.

For the group with diabetes, the mean age at onset was 8.77 years (SD = 4.74) and the mean duration was 6.90 years (SD= 4.84). Eleven adolescents with diabetes (35.5%) reported that they were in their target blood glucose range at their most recent glucose test prior to the neuropsychological assessment while 18 (58.10%) reported being higher than their target range and one adolescent (3.2%) reported being lower than her target
Table 1

*Description of Participant Demographic Variables*

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Mean (S.D.) Diabetes (N=31)</th>
<th>Mean (S.D.) No Diabetes (N=31)</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>15.61(1.334)</td>
<td>14.90(1.248)</td>
<td>-2.164</td>
<td>.034</td>
</tr>
<tr>
<td>IQ</td>
<td>96.90(13.529)</td>
<td>99.55(15.752)</td>
<td>.709</td>
<td>.481</td>
</tr>
<tr>
<td>BYI-D T-score</td>
<td>49.84(7.493)</td>
<td>51.52(9.726)</td>
<td>.761</td>
<td>.450</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable Name and Level</th>
<th>n (%) Diabetes (N=31)</th>
<th>n (%) No Diabetes (N=31)</th>
<th>Mann-Whitney Test Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>434.000</td>
<td>.449</td>
</tr>
<tr>
<td>Male</td>
<td>18(58.1)</td>
<td>15(48.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13(41.9)</td>
<td>16(51.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>462.500</td>
<td>.774</td>
</tr>
<tr>
<td>African American</td>
<td>1(3.2)</td>
<td>2(6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1(3.2)</td>
<td>0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>17(54.8)</td>
<td>17(54.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>12(38.7)</td>
<td>12(38.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunch Status</td>
<td></td>
<td></td>
<td>470.500</td>
<td>.870</td>
</tr>
<tr>
<td>Free</td>
<td>8(25.8)</td>
<td>10(32.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>5(16.1)</td>
<td>1(3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Price</td>
<td>18(58.1)</td>
<td>20(64.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td>276.500</td>
<td>.003</td>
</tr>
<tr>
<td>Sixth</td>
<td>0(0)</td>
<td>1(3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seventh</td>
<td>4(12.9)</td>
<td>6(19.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eighth</td>
<td>1(3.2)</td>
<td>3(9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ninth</td>
<td>5(16.1)</td>
<td>12(38.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenth</td>
<td>8(25.8)</td>
<td>6(19.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eleventh</td>
<td>11(35.5)</td>
<td>2(6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twelfth</td>
<td>2(6.5)</td>
<td>1(3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression Diagnosis (based on self-report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4(12.9)</td>
<td>4(12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27(87.1)</td>
<td>27(87.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
range. Of the 19 adolescents who were not in their target range at the time of glucose testing, nine reported that they believed target range was reached prior to neuropsychological testing. In terms of insulin therapy methods, the percentage of participants with diabetes who used insulin pumps (N=18) was 58.1% and the percentage of those who used injections (N=13) was 41.9%. Nine participants (29.0%) reported that they have experienced severe hypoglycemic episodes in which they required emergency response treatment or help to recover. These results are shown in Tables 2 and 3.

Table 2

Means and Standard Deviations of Diabetes-related Variables

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>8.77</td>
<td>4.738</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>6.90</td>
<td>4.84</td>
</tr>
</tbody>
</table>

Table 3

Number and Percentage of Diabetic Participants for Diabetes-related Variables

<table>
<thead>
<tr>
<th>Variable Name and Level</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experienced Severe Hypoglycemic Episode</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9(29.0)</td>
</tr>
<tr>
<td>No</td>
<td>22(71.0)</td>
</tr>
<tr>
<td>Blood Glucose Range during Neuropsychological Testing</td>
<td></td>
</tr>
<tr>
<td>In target range according to last glucose test</td>
<td>11(35.5)</td>
</tr>
<tr>
<td>High according to last glucose test</td>
<td>18(58.1)</td>
</tr>
<tr>
<td>Low according to last glucose test</td>
<td>1(3.2)</td>
</tr>
<tr>
<td>No response</td>
<td>1(3.2)</td>
</tr>
<tr>
<td>Type of Insulin Therapy</td>
<td></td>
</tr>
<tr>
<td>Pump</td>
<td>18(58.1)</td>
</tr>
<tr>
<td>Injections</td>
<td>13(41.9)</td>
</tr>
</tbody>
</table>
Relationship between Diabetes, Depressive Symptoms, and Memory

The first hypothesis stated that Type 1 diabetes and depressive symptoms scores would not produce an interaction effect on memory performance as assessed by the WRAML 2. Table 4 presents the results of the analysis of variance tests for each memory task. When GLM multivariate analyses were conducted using diabetes diagnosis, gender, ethnicity, and lunch status as fixed factors and using BDI-Y II T-score, age, and IQ as covariates, results from Roy’s Largest Root test showed that the interaction effect of diabetes and depressive symptoms score was statistically significant in explaining the variance among neuropsychological test scores ($F = 3.045, p = .009, \eta^2 = .504$). Specifically, the interaction effect of diabetes and depressive symptoms score was statistically significant for verbal memory ($F = 6.663, p = .003, \eta^2 = .260$), verbal recognition ($F = 4.192, p = .023, \eta^2 = .181$), and verbal memory delayed ($F = 4.792, p = .014, \eta^2 = .201$) but not for visual memory ($F = 2.110, p = .135, \eta^2 = .100$), verbal working memory ($F = 1.740, p = .189, \eta^2 = .084$), or visual recognition ($F = 2.780, p = .075, \eta^2 = .128$). Main effects for diabetes ($F = .863, p = .576, \eta^2 = .229$) and depressive symptoms scores ($F = 1.951, p = .078, \eta^2 = .402$) on neuropsychological test scores were not significant.
Table 4

*Analysis of Variance for Neuropsychological Test Performance by Diabetes x Depressive Symptoms Interaction*

<table>
<thead>
<tr>
<th>Neuropsychological Domain Memory</th>
<th>Subscale/Subtest</th>
<th>df</th>
<th>F</th>
<th>p-value</th>
<th>Eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Verbal Working Memory</td>
<td>2</td>
<td>1.740</td>
<td>.189</td>
<td>.084</td>
</tr>
<tr>
<td></td>
<td>Verbal Memory</td>
<td>2</td>
<td>6.663</td>
<td>.003*</td>
<td>.260</td>
</tr>
<tr>
<td></td>
<td>Visual Memory</td>
<td>2</td>
<td>2.110</td>
<td>.135</td>
<td>.100</td>
</tr>
<tr>
<td></td>
<td>Story Delay</td>
<td>2</td>
<td>2.911</td>
<td>.067</td>
<td>.133</td>
</tr>
<tr>
<td></td>
<td>Word List Delay</td>
<td>2</td>
<td>4.792</td>
<td>.014*</td>
<td>.201</td>
</tr>
<tr>
<td></td>
<td>Verbal Recognition</td>
<td>2</td>
<td>4.192</td>
<td>.023*</td>
<td>.181</td>
</tr>
<tr>
<td></td>
<td>Visual Recognition</td>
<td>2</td>
<td>2.780</td>
<td>.075</td>
<td>.128</td>
</tr>
<tr>
<td>Learning</td>
<td>Word List Learning</td>
<td>2</td>
<td>6.841</td>
<td>.003*</td>
<td>.265</td>
</tr>
<tr>
<td>Attention</td>
<td>Attention/Concentration</td>
<td>2</td>
<td>7.566</td>
<td>.002*</td>
<td>.285</td>
</tr>
<tr>
<td></td>
<td>Stroop Interference</td>
<td>2</td>
<td>.541</td>
<td>.587</td>
<td>.028</td>
</tr>
</tbody>
</table>

* significant at the p>.05 level

An interaction plot using the mean verbal memory performance scores for diabetic and non-diabetic participants in each of three depressive symptom score groups (BDI-Y II T-scores 30-49, 50-59, 60-80) showed that when depressive symptoms increased to T-scores in the “at risk” and/or “clinically significant” ranges, memory performance decreased (see Figure 1).
Figure 1. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal memory performance scores.

* significant at the p>.05 level

An interaction plot using the mean verbal recognition performance scores for diabetic and non-diabetic groups in each of three depressive symptom score groups (BDI-Y II T-scores 30-49, 50-59, 60-80) indicated that depressive symptoms scores reported by adolescents with diabetes to be at or above the median were associated with lower verbal recognition scores than below median depressive symptoms scores. The adolescents without diabetes tended to have lower verbal recognition scores when depressive symptoms scores were either below the median or in the “at risk” or “clinically significant” ranges and performed best when their depressive symptoms scores were above the median and in the average range (See Figure 2).
Figure 2. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal recognition scores.

* significant at the p>.05 level

An interaction plot using the mean verbal memory delayed performance scores for diabetic and non-diabetic groups in each of three depressive symptom score groups (BDI-Y II T-scores 30-49, 50-59, 60-80) showed a similar pattern of decreasing performance for both diabetics and non-diabetics scores as depressive symptoms scores increased from above the median to “at risk” and “clinically significant” ranges (see Figure 3). However, when self-reported depressive symptoms scores were below the median, the non-diabetic group performed better than the diabetic group. In summary, performance on immediate verbal memory and delayed verbal memory tasks showed
different patterns when the interaction between Type 1 diabetes and depressive symptoms scores was considered.

Figure 3. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal memory delayed scores.

* significant at the p>.05 level

When a 2 (diabetes and no diabetes) x 2 (depressive symptom condition: below median depressive symptoms score and above median depressive symptoms score) x 10 (neuropsychological test scores) MANOVA was performed with age, gender, ethnicity, lunch status, and IQ as covariates, results showed that the interaction between diabetes and depressive symptoms had a significant effect on visual memory ($F = 4.299$, $p = .016$, $\eta^2 = .370$) but not on any other measures of memory (see Table 5). Thus, results
indicated that only visual memory was affected by the interaction of diabetes and depressive symptoms when mean memory scores for adolescents who endorsed depressive symptoms scores that were elevated above the median were compared to mean memory scores for adolescents who endorsed below the median depressive symptoms scores. As shown in Table 5, the group of adolescents with diabetes who reported below the median depressive symptoms scores tended to perform poorer at visual memory tasks than the group of adolescents without diabetes who reported below the median depressive symptoms scores. However, a post hoc Tukey-HSD test resulted in non-significant differences in visual memory performance across groups when covariates were not included in the analysis. These post-hoc results support the results of the earlier analysis in which depressive symptoms scores were used as a continuous variable and visual memory performance was significantly not affected by the interaction between diabetes and depressive symptoms.

**Relationship between Diabetes, Depressive Symptoms, and Learning**

The second hypothesis stated that Type 1 diabetes and depressive symptoms would not produce an interaction effect on learning as assessed by the word list learning task on the WRAML2. Analyses were conducted including age, gender, ethnicity, lunch status, and IQ as covariates. Results showed that the interaction between diabetes and depressive symptoms scores had a significant effect on the ability to learn a list of words presented orally ($F = 6.841$, $p = .003$, $\eta^2 = .265$) (Table 4). A plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on list learning scores showed that as depressive symptoms scores increased, verbal learning scores decreased for
Table 5

Means and Standard Deviations for Neuropsychological Test Performance

<table>
<thead>
<tr>
<th>Neuropsychological Subscale/Subtest</th>
<th>Diabetics</th>
<th></th>
<th>Non-diabetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Dep</td>
<td>Low Dep</td>
<td>High Dep</td>
<td>Low Dep</td>
</tr>
<tr>
<td>Domain</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>N=14</td>
<td>n=17</td>
<td>n=14</td>
<td>n=17</td>
</tr>
</tbody>
</table>

Memory

<table>
<thead>
<tr>
<th>Subscale/Subtest</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Working Memory&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.14</td>
<td>9.41</td>
</tr>
<tr>
<td></td>
<td>(2.958)</td>
<td>(2.895)</td>
</tr>
<tr>
<td>Verbal Memory&lt;sup&gt;b&lt;/sup&gt;</td>
<td>101.50</td>
<td>103.12</td>
</tr>
<tr>
<td></td>
<td>(11.030)</td>
<td>(13.499)</td>
</tr>
<tr>
<td>Visual Memory&lt;sup&gt;*b&lt;/sup&gt;</td>
<td>96.14</td>
<td>91.53</td>
</tr>
<tr>
<td></td>
<td>(12.253)</td>
<td>(9.792)</td>
</tr>
<tr>
<td>Story Delay&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.36</td>
<td>10.88</td>
</tr>
<tr>
<td></td>
<td>(1.781)</td>
<td>(3.039)</td>
</tr>
<tr>
<td>Word List Delay&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.57</td>
<td>10.47</td>
</tr>
<tr>
<td></td>
<td>(2.472)</td>
<td>(2.918)</td>
</tr>
<tr>
<td>Verbal Recognition&lt;sup&gt;b&lt;/sup&gt;</td>
<td>102.64</td>
<td>106.12</td>
</tr>
<tr>
<td></td>
<td>(11.098)</td>
<td>(13.761)</td>
</tr>
<tr>
<td>Visual Recognition&lt;sup&gt;b&lt;/sup&gt;</td>
<td>101.93</td>
<td>97.82</td>
</tr>
<tr>
<td></td>
<td>(19.913)</td>
<td>(16.264)</td>
</tr>
</tbody>
</table>

Learning

<table>
<thead>
<tr>
<th>Subscale/Subtest</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Learning&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td></td>
<td>(2.572)</td>
<td>(2.625)</td>
</tr>
</tbody>
</table>

Attention

<table>
<thead>
<tr>
<th>Subscale/Subtest</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Concentration&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90.00</td>
<td>92.29</td>
</tr>
<tr>
<td></td>
<td>(14.671)</td>
<td>(16.480)</td>
</tr>
<tr>
<td>Stroop Interference&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52.9857</td>
<td>54.9000</td>
</tr>
<tr>
<td></td>
<td>(7.4120)</td>
<td>(9.4006)</td>
</tr>
</tbody>
</table>

* statistically significant at p<.05

<sup>a</sup>= Scaled Score Mean = 10, Standard Deviation = 3
<sup>b</sup>=Standard Score Mean = 100, Standard Deviation = 15
<sup>c</sup>= T-Score Mean Score = 50, Standard Deviation=10
adolescents without diabetes (see Figure 4). For the group with diabetes, verbal learning scores were highest when depressive symptoms scores above the median and in average range.

When depressive symptoms scores were used as a grouping variable to form two groups (above the median depressive symptoms score and below the median depressive symptoms score), results from a MANOVA that included age, gender, ethnicity, lunch status, and IQ as covariates showed no statistical evidence linking the interaction between diabetes and depressive symptoms to list learning performance. This finding differs from

![Figure 4. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on verbal learning scores.](image)

* significant at the p>.05 level
the previously mentioned finding in that differences in list learning performance were found to be statistically significant when depressive symptoms scores were considered as a continuous variable.

**Relationship between Diabetes, Depressive Symptoms, and Attention**

The third hypothesis stated that Type 1 diabetes and depressive symptoms scores would not produce an interaction effect on attention performance as assessed by the Attention/Concentration index of the WRAML2 and the Stroop Interference score measuring attention/inhibition on the Stroop Color and Word Test. Table 4 presents the results from the analysis of variance tests including p values. Analyses were conducted that included age, gender, ethnicity, lunch status, and IQ as covariates. Results showed that there was an interaction effect for diabetes and depressive symptoms scores on attention/concentration \(F = 7.566, p = .002, \eta^2 = .285\), but not for attention/inhibition \(F = .541, p = .587, \eta^2 = .028\). A plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on attention/concentration scores showed that the adolescents without diabetes tended to have lower attention/concentration scores as depressive symptoms scores increased whereas the adolescents with diabetes scored highest on attention/concentration performance when their depressive symptoms scores were above the median and in the average range (see Figure 5).

When depressive symptoms scores were used as a grouping variable to form two groups (above the median depressive symptoms scores and below the median depressive symptoms scores), results based on a MANOVA with age, gender, ethnicity, lunch status, and IQ as covariates, showed that the interaction between diabetes and depressive
symptoms scores was non-significant for both attention/concentration and attention/inhibition performances. Age, gender, ethnicity, lunch status, and IQ were included as covariates. Overall, attention/concentration was found to be affected by the interaction between diabetes and depressive symptoms when depressive symptoms scores were considered to be a continuous variable rather than a dichotomous variable. The non-significant effect on attention/inhibition performance was supported by both analyses.

Figure 5. Plot of the interaction effect of depressive symptoms scores and Type 1 diabetes on attention/concentration scores.

* significant at the p>.05 level
**Relationship between Diabetes-related Variables and Depressive Symptoms**

Standard multiple regression analyses were conducted to determine the extent to which diabetes disease-related variables were predictive of depressive symptoms scores that adolescents reported. When the four diabetes-related variables (age of diabetes onset, duration of diabetes, presence of severe hypoglycemic episodes, type of insulin therapy) were entered into the model, the overall model did not significantly predict depressive symptoms scores ($R^2 = .103$, $R^2_{adj} = -.036$, $F(4,26) = .743$, $p = .572$). However, the assumption of multicollinearity was violated by two variables, age of onset (Tolerance = .091, VIF = 10.951) and diabetes duration (Tolerance = .098, VIF = 10.201). Diabetes duration was removed from the model due to its high correlation with age of diabetes onset. After removal of this variable, regression results indicated that the overall model still did not significantly predict depressive symptoms score ($R^2 = .071$, $R^2_{adj} = -.032$, $F(3,27) = .692$, $p = .565$). When diabetes duration was reentered into the regression model and age of onset was removed, results were found to be similar to those of the previous analyses ($R^2 = .077$, $R^2_{adj} = -.026$, $F(3,27) = .751$, $p = .532$). A summary of regression coefficients is presented in Table 6 and indicates that none of the diabetes-related variables (age of diabetes onset, duration of diabetes, presence of severe hypoglycemic episodes, type of insulin therapy) significantly contributed to any of the models.
Table 6

Summary of Regression Analysis for Variables Predicting Depressive Symptoms in Adolescents with Diabetes (N=31)

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>beta</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>.837</td>
<td>.529</td>
<td>.861</td>
<td>.397</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>.873</td>
<td>.564</td>
<td>.950</td>
<td>.351</td>
</tr>
<tr>
<td>Presence of Severe Hypoglycemic Episodes</td>
<td>2.621</td>
<td>.161</td>
<td>.823</td>
<td>.418</td>
</tr>
<tr>
<td>Type of Insulin Therapy</td>
<td>2.885</td>
<td>.193</td>
<td>.974</td>
<td>.339</td>
</tr>
</tbody>
</table>

Summary

Overall, results showed that performance in specific areas of memory, learning, and attention differed for adolescents with diabetes compared to adolescents without diabetes when self-reported depressive symptoms were included in the analyses. Specific areas that showed an interaction effect between diabetes and depressive symptoms were verbal memory, verbal memory delayed, verbal recognition, verbal list learning, and attention/concentration. The use of depressive symptoms scores as a dichotomous variable (above median and below median) yielded non-significant results with the exception of visual memory. However, post-hoc analyses did not support this finding when covariates were removed. Regression analyses showed that none of the diabetes-related variables included in the study were predictive of depressive symptoms scores that adolescents reported. Chapter 5 will provide a discussion of these results and their implications for further research.
CHAPTER 5
DISCUSSION

This chapter discusses the results which were obtained from this study, including how the present results either support or are different from previous research. Possible limitations of the study will then be discussed as well as future directions for research.

Purpose of the Study

There were two primary purposes for conducting this research. The first purpose was to investigate the relationship among diabetes, depressive symptoms, and neuropsychological functioning. The second purpose was to examine the relationship between diabetes disease-related factors and depressive symptoms scores. The first three hypotheses addressed questions related to neuropsychological functioning whereas the fourth hypothesis addressed the relationship of disease-related factors and depressive symptoms.

Relationship among Diabetes, Depressive Symptoms, and Neuropsychological Functioning

Relationship between diabetes, depressive symptoms, memory and learning. The first set of hypotheses used participants’ scores on subscales and subtests of the WRAML2 and the Stroop test to investigate neuropsychological functioning. Thus, the present study comprises the first attempt to investigate the interaction effect of diabetes and depressive symptoms on neuropsychological functioning in adolescents. In general, statistical analyses (MANOVA) that were conducted to test these hypotheses resulted in significant interaction effects between diabetes and depressive symptoms on performance
in several areas of memory, learning, and attention. Specifically, the interaction between diabetes and depressive symptoms explained a significant amount of variance in verbal memory, verbal recognition performance, and verbal memory delayed scores as well as for verbal list learning when demographic variables (age, gender, ethnicity, lunch status, IQ) were included in the model as covariates. Verbal memory performance for both the diabetic and non-diabetic groups was highest when depressive symptoms scores were above the median and in average range. Verbal memory performance for both the diabetic and non-diabetic groups was lowest when depressive symptoms scores were elevated to either the “at risk” or “clinically significant” ranges. However, mean verbal memory performance across the range of depressive symptom T-scores was less variable for adolescents with diabetes than for adolescents without diabetes as illustrated by Figure 1. In terms of verbal recognition performance, depressive symptoms scores reported by adolescents with diabetes to be at or above the median were associated with lower verbal recognition scores than below median depressive symptoms scores. The adolescents without diabetes tended to have lower verbal recognition scores when depressive symptoms scores were either below the median or in the “at risk” or “clinically significant” ranges and performed best when their depressive symptoms scores were above the median and in the average range. Examining verbal memory delayed performance, performance scores decreased when depressive symptoms scores increased from above the median in average range to “at risk” and “clinically significant” ranges for both the diabetic and non-diabetic groups. The diabetic and non-diabetic groups differed in their performance patterns in that the diabetic group who reported below
median depressive symptoms scores performed worse than those who reported above the median, average range depressive symptoms scores whereas the non-diabetic group who reported below median depressive symptoms scores performed better than those who reported above the median, average range depressive symptoms scores. The finding that diabetes comorbid with elevated depressive symptoms is associated with declines in verbal memory performance is similar to findings from an adult sample (Watari et al., 2006) comparing depressed Type 2 diabetics, non-depressed Type 2 diabetics, and healthy adults. This suggests that there may be commonalities between adults and adolescents in the types of neuropsychological functions that are affected. However, the study by Watari et al. did not include depressed non-diabetic participants in their sample, and therefore future research is needed to examine the differences in interaction effects that the present study found between adolescents with and without diabetes.

These findings have implications on the instructional strategies and educational programs that would be most effective for adolescents with diabetes. Specifically, given that immediate and delayed verbal memory and recognition are impacted by the interaction between diabetes and depressive symptoms, adolescents who experience these two conditions should be provided with visual supports for their lessons both at school and in regards to their diabetes education. That is, both academic instruction and diabetes education programs designed to help adolescents manage their diabetes by educating them about topics such as how to count carbohydrates and bolus before meals should provide visual materials and demonstrations to supplement verbal information. It is important to recognize the memory and learning differences in adolescents with diabetes.
and depression so that they can be given the tools for better diabetes management in an appropriate way and have a better chance at changing their lifelong outcomes through better management of diabetes, which could also lead to a reduction of depressive symptoms.

**Relationship between diabetes, depressive symptoms, and attention.** The interaction effect between diabetes and depressive symptoms was significant for attention/concentration performance. Although there is a dearth of literature on this topic, the findings from this study differ from those by Northam et al. (1995) in which parent and teacher rated Anxiety/Depressed and Internalizing scales on the CBCL were not significantly correlated with the Freedom from Distractibility index of the WISC-R for either diabetic or non-diabetic children. That is to say, the relationship between depressive symptoms and attention for children both with and without diabetes was non-significant and may have been comparable across groups. However, a test of significance comparing the correlation coefficients between psychosocial variables and neuropsychological test scores across groups was not reported in Northam’s study. Therefore, it is unclear whether the correlations between depressive symptoms and attention performance were similar in magnitude and direction for children with diabetes as for children without diabetes. The present study suggests that there may have been differences in these correlations given the present study’s findings of different patterns of attention performance for diabetics compared to non-diabetics when depressive symptoms scores are considered.
Compared to the literature on the effects of depression on attention, the present study supported previous research. For example, Cataldo et al. (2005) found that depressed children and adolescents had more difficulty sustaining attention than healthy children. The results from the present study showed that adolescents without diabetes performed worse on attention tasks as their depressive symptoms scores increased.

The implication of the present finding is that adolescents with diabetes and depression may have difficulty paying attention and concentrating on tasks. Instructional strategies should include checks for understanding to make sure that the adolescent is attending to and able to repeat back the information being presented.

In this study, attention/inhibition did not appear to be impacted by the interaction between diabetes and depressive symptoms. However, research with adults who have Type 2 diabetes and depression (Watari et al., 2006) has yielded a significant interaction effect for depression and diabetes on attention and executive functioning. Although Watari et al. included the Stroop test in their test battery, similar to the present study, various other measures were used to assess attention and executive functioning constructs in their study which could account for the different conclusions. Specific scores for attention/inhibition were not reported in the Watari et al study. However, the disparate results could also be due to maturational differences and the limitations involved when comparing adult findings with adolescent findings.

When the data were re-analyzed to compare means across groups in a 2 (diabetes and no diabetes) x 2 (depressive symptom condition: below median depressive symptoms scores and above median depressive symptoms scores) MANOVA, performance on
neuropsychological tests was not significantly different across groups with the exception of performance on visual memory tasks. This finding suggests that the effect of diabetes on most domains of neuropsychological functioning does not depend on depressive symptoms scores being above or below the median. However, for visual memory tasks, the effect of diabetes and depressive symptoms was different for adolescents who had above the median depressive symptoms scores compared to below median depressive symptoms scores. The differences in results between this analysis and the previously mentioned analysis procedures could be explained by the masking effect that occurs when depressive symptoms are used as a dichotomous variable rather than a continuous variable. That is to say, truncating data points can lead to less sensitive analyses. The fact that visual memory was found to be an area of significance when data were truncated could be a chance finding as a result of running many analyses. Thus, these findings need to be replicated in future research with adolescent participants.

Several explanations are offered for these results. First, adolescents with diabetes may have already learned to compensate for memory, learning, and attention difficulties in particular areas and so are less affected by the addition of depressive symptoms compared to adolescents without diabetes. Alternatively, depressive symptoms in adolescents with diabetes could be a different construct compared to adolescents without diabetes and therefore associated with different neurological correlates and neuropsychological outcomes. That is to say, the syndrome of depression may differ between groups. Research using factor analysis on a depressive symptoms rating scale found that there were three factors underlying the symptoms: anxiety, psychomotor
retardation and depressed mood, and cognitive performance (Bench, Friston, Brown, Frackowiak, & Dolan, 1993). Each of these three factors was associated with changes in regional cerebral blood flow in separate areas. Given that different types of symptoms are associated with different regions of brain activity, a future study should consider types of depressive symptoms reported to see if differences between adolescents with diabetes and without diabetes exist and if symptom type impacts neuropsychological performance.

Another explanation for the interaction effect of diabetes and depressive symptoms on neuropsychological performance is that blood glucose is a moderator variable. It has been shown that blood glucose levels are correlated with outcomes on self-report mood scales (Gonder-Frederick, Cox, Bobbitt, & Pennebaker, 1989) and that blood glucose levels also underlie the effect of diabetes on neuropsychological performance as seen in the case of hypoglycemia (Bade-White & Obrzut, 2009). Therefore, what has been thought to be an interaction effect could be explained by a third variable, blood glucose level. However, when post-hoc analyses were conducted to investigate the effect of blood glucose range (in target range, high, low) no significant differences were found. Perhaps a stricter measurement such as the researcher testing participants’ glucose at time of neuropsychological testing rather than having participants report their most recent test results would have been more sensitive to effects on neuropsychological testing.

**Relationship between Diabetes-related Factors and Depressive Symptoms**

The variables of age of diabetes onset, duration of diabetes, presence of severe hypoglycemic episodes, and type of insulin delivery do not appear to be predictive of the
number of depressive symptoms that adolescents with diabetes report. These findings are not supported by previous literature in that other studies with children and adolescents found significant correlations between diabetes-related variables and depressive symptoms (Hood et al., 2006; Malik & Koot, 2009; McGrady et al., 2009). McGrady et al. (2009) found that glycemic control as measured by glycated hemoglobin (A1C), a measure that reflects the average level of glucose to which red blood cells have been exposed during their life cycle, was related to number of depressive symptoms as measured by the Children’s Depression Inventory (CDI) in adolescents with diabetes. Higher A1C values were associated with more depressive symptoms. Further analysis showed that frequency of blood glucose monitoring was a mediator variable in the relationship between glycemic control and depressive symptoms. It was posited that adolescents with diabetes and depressive symptoms may have difficulty initiating tasks for diabetes management, carrying them out, and believing they will be effective.

Similarly, Hood et al. (2006) found that youth with diabetes who had elevated depressive symptoms as measured by the CDI were also more likely to have higher A1C values or more glucose in the blood stream. They also conducted analyses with a variety of other diabetes-related variables (youth-reported diabetes-specific family conflict, negative affect regarding blood glucose monitoring, and parent-reported diabetes-specific burden) which were found to be significant predictors of CDI scores. Another study similarly found that glycemic control was a significant predictor of both diabetes-related quality of life and psychopathology in adolescents (Malik & Koot, 2009). Additionally, these authors found that diabetes-related stress partially mediated the relationship
between glycemic control and psychopathology, including depression. Findings from these recent studies suggest that while certain diabetes-related variables, such as A1C, blood glucose monitoring, and diabetes-related stress, predict the number of depressive symptoms, the combination of diabetes-related variables included in the present study (age of onset, diabetes duration, type of insulin delivery, presence of severe hypoglycemic episodes) were not sufficient to significantly predict the number and frequency of depressive symptoms. It could be that the relationship between number and frequency of depressive symptoms experienced over the last two weeks and diabetes-related variables in adolescents is more likely to be significant for variables that involve current diabetes-related behavior rather than historical variables such as age of onset.

Limitations of the Study

Several factors may limit the validity and/or reliability of this study. Firstly, sampling procedures may have restricted generalizability. The sample was not entirely random as some participants were referred by friends and family of participants. Also, fewer than expected depressed adolescents participated in the study as prevalence data has shown that approximately 18% of adolescents are depressed (Kokkonen & Kokkonen, 1995) and the current sample had a much smaller proportion of adolescents who reached clinically significant (3.2%) or at-risk (14.5%) depression cutoff scores. There may be inherent differences between depressed adolescents who were willing to participate in the study and depressed adolescents who declined participation. In addition, some may argue that increased validity would have occurred through the use of a comparison group consisting of depressed adolescents and a comparison group consisting
of depressed adolescents with diabetes. However, others may argue that the use of number of depressive symptoms as a continuous variable permitted a more robust analysis given that no data were lost due to grouping.

In terms of data collection, this study used self-report measures for disease-related variables such as age of onset and presence of severe hypoglycemic episodes. Self-report measures are not always as accurate as medical records; however, participants were told ahead of time that these questions would be asked so that they had time to consult their physician or other family members. Data was not collected regarding glycemic control over several months nor reasons for refusal to participate. Both of these pieces of information could have enriched the interpretation of the current study’s results and their inclusion is recommended for future studies.

Another limitation of the present study is that treatments for diabetes and/or depression may have impacted performance on neuropsychological tests. However, given the ethical concern of withholding treatment, treatment was not denied. Data were collected regarding current treatment type and used in post hoc analyses when warranted.

Caution should be used when hypotheses are generated based on older studies which were conducted nearly two decades ago as technological advances have been made in methods for monitoring and treating diabetes. Also, using literature on adults provides limited support for hypotheses regarding adolescents’ neuropsychological functioning because of the effect of historical variables such as response to treatment and management issues and how these interact with maturation (Desrocher & Rovet, 2004).
Lastly, analyses from the fourth hypothesis may not have been sensitive enough to detect a significant relationship due to the measures used for diabetes-related variables. Specifically, the self-report methods may have been less accurate than other studies. Also, the fourth hypothesis involved only the participants with diabetes which was a smaller sample size (n=31).

**Future Directions**

The results of this study suggest that there are differences in memory, learning, and attention abilities for adolescents who have diabetes and elevated depressive symptoms when the covariates of age, gender, ethnicity, lunch status, and IQ are considered. In terms of applying these findings to academic and diabetes management interventions for adolescents, future studies should evaluate the efficacy of interventions involving visual supports and strategies to improve attention and concentration. These findings could also be useful in designing diabetes education programs for adolescents that facilitate diabetes management thereby improving glycemic control and possibly depressive symptoms. This study also provides further support of the implications of the interaction between diabetes and depressive symptoms on neuropsychological functioning and the necessity of developing treatment plans that monitor and address both conditions.

Although this study included data on participants’ blood glucose level at time of neuropsychological and psychological testing in order to examine short-term influences, level of glycemic control over time was not examined in this study. In order to investigate the role of metabolic control and its long-term effects, future studies should include
hemoglobin data for participants with diabetes in order to include quality of glycemic control as a factor.

Furthermore, longitudinal studies are necessary to discover whether the interaction between diabetes and depressive symptoms on neuropsychological functioning changes over time for adolescents as they progress through adolescence and continue to adulthood. Longitudinal studies are needed to elucidate the impact of diabetes and depression on glycemic control and academic achievement over time as long-term and short-term effects may differ. Specifically, there may be critical periods where intervention is more effective and particular periods where different intervention types are more effective than others. Overall, the next steps in research should promote expansion of this study’s application to improve learning, diabetes management, and mental health in adolescents with Type 1 diabetes.
APPENDIX A: DEMOGRAPHIC QUESTIONNAIRE

Please answer the following questions. Do NOT write your name on this paper.

1. How old are you?

2. Are you male or female?

3. What grade are you in at school (if it is summer, what grade did you most recently complete)?

4. What race do you consider yourself to be? Check all that apply:
   - [] American Indian or Alaska Native
   - [] Asian
   - [] Black or African American
   - [] Native Hawaiian or Other Pacific Islander
   - [] White
   - [] Hispanic
   - [] Other (Please specify: _______________)

5. What is your school lunch status?
   - [] free
   - [] reduced
   - [] full price

6. What type of grades do you generally get?
   - [] Mostly A’s
   - [] Some A’s & B’s
   - [] Mostly B’s
   - [] Some B’s & C’s
   - [] Mostly C’s
   - [] Some C’s & D’s
   - [] Mostly D’s
   - [] Some D’s & F’s
   - [] Mostly F’s

7. Have you ever been diagnosed with depression?
   If yes, are you currently receiving treatment?
   Please specify what type of treatment (i.e. medication, therapy, etc.):

If you have diabetes:

8. How old were you when you were first diagnosed with diabetes?

9. How long have you had diabetes?

10. Have you ever had a severe hypoglycemic episode (glucose <50) in which you needed emergency response treatment or help to recover?

11. What was your most recent blood glucose reading? How long ago was it?

12. How does this number compare to your target range? [] high  [] low  [] in target range
    If it was high or low, do you think you are in target range now?

13. What type of insulin treatment do you use (i.e. pump, injections)?
APPENDIX B: FLYER POSTER

WANTED: TEENAGER PARTICIPANTS!

We are looking for teenagers between the ages of 13 and 17 years old to participate in a research study that will compare memory and attention performance of teenagers with type 1 diabetes, teenagers with depression, teenagers with both type 1 diabetes and depression, and healthy teenagers. If you fit into any of these four categories you may be eligible to participate!

Participation can be done in one visit. If interested, please contact Lauren at (520)408-7099 or by email at lwheel02@email.arizona.edu. A thank you gift will be provided.
APPENDIX C: FLYER HANDOUT

WANTED: TEENAGER PARTICIPANTS!

We are looking for teenagers to participate in a research study that will compare memory and attention performance of teenagers with type 1 diabetes, teenagers with depression, teenagers with both type 1 diabetes and depression, and healthy teenagers. Teenagers who fit into one of these four categories may be eligible to participate.

Eligibility Criteria:
- Ages 13-17
- Able to speak and understand English
- Interested in participating in an assessment session focused on memory and attention performance that will take approximately 2-2.5 hours

Exclusion Criteria:
- have a significant history of psychiatric or neurological illness other than depression
- have a history of dependence on alcohol or illicit drugs
- have a diagnosed developmental or learning disability that could impact neuropsychological testing such as ADHD.

Participation can be done in one visit. Participants will receive a giftcard. If interested, please contact Lauren at (520)408-7099 or by email at lwheel02@email.arizona.edu.
APPENDIX D: ADOLESCENT ASSENT FORM

ADOLESCENT ASSENT FORM

Project Title: A Study of the Neuropsychological Effects of Diabetes Comorbid with Depression in Adolescents

You are being asked to read this form so that you know about this research study. Federal regulations require that you know about the study and the risks involved. If you decide to participate in this study, signing this form will say that you know about this study. If you decide you do not want to participate, that is okay.

WHY IS THIS STUDY BEING DONE?
You have the choice for to participate in this research project. The purpose of this project is to compare memory and attention performance of teenagers who have diabetes, teenagers who have depression, teenagers who have both diabetes and depression, and teenagers who are healthy.

WHY ARE YOU BEING ASKED TO BE IN THIS STUDY?
To be in this study, you must 1) be 13 through 17 years of age, 2) be able to speak and understand English, and 3) fit one of the following four categories: have type 1 diabetes only, have depressive symptoms only, have type 1 diabetes and depressive symptoms, be healthy. Eighty people (subjects) will be enrolled in this study locally.

WHAT ARE THE ALTERNATIVES TO BEING IN THIS STUDY?
This study does not provide treatment. If you need physical or mental healthcare, you should tell your parent/legal guardian to contact your doctor to discuss what would be right for you.

WHAT WILL YOU BE ASKED TO DO IN THIS STUDY?
Your participation in this study will last up to 2.5 hours and can be completed in one visit and one phonecall. The visit is described below.

Visit
This visit will last about 1.5-2 hours. During this visit you will complete tests of different types of memory, learning, and attention as well as complete a questionnaire that screens for depression. You may choose not to respond to any question that makes you feel uncomfortable or embarrassed. You will also be asked to fill out a brief demographic questionnaire that asks about your age, race/ethnicity, grade, gender, and diabetes-related questions if applicable. The results from the depression scale will be communicated to you at the end of this visit.
Phonecall
The results of the memory and attention tests will be communicated to you via a pre-arranged phonecall.

ARE THERE ANY RISKS?
One risk from participating in this study is a possible loss of confidentiality; if you tell the researcher about plans to harm yourself or others it is required by law that this information is reported. Another potential risk of participating in this study is that you may learn that you have depressive symptoms that you did not know about. There is also the risk of feeling uncomfortable about certain questions. However, you do not have to answer questions that make you uncomfortable.

ARE THERE ANY BENEFITS?
There may be no direct benefit to you by being in this study. However, you may learn about your memory and attention skills and use this information to improve your learning and study strategies. For example, a participant may learn that he is better at remembering things that he sees compared to things that he hears. Another potential benefit is the identification of depressive symptoms, if they exist, and referral for treatment if necessary. What the researchers find out from this study may help other people do future research on ways to help teenagers with diabetes and depression learn more easily and do better in school.

WILL INFORMATION FROM THIS STUDY BE KEPT CONFIDENTIAL?
Information about you will be stored in a locked file cabinet and/or computer files protected with a password. Information about you will be kept confidential to the extent of the law. People who have access to your information include the researchers and also representatives of regulatory agencies (including the University of Arizona Human Subjects Protection Program) who make sure that the study is being run correctly.

WILL I BE PAID TO BE IN THIS STUDY?
There is no cost to you for being in this study except your time. You will receive a $15 giftcard to i-tunes or Blockbuster or cash (your choice) for participating.

WHO CAN BE CONTACTED ABOUT THIS STUDY?
If you have any questions or concerns, you can call the Principal Investigator, Lauren Wheeler, B.S. at (520) 408-7099. If you have questions about your rights as a research subject you can call the University of Arizona Human Subjects Protection Program office at (520) 626-6721. If you have questions, complaints, or concerns about the research and cannot reach the Principal Investigator; or want to talk to someone other than the Investigator, you can call the University of Arizona Human Subjects Protection Program office. (If out of state use the toll-free number 1-866-278-1455.) If you would like to contact the Human Subjects Protection Program online (this can be anonymous), please visit http://www.irb.arizona.edu/contact/.

STATEMENT OF CONSENT
I confirm that the procedures of the study have been explained to me. I understand that I can refuse (say no) to be in this study. My doctors or parents cannot make me be in the study if I do not want to be in it. If I agree to be in the study but change my mind later, I can stop being in the study.
APPENDIX E : PARENT CONSENT FORM

PARENT/LEGAL GUARDIAN PERMISSION FORM

Project Title: A Study of the Neuropsychological Effects of Diabetes Comorbid with Depression in Adolescents

You are being asked to read this form so that you know about this research study. Federal regulations require that you know about the study and the risks involved. If you decide that you want your child (adolescent) to participate in this study, signing this form will say that you know about this study. If you decide you do not want your adolescent to participate, that is okay. There will be no penalty to you or your adolescent and your adolescent will not lose any benefit which s/he would normally have.

WHY IS THIS STUDY BEING DONE?
You have the choice for your adolescent to participate in this research project. The purpose of this project is to examine the relationship between diabetes, depression, memory, learning, and attention in adolescents. The ultimate goal is to gain information that will help us create better learning strategies for adolescents who have diabetes and depression.

WHY IS YOUR ADOLESCENT BEING ASKED TO BE IN THIS STUDY?
To be in this study, your adolescent must 1) be 13 through 17 years of age, 2) be able to speak and understand English, and 3) fit one of the following four categories: has type 1 diabetes only, has depressive symptoms only, has type 1 diabetes and depressive symptoms, is healthy. Eighty people (subjects) will be enrolled in this study locally.

WHAT ARE THE ALTERNATIVES TO BEING IN THIS STUDY?
This study does not provide treatment. If your adolescent needs a referral for physical or mental healthcare, you should contact your adolescent’s personal doctor to discuss what would be right for your adolescent.

WHAT WILL YOUR ADOLESCENT BE ASKED TO DO IN THIS STUDY?
Your adolescent’s participation in this study will last up to 2.5 hours and can be completed in one visit and one phonecall. The visit is described below.

Visit
This visit will last about 1.5-2 hours. During this visit your adolescent will complete tests of different types of memory, learning, and attention as well as complete a questionnaire
that screens for depression. Your adolescent may choose not to respond to any question that makes him/her feel uncomfortable or embarrassed. If your adolescent already completed the Beck Youth Inventories, Second Edition (BYI-II) as part of his/her participation in the study titled: Integrating Medical and Psychological Services For Adolescents with Diabetes, by signing this consent form you give permission for the principal investigator to access the BYI-II protocol from that study. Your adolescent will also be asked to fill out a brief demographic questionnaire that asks about your adolescent’s age, race/ethnicity, grade, gender, and diabetes-related questions if applicable. Your adolescent will be instructed to not write his/her name on the form and there will not be a way to link his/her responses to him/her. The results from the depression scale will be communicated to you at the end of this visit. If your adolescent has been identified as having elevated depressive symptoms and you choose to seek treatment, you will be provided names of local service providers who are covered by different local insurance plans, have sliding scale fees, or charge minimal cost. You will also have the opportunity to have any questions answered regarding these results.

Phonecall
The results of the memory and attention tests will be communicated to you via a pre-arranged phonecall.

ARE THERE ANY RISKS TO MY ADOLESCENT?
One risk from participating in this study is a possible loss of confidentiality; if your adolescent indicates immediate harm to self or others it is required by law that this information is reported. Another potential risk of participating in this study is that your adolescent may learn that he/she has depressive symptoms that had not been previously identified and could experience discomfort or distress. Related to this is the risk of feeling discomfort or distress from answering questions about emotional and behavioral issues that your adolescent experiences. However, your adolescent does not have to respond to questions that make him/her uncomfortable.

ARE THERE ANY BENEFITS TO MY ADOLESCENT?
There may be no direct benefit to your adolescent by being in this study. Possible benefits for your adolescent’s participation include verbal feedback regarding the results of the assessment. These findings may be used to improve his/her learning and study strategies. For example, a participant may learn that he is better at remembering information that he sees compared to information that he hears. Another potential benefit is the identification of depressive symptoms, if they exist, and referral for treatment if warranted. What the researchers find out from this study may help other people create interventions that improve cognitive functioning and academic success for adolescents who have diabetes and depressive symptoms. These findings will provide the basis for future research on evidence-based interventions with this population.

WILL INFORMATION FROM THIS STUDY BE KEPT CONFIDENTIAL?
Information about your adolescent will be stored in a locked file cabinet and/or computer files protected with a password. Information about your adolescent will be kept confidential to the extent of the law. People who have access to your adolescent’s information include the Principal...
Investigator and study personnel. In addition, representatives of regulatory agencies (including the University of Arizona Human Subjects Protection Program) may access your adolescent’s records to make sure the study is being run correctly and that information is collected properly. If there are any reports about this study, your adolescent’s name will not be in them. This consent form will be filed in an official area.

**WILL I OR MY ADOLESCENT BE PAID TO BE IN THIS STUDY?**
There is no cost to you or your adolescent for being in this study except your adolescent’s and your time. Your adolescent will receive a $15 giftcard to i-tunes or Blockbuster or cash for participating.

**WHO CAN BE CONTACTED ABOUT THIS STUDY?**
You or your adolescent can call the Principal Investigator to tell him/her about a concern or complaint about this research study. The Principal Investigator, Lauren Wheeler, B.S., can be called at (520) 408-7099. If you have questions about your adolescent’s rights as a research subject you or your adolescent may call the University of Arizona Human Subjects Protection Program office at (520) 626-6721. If you or your adolescent have questions, complaints, or concerns about the research and cannot reach the Principal Investigator; or want to talk to someone other than the Investigator, you or your adolescent may call the University of Arizona Human Subjects Protection Program office. (If out of state use the toll-free number 1-866-278-1455.) If you or your adolescent would like to contact the Human Subjects Protection Program via the web (this can be anonymous), please visit [http://www.irb.arizona.edu/contact/](http://www.irb.arizona.edu/contact/).

**RESEARCH RELATED INJURY**
Immediate and necessary care for side effects may not be provided without charge if you are injured because of participation in this research project. The University of Arizona will neither provide for the costs of further treatment beyond immediate necessary care nor provide monetary compensation for such injury. Side effects or harm are possible in any research program despite the use of high standards of care and could occur through no fault of your adolescent or the investigator involved. Known side effects have been described in this consent form. However, unforeseeable harm also may occur and require care. You do not give up any of your or your adolescent’s legal rights by signing this form. If you believe your adolescent has been injured because of the research or you are billed for medical care for injuries that you feel has been caused by the research, you should contact the Principal Investigator, Lauren Wheeler, B.S., at (520) 408-7099.

**STATEMENT OF CONSENT**
The procedures, risks, and benefits of this study have been told to me and I agree for my adolescent to be in this study and sign this form. My questions have been answered. I may ask more questions whenever I want. My adolescent can stop participating in this study at any time and there will be no bad feelings. My adolescent’s medical care will not change if s/he quits. The researcher can remove my adolescent from the study at any time and tell me why my adolescent has to stop. New information about this research study will be given to me/my adolescent as it is available. My adolescent and I do not give up any legal rights by signing this form. A copy of this signed consent form will be given to me.
INVESTIGATOR'S AFFIDAVIT:
Either I have or my agent has carefully explained to the subject the nature of the above project. I hereby certify that to the best of my knowledge the person who signed this consent form was informed of the nature, demands, benefits, and risks involved in his/her participation.

Signature of Presenter Date

Signature of Investigator Date
APPENDIX F: IRB APPROVAL FORMS

THE UNIVERSITY OF ARIZONA

Human Subjects Protection Program

1618 E. Helen St.,
P.O. Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://www.irb.arizona.edu

27 February 2009

Lauren Wheeler (Graduate Student)
Faculty Advisor: John E. Obrzut, PhD
Department of Special Education, Rehabilitation and School Psychology (SERSP)
PO Box 210069

RE: PROJECT NO. 09-0031-02 A Study of the Neuropsychological Effects of Diabetes Comorbid with Depression in Adolescents

Dear Ms. Wheeler:

We received your 27 February 2009 response to Committee letter and revised Project Review form for the above referenced project. All of the conditions as set out in Committee’s 24 February 2009 and 27 January 2009 letters (relevant to the 01/26/09 and 02/23/09 Full Board reviews) were addressed in the investigator’s 02/04/09 and 02/27/09 letters and the accompanying submitted revised materials. Therefore, approval for this subjects-at-risk project is granted an expiration date of 22 February 2010. Please make copies of the attached IRB stamped consent documents to consent your subjects. Note that approval of this project includes the following documents: Revised Project Review Form, Revised Advertisement version 02/04/09, Parent Guardian Permission Form version 02/04/09 and Adolescent Assent Form version 02/04/09.

The Institutional Review Board (IRB) of the University of Arizona has a current Federalwide Assurance of compliance, FWA00004218, which is on file with the Department of Health and Human Services and covers this activity.

Approval is granted with the understanding that no further changes or additions will be made either to the procedures followed or the consent form(s) used (copies of which we have on file) without the knowledge and approval of the Institutional Review Board. Any research related physical or psychological harm to any subject must also be reported to the appropriate committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Elaine G. Jones, PhD, RN, FNAP
Chair, IRB 2

EGJ/ssj
cc: Departmental/College Review Committee

Arizona’s First University – Since 1885
HSPP Correspondence Form

Date: 06/18/09
Investigator: Lauren Wheeler, Graduate Student
Advisor: John Ohnmitz, PhD
Project No./Title: 08-0031-02 A Study of the Neuropsychological Effects of Diabetes Comorbid with Depression in Adolescents
Current Period of Approval: 02/23/09 – 02/22/10

IRB Committee Information

☐ IRB1 – IRB00000231
☐ IRB2 – IRB00001751
☐ IRB3 – IRB00003012
☐ IRB4 – IRB00005448
☐ Administrative Action
FWA Number: FWA00004218

☐ Full Committee Review
☐ 1st review – Conditions met –
☐ Expedited Review – 06/18/09
☐ Facilitated Review –
☐ Administrative/Exempt Review –

Nature of Submission

☐ New Project
☐ Amendment
☐ Unanticipated Problem Involving Risks to Subjects or Others
☐ Response to IRB Committee
☐ Other (define):

☐ Continuing Review
☐ Protocol Deviation/Violation/Waiver
☐ Non-Compliance
☐ Not Applicable

Documents Reviewed Concurrently

☐ Request for Amendment Form – PI Initiated Changes (dated 06/01/09)

☐ Consenting Instruments:
  Parent/Legal Guardian Permission Form (version 06/01/09)
  Adolescent Assent Form (version 06/01/09)
  Re-consent: ☐ All ☐ Current Only ☐ Not Required

Description of Submission

Revised Parental Permission/Adolescent Assent form [Change the length of time needed to complete the research]; additional recruitment site [Family Services]; new/revised study documents [New Flyers 2]; no change amount of time needed for the research and indicate that compensation will be provided]

Reminders: Continuing Review materials should be submitted 30–45 days prior to the expiration date to obtain project re-approval

- Projects may be concluded or withdrawn at any time using the forms available at www.irb.arizona.edu
- No changes to a project may be made prior to IRB approval except to eliminate apparent immediate hazard to subjects.
- Original signed consent form must be stored in the designated departmental location determined by the Department Head.

Arizona’s First University – Since 1885

Form version: 06/11/09
<table>
<thead>
<tr>
<th>Committee Chair Determination</th>
<th>Additional Determination(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Approved as submitted</td>
<td></td>
</tr>
<tr>
<td>☐ Not Required</td>
<td></td>
</tr>
</tbody>
</table>

Thomas K. Park  
Co-Chair, IRB 2 Committee  
UA Institutional Review Board  

TKP-les  
cc: Departmental Review Chair
REFERENCES


Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention.

doi:10.1016/S0006-8993(97)00648-3

doi:10.2337/diacare.14.10.922

doi:10.1159/000069325

doi:10.1007/s00125-007-0615-2

doi:10.1016/S0022-3476(89)80642-0


[doi:10.2337/diacare.28.6.1431](https://doi.org/10.2337/diacare.28.6.1431)


Lunetta, M., Damanti, A. R., Fabbri, G., Lombardo, M., Di Mauro, M., & Mughini, L.


Manschot, S. M., Brands, A. M. A., van der Grond, J., Kessels, R. P. C., Algra, A.,


facts/index.aspx


hypoglycemia in youth with Type 1 diabetes. *Diabetes Care, 30*, 2331–2337. doi:10.2337/dc07-0351


Sarac, K., Alkinci, A., Alkan, A., Aslan, M., Baysal, T., & Ozcan, C. (2005). Brain metabolite changes on proton magnetic resonance spectroscopy in children with
[doi:10.1007/s00234-005-1387-3]


[doi:10.2337/diacare.19.11.1220]


[doi:10.1016/j.acn.2007.04.007]

Available from http://www.unl.edu/buros/


Archives of Clinical Neuropsychology, 21, 787-796.

doi:10.1016/j.acn.2006.06.014


doi:10.1037/0022-006X.64.6.1397