AN INVESTIGATION OF EXECUTIVE FUNCTION IMPAIRMENT IN

ADOLESCENTS AND ADULTS WITH DEPRESSION

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DEDICATION

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AN INVESTIGATION OF EXECUTIVE FUNCTION IMPAIRMENT IN ADOLESCENTS AND ADULTS WITH DEPRESSION

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Depressive illness has been associated with impairment in executive functioning (EF); however the relationship between neurocognitive dysfunction and depressive illness is not well understood. Similar deficits in EF in depressive illness have been demonstrated in the research among adults and adolescents, although the research among youth is limited. Additionally, no published reports were found that have examined developmental differences in EF among youth and adults with depression. The current pilot study sought to provide information on the influences of age and depressive illness status on EF, as well as the extent to which deficits in EF are evidenced in youngsters

with depression. An additional purpose of this study was to provide information on the utility of age-appropriate measures in assessing EF in youth.

Data were analyzed on 105 participants (depressed adolescents and depressed adults, and their healthy counterparts) on ten outcome measures of EF. The performance of all groups fell within the average range across all ten outcome measures; however, significant group differences emerged on several outcomes on the Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III COG). Additionally, adolescents with depression demonstrated a decreased performance across the majority of EF measures compared to their healthy counterparts, although these differences were not significant.

Results from the current study revealed a significantly lower performance among depressed adolescents compared to both depressed and healthy adults on tasks involving processing speed, interference control and sustained attention ability. This finding suggests that depressive illness during early life may have mild effects on select executive functions (EFs), such as those that remain underdeveloped in youth.

Results also revealed a decreased performance among both depressed and healthy adolescents compared to healthy adults on tasks involving planning ability, interference control or inhibition, and mental flexibility. This finding suggests that EF may be less reliable in youth, due to the ongoing maturation of this system in youngsters, and may improve with age. Finally, differences in performance in EF emerged only on the WJ-III COG, but not on other measures, which suggests that the WJ-III COG offers sensitivity in detecting developmental differences in EF among youth and adults.

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CHAPTER ONE
Introduction

Researchers have established that neuropsychological impairment is associated with adult depressive illness, with important implications related to deficits in executive functioning (EF) (Zakzanis, Leach, & Kaplan, 1998). The extent to which impaired EF is evidenced in depressive illness during the early years, however, remains unclear. Pediatric depression has only become recognized as a distinct clinical disorder within the past thirty years (Sohlberg, 1989), and the more recent research has suggested developmental and functional impairment associated with this disorder (Rao & Chen, 2009). Furthermore, depressive illness affects many youngsters, with prevalence estimates suggesting that up to 25% of all youth in the United States may experience a major depressive episode (MDE) by 18 years of age (Kessler, Avenevoli, & Merikangas, 2001). Additionally, the presence of at least one depressive symptom has been evidenced in up to 60% of all adolescents (Harrington & Clark, 1998).

Depression is now recognized as the most prevalent mental disorder (Kessler et al., 2005; Kessler & Walters, 1998). Furthermore, major depressive disorder (MDD) has been identified as the fourth leading cause of disability worldwide (Moussavi et al., 2007), and functional impairment associated with MDD and the cost to society have been compared to diseases such as cancer and cardiovascular disease (Kyte & Goodyer, 2008). Additionally, depressive illness with an early age of onset has been associated with greater illness severity (Zisook et al., 2007), and significant impairment in daily living (Kessler et al., 2001). Furthermore, a review by Rao and Chen (2009) suggests that the presence of depressive symptomatology during the early years may interfere with social,

cognitive and emotional development, and related difficulties have been shown to continue into adulthood (Rao, 2006).

In order to gain a better understanding of the correlates and changes that occur in depression, this area of research has flourished and has produced an extensive body of literature. The majority of research on neuropsychological impairment in depression has been derived from studies on middle-aged and elderly persons, with a more recent focus on young adulthood (Castaneda et al., 2008a). There remains, however, a gap in the literature on neuropsychological functioning in depressed youth. As a chronic disorder, implications of investigating EF impairment in adolescent depression are twofold, and are underscored by greater impairment in cognitive functioning associated with multiple episodes over the life course of individuals with an early age of onset (Burcusa & Iacono, 2007). From a clinical perspective, early treatment interventions may target cognitive, emotional and behavioral symptoms associated with impaired EF in depression, and improve prognostic outcomes. Secondly, information gleaned may further contribute to the literature on the identification of underlying brain regions involved in EF.

In addressing the question of the extent to which executive dysfunction is evidenced in depressed adolescents, three neuropsychological measures assessing different components of EF were used in the current study. These include two widely used measures, the Wisconsin Card Sorting Test (WCST; Berg, 1948; Heaton, 1981) and Trail Making Test – B (TMT-B; Reitan & Wolfson, 1985), as well as selected subtests from the Woodcock-Johnson III Tests of Cognitive Abilities – Third Edition (WJ-III COG; Woodcock, McGrew, & Mather, 2001). The WCST and TMT-B are traditionally used to assess cognitive flexibility and related functioning in attentional control, and the

WCST more specifically in planning and problem-solving abilities (Ravnkilde et al., 2002). The selected subtests from the WJ-III COG also yield information on cognitive flexibility, as well as other aspects of EF, including planning and interference control abilities [inhibition], and this measure has not previously been reported in the literature on depressed youth. The WJ-III COG is appropriate for school-aged individuals as well as adults (Mather & Woodcock, 2001), and a relative strength of this instrument is its inclusion of an Executive Processes Cluster (EPC), which increases reliability through the assessment of multiple components of EF (Mather & Woodcock, 2001).

This pilot study was conducted as part of a larger ongoing study on the examination of pathophysiological markers associated with onset and clinical course of depression. The current investigation examined possible developmental differences in EF associated with depressive illness among adolescents and adults. Additionally, the extent to which deficits in EF are evidenced among depressed adolescents in comparison to healthy adolescents was also examined. Furthermore, an additional intention of this study was to provide information on the utility of age- and developmentally-appropriate measures of EF in younger populations.

CHAPTER TWO
Review of the Literature

Major Depressive Disorder

MDD is characterized as an affective disorder, with cognitive aspects inherent within the disorder (DSM-IV-TR; American Psychiatric Association (APA), 2000), and the importance of cognitive disturbances in depression has been highlighted in the literature more recently (Hammar & Ardal, 2009). A DSM-IV diagnosis of MDD requires the presence of the following: (1) dysphoric mood, or in children, irritability (Kessler et al., 2001), or (2) decreased interest or lack of pleasure in daily activities [anhedonia]. Four concomitant symptoms of physical and/or cognitive changes are also mandatory. Physical symptoms include weight changes, fatigue or low energy, hypersomnia or insomnia, and psychomotor agitation or retardation. Cognitive symptoms include thoughts of worthlessness and/or inappropriate guilt, a diminished ability to think or concentrate, and recurrent thoughts of death or suicidal ideation. These symptoms must be present for at least two weeks and cause impairment in daily functioning in order to warrant a diagnosis of MDD (DSM-IV-TR; APA, 2000).

Clinical presentations of MDD share many of the same features in child, adolescent and adult populations (Kovacs, 1999; Lewinsohn, Pettit, Joiner, & Seeley, 2003; Ryan, 2001); however, certain developmental differences have been observed among these age groups. In a review on developmental correlates associated with adolescent depression, Rao and Chen (2009) reported that somatic complaints and

behavior problems are more common in children and adolescents than adults, and adolescents have a higher prevalence of hypersomnia. Additionally, melancholic and psychotic symptoms appear to occur less frequently in children as compared to adolescents and adults. Other researchers have suggested that impaired cognition has been strongly associated with adult depression (Castaneda et al., 2008a), although empirical support for cognitive deficits in youth is limited. Anecdotal reporting of difficulties in attention, concentration and problem-solving abilities among depressed youth, however, suggests cognitive deficits among this population (Anderson, Anderson, Jacobs, & Smith, 2008; Favre et al., 2009).

MDD is now recognized as a chronic illness (Rush, 2001), with similar rates of recurrence reported among youth and adults (Coryell et al., 1994; Hart, Craighead, & Craighead, 2001; Solomon et al., 2000). In younger populations, probabilities of developing subsequent episodes following recovery have been estimated at 40% by two years and 70% by five years (Avenoli & Steinberg, 2001; Lewinsohn, Clarke, Seeley, & Rohde, 1994; Rao, 2006), with a continuation of recurrence into adulthood for many of these youth (Dunn & Goodyer, 2006; Lewinsohn, Rohde, Klein, & Seeley, 1999; Rao, 2006). In adult depression, the risk of recurrence is highest within the first year following a first episode, and probabilities of 50% of recurrence within two years and 80% during the lifetime have been reported (Mueller et al., 1999).

Early-onset of depressive illness

Some researchers have suggested that depressive illness beginning during early life may be the most serious and severe form of mood disorder (Kessler et al., 2001). In

comparison to adult onset illness, implications of an early-onset include greater cognitive dysfunction (Castaneda et al., 2008a), which is likely due to the continuing development of the neural system in youngsters; greater "psychosocial scarring" (Rohde, Lewinsohn, & Seeley, 1994); increased rates of comorbidity (Rohde, Lewinsohn, & Seeley, 1991), and an increased risk for recurrence (Burcusa & Iacono, 2007). Additionally, the early teen years are associated with a heightened risk for developing a depressive disorder, with an increase in vulnerability continuing through late adolescence (Giaconia et al., 1994; Hankin et al., 1998; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Lifetime prevalence estimates have been reported to be 15% to 25% by late adolescence (Giaconia, et al., 1994; Hankin et al., 1998; Weissman et al., 1997).

Functional impairment associated with depression

Impairment has been identified in various functional domains in depressive illness and is evidenced across the life span. Among depressed youth, the research has demonstrated poorer academic performance and achievement, difficulties in interpersonal relationships, higher rates of school drop-outs, increased frequency of suicidal behaviors, delinquency, and substance use (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996; Merry, McDowell, Hetrick, Bir, & Muller, 2004). Among depressed adult populations, impairment has been evidenced in disrupted occupational functioning, difficulties in family and social relationships, overall poorer quality of life, and disability (Hammar & Ardal, 2009; Papakostas et al., 2004). Furthermore, greater functional impairment has been observed in those adults whose depressive illness began at an early age (Zisook et al., 2007). For example, in a review of the literature, Rao (2006) reported increased rates

of criminal behavior, dysfunctional interpersonal relationships, early pregnancy, lower educational attainment, poor occupational functioning, unemployment and suicidal behavior among these adults.

Cognitive impairment associated with depression

Studies examining cognitive symptomatology in depressive illness have identified specific areas of impairment, including deficits in EF, reduced attention and memory, slower processing speed, and negative cognitive biases in one's view of the self and others, and the future (Beck, Rush, Shaw, & Emery, 1979; Kyte & Goodyer, 2008; Thomas et al., 2009). Furthermore, an association between cognitive functioning and mood has been suggested, (Kyte & Goodyer, 2008), with cognitive impairment negatively related to functional recovery from depressive illness (Jaeger, Berns, Uzelac, & Davis-Conway, 2006).

Neural Structures Implicated in Depressive Illness

Brain structures that have been implicated in the pathophysiology of depression include the prefrontal cortex (PFC) and limbic system (Fossati, Ergis, & Allilaire, 2002; Mayberg et al., 1999). The limbic system is comprised of subcortical neural structures located within the medial temporal lobe, including the hippocampus and amygdala, hypothalamus, anterior thalamus, cingulate gyrus, orbitofrontal cortex (OFC), and basal ganglia (Gazzinga, Ivry, & Mangum, 2009). The PFC is primarily responsible for higher-level cognitive functions that control and direct lower-level brain functions (Stuss

& Levine, 2002). The limbic system is primarily involved in the processing of emotional stimuli and organization of emotional expression (Drevets, Price, & Furey, 2008). More recently, neural networks connecting frontal areas to limbic and medial temporal regions, specifically the anterior cingulate cortex (ACC) and medial frontal regions (Tekin & Cummings, 2002), have been implicated in disturbances observed in cognitive processing in depression (Mayberg et al., 1999; Porter, Bourke, & Gallagher, 2007).

The PFC is comprised of three main regions, including the dorsolateral prefrontal cortex (DLPFC), OFC, and the ACC and medial frontal regions (Gazzinga et al., 2009). These frontal areas are involved in both cognitive and emotional processing and have been described as the "most commonly and strongly related [brain structures] to emotional and social behavior" (Stuss & Levine, 2002, p. 417). The DLPFC serves a primary role in EF and is part of a neural system originating from the hippocampus (Stuss & Levine, 2002). More specifically, the DLPFC is involved in spatial and conceptual reasoning (Stuss & Levine, 2002), as well as decision-making and response selection (Gazzinga et al., 2009). The OFC system, which connects the frontal "monitoring" circuitry to the limbic system, has been recognized as contributing to emotional lability and behavioral inhibition (Tekin & Cummings, 2002). The ACC has been associated with selective attention and mood regulation, as well as the cognitive distortions and maladaptive thought processes commonly observed in depressive illness (Serra-Mestres & Ring, 2002).

The role of the limbic system in emotional processing and the organization of emotional expression has been a focus of the depression research. Particularly, significant attention has been paid to the hippocampus and amygdala, and the interaction between

them (Phelps, 2004). The amygdala serves a primary role in the regulation of affect, specifically in the processing of socioemotional stimuli and fear conditioning (Gazzinga et al., 2009; Rosso et al., 2005). The hippocampus is central to learning, and is essential for the consolidation and initial storage of information for autobiographical, or episodic, memories (Gazzinga et al., 2009). Episodic memories are those that specifically relate to the self and one's experiences, as compared to semantic memory, which involves the storage of factual information which is not personally relevant (Gazzinga et al, 2009). Furthermore, the interplay between the amygdala and the hippocampus is of particular interest in the depression literature. Phelps (2004) suggested that "…memories for emotional events have a persistence and vividness that other memories seem to lack….due to the amygdala's influence on the encoding and storage of hippocampal-dependent memories" (p. 198).

Neurobiological correlates of cognitive impairment in depression

Researchers have identified both structural and functional abnormalities of the PFC that are implicated in neuropsychological dysfunction in depression. For example, lesion studies reveal that depression is exhibited in patients with lesions of the frontal cortex and caudate nucleus (Tekin & Cummings, 2002). Post-mortem studies have shown reduced cortical thickness, neuronal size and neuronal and glial densities in depressed individuals (Rajkowska et al., 1999). Regarding functional impairment, Rogers et al. (2004) found reduced metabolic activity of the DLPFC and ACC, and hyperactivity of the OFC in depressed individuals. Additionally, in their review of the literature, Holmes and Pizzagalli (2008) reported abnormal activation in the PFC and the ACC in depressed

subjects during tasks of conflict monitoring. Finally, Drevets and colleagues (2008) have suggested an association between neural networks involving the medial prefrontal cortex (MPFC) and limbic structures in mood-related disturbances of cognitive performance and emotional processing, as well as neurotransmission, autonomic regulation and neuroendocrine responses.

Limbic structures associated with cognitive impairment in depression

The implications of structural changes in the limbic system in depression are of significance, especially considering the primary role of these neural structures in affect regulation and the effects of dysphoric mood on cognition (Porter et al., 2007). Much of the research on these neurobiological substrates of emotional processing in depression has focused on the hippocampus and amygdala, as these brain structures have been found to be compromised in depressive illness. For example, reduced hippocampal volumes have been identified in both depressed adults (Campbell, Marriott, Nahmias, & MacQueen, 2004; McKinnon, Yucel, Nazorov, & MacQueen, 2004) and depressed youth (Campbell et al., 2004; MacMaster et al., 2008; McKinnon et al., 2004; Rao et al., 2010).

In the adult literature, factors that appear to mediate hippocampal atrophy in depression include longer duration of illness, and greater number of depressive episodes (Campbell et al., 2004; Frodl et al, 2008; Kronmuller et al., 2008; MacQueen et al., 2003; McKinnon, et al., 2004; Porter et al., 2007; Sheline, Sanghavi, Mintun, & Gado, 1999); although, these findings have not been replicated in youth (Campbell et al., 2004). Early-life adversity, however, has been associated with reduced hippocampal volumes in depressed adolescents. In a recent investigation, Rao et al. (2010) found smaller

hippocampal volumes in both depressed adolescents and healthy adolescents at high-risk for developing depressive disorders, with smaller hippocampal volumes related to increased levels of early-life adversity.

The research on changes in amygdala volumes in adult depression has produced mixed results. For example, a review of the literature reveals that some researchers have found enlarged amygdala volumes whereas other studies have shown reduced or no change in amygdala volumes (Rosso et al., 2005). Mixed findings have also been reported in the literature on youth, with both reduced amygdala volumes (Rosso et al., 2005) and greater amygdala volumes found (MacMillan et al., 2003).

Neurochemical correlates associated with cognitive impairment in depression

Hormonal changes within the hypothalamic-pituitary-adrenal (HPA) axis have been associated with cognitive impairment in depression (Porter et al., 2007). More specifically, excessive cortisol secretion has been directly related to hippocampal atrophy and neuropsychological dysfunction in depressed adult populations (Gomez, Fleming, Keller, Flores, & Schatzberg, 2004). More recently, hypercortisolemia has also been observed in depressed adolescent populations as well as in children (Lopez-Duran, Kovacs, & George, 2009); however, hypercortisolemia may be less common in children with an increase evidenced during adolescence, and becoming more robust in adults (Lopez-Duran et al., 2009).

Executive Functions

The EFs comprise one of several general domains of cognition. Others include attention, memory, learning, language, visuo-spatial processing and psychomotor speed (Geva, 2002; Hammar & Ardal, 2009). The EFs refer to a collection of diffuse, higher-order cognitive processes that are essential in self-control and the ability to carry out goal-directed behaviors (Denckla, 1994; Lezak, 1995). Various descriptions have been used in the literature to define EF, including broad cognitive domains of volition, planning, purposive action and effective performance (Lezak, 1995). The EFs are also commonly described qualitatively, as distinct cognitive processes including 1) behavior initiation, 2) inhibition of competing actions or stimuli, 3) selection of relevant task goals, 4) planning and organizing a means to solve complex problems, 5) maintaining flexibility in shifting problem-solving strategies when necessary, and 6) monitoring and evaluating behavior (Roth, Isquith, & Gioia, 2005, p.1).

Executive processes are essential in the implementation of cognitive, emotional and behavioral functions, especially when employing problem-solving strategies (Roth et al., 2005). For example, when carrying out a plan of action to achieve a desired goal, behavior must be effectively directed (Gazzinga et al. 2009), and Gazzinga and colleagues have described this cognitive process as constituting three steps. These include: 1) identifying a goal and developing subgoals; 2) considering possible consequences when choosing among goals, and 3) identifying requirements for reaching the goal.

The performance of EF relies on working memory (WM) (Denckla, 1994). Baddeley (1986) described WM as the "central executive" in the information processing system because WM "supervises" the integration of incoming information with relevant long-term memories, and temporarily stores, codes and manipulates information. The storage of incoming sensory information in short-term memory is ascribed to two sub-component systems of WM, including the phonological loop for acoustic stimuli and the visuospatial sketchpad for visual input. In depressive illness, WM has been shown to be compromised (Egeland et al., 2003; Naismith et al., 2003; Rose & Ebmeier, 2006; Taylor Tavares et al., 2007), whereby inefficient processing of this system can result in excessive rumination (James, Reichelt, Carlsonn, & McAnaney, 2008). Rumination in depressed individuals has been associated with poor problem-solving abilities (Lyubomirsky & Nolen-Hoeksema, 1995), specifically manifested in greater risk-taking and maladaptive behaviors during problem-solving (Nolen-Hoeksema & Morrow, 1991).

Developmental Differences in EF

The EFs are primarily associated with frontal lobe functioning (Denckla, 1994), and mature along a protracted course in accordance with the gradual development of the frontal brain regions (Denckla, 1994). Development of these brain structures and associated cognitive abilities originate during infancy and continue into the fourth decade of life (Denckla, 1994). Studies utilizing the WCST in child and adolescent populations have demonstrated developmental trajectories of EF, in which EF changes in accordance with age trajectories (Rosselli & Ardila, 1993).

The EFs reach full maturational levels by mid adulthood, although certain EFs have been shown to reach maturity earlier on, specifically during the adolescent years (Anderson et al., 2008). For example verbal fluency, motor sequencing, planning skills, and cognitive flexibility have been shown to be fully developed by early adolescence and goal-setting abilities by late adolescence (Anderson et al., 2008). Additionally, Kyte and Goodyer (2008) reported that pre-pubertal children have demonstrated capabilities in decision-making, memory and problem-solving. Furthermore, these researchers, among others, have suggested that children as young as eight years of age are developmentally capable of experiencing the negative biases and distortions in thoughts commonly found in depressed adults (Kyte & Goodyer, 2008; Timbremont, Braet, Bosmans, & Van Vlierberghe, 2008). In contrast, WM appears to have an extended developmental course, beginning during the preschool years and reaching mature levels in early adulthood (Anderson et al., 2008).

Measures of EF

Three general domains of EF are commonly assessed in children and adolescents, which include attentional control, goal-setting, and cognitive flexibility (Anderson et al. 2008), and numerous measures have become available to assess EF in youngsters. For example, the most widely utilized measures of EF in youth include the following: the Trail Making Test-A (TMT-A) Child's Version for attentional control; Test of Everyday Attention for Children (TEA-Ch), Complex Figure of Rey (CFR) and Tower of London (TOL) for goal-setting; and the Controlled Oral Word Association Test (COWAT), WCST, Stroop Color Word Interference Test (SCWIT), and the Category Test (CT) for cognitive

flexibility (Anderson et al., 2008). Additionally, although some of the aforementioned measures were developed specifically for adults, for example the WCST (Heaton et al., 1993), normative data have become available on child and adolescent populations and may be appropriate in assessing neuropsychological functioning in younger populations (Anderson et al., 2008)

Some of the most commonly utilized neuropsychological instruments in depressed adult populations, reported in a review by Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, and Lonnqvist (2008b), include the following: batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Luria-Nebraska Neuropsychological Battery (LNNB) that measure various components of cognition; the California Verbal Learning Test II (CVLT) and Rey Auditory Verbal Learning Test (RAVLT) in the assessment of verbal memory and learning; and, measures of cognitive flexibility which include the TMT-B, WCST, SCWIT, and COWAT.

Impairment in EF Associated with Adult Depression

Numerous studies have been published on neurocognitive functioning in adult depression, with many revealing deficits in EF (for reviews, see Austin, Mitchell, & Goodwin 2001; Castaneda et al., 2008b; Hammar & Ardal, 2009; McClintock, Husain, Greer, & Cullum, 2010). Additionally, researchers have identified certain factors that appear to mediate EF impairment in depression, which include illness severity (Castaneda et al., 2008a; McDerrmott & Ebmeier, 2009), and stage and length of illness (Grant, Thase, & Sweeney, 2001; Hammar & Ardal, 2009); however, the findings are mixed. For

example, in their review of the literature, Austin and colleagues (2001) identified nine studies that found no correlation between depression severity and neurocognitive tasks, and 11 studies revealing an association. Additionally, due to the extensive literature on cognitive functioning in depressive illness in adults, and for the purpose of the current study, recently published reviews on EF impairment in adult depression will be further described, with the exception of one study on young adulthood, and a greater focus will be placed on specific studies of EF impairment in depressed youth.

Hammar and Ardal (2009) conducted a review of studies published within the past ten years on several domains of cognitive functioning in the acute phase of depressive illness, including EF, attention, memory, and psychomotor speed. Of the 17 studies reviewed specifically on EF, deficits in EF were identified among the depressed samples in 13 studies, specifically in mental flexibility, behavior inhibition, problem-solving and planning, verbal fluency, and working memory. Additionally, four studies reported normal performance on measures of EF among the depressed samples. These researchers concluded that there is substantial evidence suggestive of EF impairment in adult depression during the acute phase of illness.

In a review of the literature on depression in young adulthood, specifically those individuals between the ages of 18 to 51 years, Castaneda et al. (2008b) identified seven studies investigating EF impairment among this population. Although sampling methodology varied among the studies, impairment in EF was evidenced across all studies. The majority of these studies utilized commonly employed measures of EF (i.e., WCST, SCWIT, TMT-B), which primarily assess cognitive flexibility. Additionally, one of the studies (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999) employed additional

measures, including the Delis Test, which is a more recently developed card sorting test, as well as Verbal Fluency, and found impairment in concept formation and initiation ability among the depressed group. Based on these outcomes, Castaneda and colleagues (2008b) suggested that impairment in EF is a significant problem among this age group and that "executive dysfunction appears to be a key factor of MDD in young adulthood" (p. 17). Furthermore, these authors have suggested a relationship between impairment in EF and depression severity, with young adults with psychotic depression showing greater executive dysfunction than those without psychotic depressive illness.

Finally, Grant et al. (2001) examined cognitive disturbances in ambulatory, non-chronic young adults with MDD. Their sample was comprised of 123 outpatients of whom none of the participants had experienced a depressive episode for longer than 24 months. These investigators found evidence of mild impairment in one task of problem-solving strategies and mental flexibility among participants; however, they were unable to identify any pattern of dysfunction across multiple tasks. They concluded that depression alone does not appear to account for deficits in EF in young adults, but that level of impairment may be related to severity of illness.

Limitations of the Adult Literature

Although executive dysfunction has been widely identified in adults with depressive illness, the results are mixed, and this appears to be partially explained by the heterogeneity in sampling procedures across studies (McClintock et al., 2010). Some of these methodological differences across samples include inpatient vs. outpatient status; age of onset; stage and severity of illness; medication effects; and, comorbidity.

Furthermore, various neuropsychological instruments have been utilized in the assessment of different components of EF, which further limits the identification of any conclusive neuropsychological profile of adult depressive illness (McClintock et al., 2010).

Impairment in EF Associated with Depressive Illness in Youth

The extent to which EF impairment is evidenced during the early years in depressive illness remains elusive, and the paucity of research in this area appears to be due to several factors. For example, some researchers suggest that depression remains undetected and untreated in this age group (Favre et al., 2009). Emslie (2008) recently reported that less than half of all depressed children and adolescents ever receive treatment for depression. Additionally, some of the neurobiological developmental models have suggested that due to the continuing development of the PFC during childhood and adolescence, EF abilities may remain developmentally immature in youth and not fully accessible to empirical investigation (Johnson, Blum, & Giedd, 2009; Kyte, Goodyer, & Sahakian, 2005). Finally, some of the commonly used neuropsychological instruments to assess EF have been developed for adults (Anderson et al., 2008; Usher, 1999). Although normative data are available for many of these measures on child and adolescent populations, some researchers have suggested that these measures may lack adequate sensitivity in detecting developmental differences in EF, or may measure different aspects of EF in youth compared to adults (Anderson et al., 2008).

Nevertheless, empirical support suggesting impairment in EF in depressed youth has recently appeared in the literature. Specifically, deficits have been reported in cognitive flexibility, behavioral inhibition, decision-making, and spatial WM within this population (Kyte et al., 2005; Matthews, Coghill, & Rhodes, 2008; Wilkinson & Goodyer, 2006). To date, four published studies specifically examining EF impairment in depressive illness in youngsters can be found in the literature. In terms of the research on depressive illness in youth, the descriptive term "youth" has not been well defined (Rao & Chen, 2009). Hence, in order to provide a better understanding of the developmental profiles of individuals under investigation, the current study will use the term "youth" in the following discussion to indicate both children and adolescents, specifically individuals ranging in age from eight to 17 years. Additionally, in the majority of studies published on depression in youngsters, chronological age is used to make distinctions between children and adolescents, with childhood including individuals 12 years of age and younger, and adolescents including those individuals between 13 and 18 years of age (Rao & Chen, 2009).

Favre et al. (2009) recently examined impairment in EF and possible relationships between depression severity and impaired EF in depressed children and adolescents. The depressed group was comprised of 39 participants, with 24 age-matched healthy participants in the control group. All participants were between the ages of 8 and 17 years. Among the depressed group, 21 had comorbid diagnoses, consisting of attention-deficit/hyperactivity disorder (ADHD), dysthymia, oppositional-defiant disorder, and generalized anxiety disorder. All participants were medication free for at least two weeks prior to the study. Measures used to assess EF included the WCST,

TMT-B, COWAT, and SCWIT, and the Children's Depression Rating Scale-Revised (CDRS-R) was used to measure depression severity. Results of the study indicated no significant differences between the depressed and control groups on any measures of EF. Additionally, no relationships were reported between depression severity and EF impairment.

Matthews et al. (2008) investigated the effects of early-onset depression on impairment in EF and memory among female adolescents. All participants were between the ages of 12 and 16 years, with 14 in the depressed group diagnosed with moderate or severe depression, and 14 gender and age-matched healthy control subjects. Among the depressed group, none had any history of medication treatment for MDD. Assessments included nine subtests from the CANTAB, specifically assessing WM, planning, visual memory and attention. Testing revealed no differences between groups on most tasks of EF. However, differences were found in spatial WM, with poorer performance observed in the depressed group.

Wilkinson and Goodyer (2006) examined cognitive flexibility and the effects of mood-related ruminations on performance speed of shifting cognitive sets in youth with depression. Study participants included 40 depressed adolescents, 20 of whom were currently taking anti-depressant medication, and 38 age and gender-matched healthy control subjects. All participants were between 11 and 17 years of age. Several areas of cognition were measured in the study, including attentional control and set-shifting abilities, selective and sustained attention, and rumination severity. Assessment of cognitive flexibility, attentional control and selective attention consisted of five subtests from the TEA-Ch. Rumination severity was measured by the Responses to Depression

Questionnaire. Results revealed slower performance in attentional shifting in the depressed group, with a trend evidenced in greater errors in attentional switching tasks. However, slower shifting speed was not accounted for by mood-related ruminations.

Kyte et al. (2005) investigated EF deficits in first episode depression in adolescents. Specific EF deficits were examined, including attentional flexibility, behavioral inhibition, and decision-making. The depressed group was comprised of 30 adolescents, with 49 adolescents in the control group. The mean age of participants was 15 years. Among the depressed group, 18 had comorbid psychiatric diagnoses, including ADHD, anxiety disorders, obsessive-compulsive disorder, substance abuse, oppositional-defiant disorder, conduct disorder and posttraumatic stress disorder. Additionally, three participants in the depressed group were currently taking antidepressant medication, and five participants had past histories of medication treatment for depression. Three subtests from the CANTAB were used to assess EF. Results revealed no differences in cognitive flexibility between the depressed and non-depressed groups, although differences in behavioral inhibition and affective responses were observed. The depressed group exhibited greater attention towards sad stimuli, as well as impairment in decision-making tasks which was evidenced by more impulsive responding in decision-making.

Limitations of the Literature on Depressed Youth

Consistent with the adult literature, mixed outcomes on EF deficits in depressed youth have been reported. In addition to methodological differences in sampling procedures, modest sample sizes may also pose limitations on the interpretation of results. Differences identified among the aforementioned study samples include gender, length of

illness, medication status and comorbidity. Assessment measures of EF also varied across studies. For example, one study employed the WCST, TMT, COWAT, and the SCWIT (Favre, et al., 2009); two studies utilized different subtests from the CANTAB, with the exception of one subtest (Kyte & Goodyer, 2008; Matthews et al., 2008), and subtests from the TEA-Ch were used in one study (Wilkinson & Goodyer, 2006).

A Comparison of EF Impairment in Adults and Youth with Depression

Similar deficits in EF have been demonstrated in the research among adults and youth with depression, including deficits in cognitive flexibility (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Naismith, et al., 2003; Wilkinson & Goodyer, 2006); behavioral inhibition (Den Hartog, Derix, Van Bemmel, Kremer & Jolles, 2003; Gohier et al., 2009; Kyte et al., 2005; Markela-Lerenc, Kaiser, Fiedler, Weisbrod, & Mundt, 2006, and WM (Egeland et al., 2003; Matthews et al., 2008; Rose & Ebmeier, 2006). However, the research on EF in depressed youngsters is limited, and additional research is warranted in further investigating this phenomenon in this age group. Of the four studies reviewed on youth, one study revealed no impairment in EF in the depressed group, and three studies revealed only selective impairment, with no consistent pattern of deficits shown across multiple aspects of EF among depressed samples.

In considering possible developmental differences between depressed youth and adults on impaired executive processing, it is possible that age may play a role in moderating the effects of depressive illness on EF deficits. However, the direction of this potential moderating effect is unclear. For example, some researchers have suggested that

recurrent depressive episodes may have a neurotoxic effect on neural structures over time, which may help explain the observed executive dysfunction in adult depression (Burt, Prudic, Peyser, Clark, & Sackeim, 2000; Grant et al., 2001). This notion is further supported by empirical evidence suggesting that an early-onset of depressive illness has been associated with greater cognitive dysfunction in adulthood (Castaneda et al., 2008a). It is also possible however, that depressive illness during the early years may have a more critical impact on the developing frontal brain areas as well as the maturing EFs, as these neural structures and systems may be more vulnerable to impairment in cognitive functioning in youth.

Purpose of Study

In order to gain a better understanding of developmental differences in EF in depressive illness, the current study sought to address this concern by comparing performances of youth and adults with depression on several measures of EF. Additionally, no studies were found in the literature comparing these two age groups on EF in depressive illness. This information will be advantageous in improving upon the research on the differences in neuropsychological profiles of executive dysfunction associated with depression in adolescents and adults. A second aim of this study was to investigate the extent to which impairment in EF is evidenced in youth with depression. The relationship between depression and EF impairment in youth remains inconclusive, and the aforementioned studies have produced mixed results. In further addressing this question, three measures of neuropsychological functioning, the WCST, TMT-B, and WJ-III COG were used in

the current study. Two of these measures, the WCST and TMT-B, are widely used to assess cognitive flexibility, and studies utilizing these measures in the literature on adult depression have revealed deficits in EF. In contrast, the previous study employing these measures among youth with depression reported no impairment in EF. Additionally, the WJ-III COG will yield information on cognitive flexibility, as well as strategic planning or problem-solving abilities, interference control, and sustained attention (Mather & Woodcock, 2001).

The inclusion of the WJ-III COG in the current study was intended to provide additional information on the use of age- and developmentally-appropriate measures of EF in younger populations. This will be the first known study to use this measure in the investigation of EF in depressed youth. Additionally, knowledge gained on the utility of the WJ-III COG in the current study may be beneficial for future studies and clinical practice, for example, in choosing among instruments to use in assessing neuropsychological functioning among youth.

Hypotheses

Hypothesis 1

The adolescent depressed group will exhibit greater impairment than the adolescent control group in EF as assessed by the WJ-III COG; the adult depressed group will exhibit greater impairment than the adult control group in EF as assessed by the WJ-III COG.

Hypothesis 2

The adolescent depressed group will exhibit no differences compared to the adolescent control group in EF as assessed by the WCST; the adult depressed group will exhibit greater impairment than the adult control group in EF as assessed by the WCST.

Hypothesis 3

The adolescent depressed group will exhibit no differences compared to the adolescent control group in EF as assessed by the TMT-B; the adult depressed group will exhibit greater impairment than the adult control group in EF as assessed by the TMT-B.

CHAPTER THREE
Methodology

Participants

Data were utilized from 105 volunteers who were part of a larger ongoing study on the pathophysiological markers associated with onset and clinical course of depression, conducted by the Adolescent Mood and Addictive Disorders Research Program at The University of Texas Southwestern Medical Center at Dallas. Recruitment methods for the larger study included advertisements in local newspapers, flyers, and local clinic and community referrals. Participants included adolescent volunteers, from 12 through 17 years of age, and adult volunteers between the ages of 18 and 50 years. All participants were compensated for travel expenses and participation in the study.

Procedure

All volunteers were required to complete an initial phone screen to determine general eligibility requirements for the larger, ongoing study. Questions asked included the presence of current and past symptoms of depression, as well as history of psychopathology. Based on the phone screen, those volunteers who appeared appropriate for the study were scheduled to come to the laboratory for an initial evaluation. Those who did not appear appropriate for the study were referred for other research studies, and

were also provided with information on community resources from which to seek treatment.

All volunteers presenting to the laboratory were required to sign an IRB approved consent/assent form and were informed of, and provided with information on HIPAA regulations before initiating any clinical interviews. For those participants under 18 years of age, a parent or legal guardian's informed consent was also obtained. Following the consenting procedure, a diagnostic interview was given to all volunteers to ascertain the presence or absence of depression and other psychiatric disorders. Participants enrolled into the depressed group were required to meet DSM-IV criteria for a current or past, non-psychotic major depressive disorder (American Psychiatric Association, 1994). Additionally, healthy participants had no current or prior history of any psychiatric diagnoses in themselves or in their first-degree relatives.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Rao, & Ryan, 1997) was administered to all participants under 18 years of age, as well as a parent. The Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN; First, Spitzer, Williams, & Gibbons, 1995) was given to all participants 18 years of age and older. Additionally, all control participants, or a parent for those individuals under 18 years of age, were administered the Family History-Research Diagnostic Criteria (FH-RDC; Andreasen, Endicott, Spitzer, & Winokur, 1977) to assess psychopathology in self and first-degree relatives.

Following the diagnostic interview, eligible participants were enrolled into the larger ongoing study and were scheduled to complete a physical exam in order to check the participant's health status. The physical exam included obtaining a blood sample and urine sample, as well as a brief physical exam and electrocardiogram. Following completion of the physical exam, the participant was scheduled for neuropsychological testing.

Neuropsychological measures used in the current study to assess EF were part of a larger test battery. Additionally, two subtests were administered from the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2004), or the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) in order to compare general intellectual abilities between the adolescent groups (depressed vs. controls) and between the adult groups (depressed vs. controls), and also serve as a possible covariate. Subtests from the WISC-IV were administered to participants who were 15 years of age or younger, and subtests from the WAIS-III were given to participants 16 years of age and above.

The following neuropsychological battery was administered to participants between the ages of 12 and 14 years in the order listed: WJ-III COG Concept Formation, Planning, and Pair Cancellation, TMT-B (Children's Version), WISC-IV Vocabulary and Block Design, and the WCST. Individuals 15 years of age completed a similar battery, except that the TMT-B (Adult Version) was used in replacement of the TMT-B (Children's Version). Participants who were 16 years of age and older completed the following assessment battery in the order listed: WJ-III COG Concept Formation,

Planning, and Pair Cancellation, TMT-B (Adult Version), WAIS-III Vocabulary and Block Design, and the WCST.

Instruments and Outcome Measures

The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)

The K-SADS-PL is a semi-structured interview designed to ascertain present and lifetime history of psychiatric illness in children and adolescents according to the DSM-IV criteria (Kaufman et al., 1997). Probes and objective criteria are provided for individual symptoms at both diagnostic threshold and sub-threshold levels. The K-SADS-PL was administered separately to the adolescent and parent, and both were re-interviewed when necessary to resolve any discrepancies. Summary scores were computed on the information obtained from both informants. Inter-rater and test-retest reliability have been established, as well as convergent and discriminant validity (Kaufman et al., 1997).

Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID – I/P W/ PSY SCREEN)

The SCID-I/P W/ PSY SCREEN is a semi-structured diagnostic interview that assesses a broad range of DSM-IV-TR Axis I disorders. Information is obtained on past and current symptomatology within a structured, hierarchical decision-tree format, which directs the clinician in determining diagnoses or rule-out criteria (First et al., 1997). Research studies on reliability and validity of the SCID report high inter-rater reliability, and moderate

test-retest reliability for current and lifetime disorders (Rogers, 2001). Moderate concurrent validity has also been established (Rogers, 2001).

Family History-Research Diagnostic Criteria (FH-RDC)

The FH-RDC is a semi-structured instrument for the evaluation of psychiatric disorders in family members. The FH-RDC is sensitive for obtaining information from knowledgeable relatives (Thompson, Orvaschel, Prusoff, & Kidd, 1982). The FH-RDC was administered to the parent of adolescent participants in order to assess psychopathology in self, spouse and offspring, and to determine eligibility criteria for normal controls. Additionally, those participants who were 18 years of age and older provided diagnostic information on their first-degree relatives.

Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)

The WISC-IV is one of the most well known and widely used measures in assessing general intellectual functioning in children and adolescents between the ages of 6 years and16 years and 11 months (Christie, 2005). The WISC-IV is comprised of 10 core and 3 supplemental subtests, yielding composite scores of full scale IQ (FSIQ) and four factor index scores (Wechsler, 2003). Index scores are based on clusters of specific areas of cognitive functioning, including verbal comprehension (VCI), perceptual reasoning (PRI), WM (WMI), and processing speed (PSI) (Wechsler, 2003). Raw scores obtained for each of the 10 subtests are converted into age-normed scaled scores. Scaled scores have a mean of 10 and a standard deviation of 3. Summed scaled scores are converted

into standard scores to obtain FSIQ and index scores. Standard scores have a mean of 100 and a standard deviation of 15. The WISC-IV is a reliable and valid instrument (Wechsler et al., 2004). Test-retest reliability and inter-rater reliability have been established for FSIQ (r =.93 and r = .98 to .99, respectively). Internal consistency for FSIQ and index scores is very high, ranging from r = .88 to r = .97 (Wechsler et al., 2004).

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)

The WAIS-III is considered the gold standard of measures of intellectual abilities for adults (Favre et al., 2009). The WAIS-III is an appropriate instrument to be used with individuals between the ages of 16 years through 89 years (Wechsler, 1997). The WAIS-III yields three composite IQ scores, including FSIQ, Verbal IQ (VIQ) and Performance IQ (PIQ), and four factor index scores. Similar to the WISC-IV, the four index scores include VCI, PRI, WMI, and PSI. Inter-rater and test-retest reliability for FSIQ are very high, with correlations averaging in the high .90s, and r = .96, respectively (Wechsler, 2002). Convergent and discriminant validity have also been established (Wechsler, 2002). Although a new version of the WAIS is now available, the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV), the current study will continue to utilize the WAIS-III in order to maintain consistency among the study measures used.

The current study used estimated FSIQ scores obtained from both the WAIS-III and WISC-IV. Estimated FSIQ scores were used to compare general intellectual functioning between groups and to serve as a possible covariate. Estimated FSIQ scores can be derived from the two subtests of Vocabulary and Block Design (Ringe, Saine,

Lacritz, Hynan, & Cullum, 2002; Sattler & Dumont, 2004). The Vocabulary subtest assesses acquired knowledge and general fund of information, with scores based on the examinee's ability to define words that are presented both orally and visually (Wechsler, 2002). Block Design is a broad measure of visual intelligence, specifically in perceptual organization, synthesis and analytic strategies (Wechsler, 2002). The Block Design subtest involves the reproduction of models using blocks in accordance with a visual stimulus.

Wisconsin Card Sorting Test (WCST)

The WCST is among the most widely used and well researched clinical neuropsychological measures of EF (Fossati et al. 1999; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). The WCST is a measure of abstract reasoning and cognitive set shifting strategies, and offers sensitivity in detecting deficits in frontal lobe damage and PFC functioning (Kolb & Whishaw, 1985). Although originally developed for adult populations, normative data are now provided on school-aged children as young as 6 and one half years of age (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

The WCST consists of four key cards and 128 response cards containing shapes of assorted forms (crosses, circles, triangles or stars), assorted colors (red, blue, yellow or green) and numbers of figures (one, two, three or four) (Heaton et al. 1993). Assessment with the WCST requires that the examinee match each of the 128 cards to one of the four key cards, based on the characteristics of form, color, and number. The examinee is not told of the sorting principle prior to beginning the task but is given immediate feedback on the correctness of the match following each card placement. Once the examinee has

made ten consecutive correct matches, the sorting principle changes and the examinee is required to use feedback to determine the next sorting principle. When the examinee continues to make incorrect matches based on the previous sorting rule, these responses are considered perseveration errors. The current study used the following scores for analyses: raw scores of categories completed and failure to maintain set, and T scores of total errors and perseverative errors.

Trail Making Test, Part B (TMT-B)

The TMT-B is a widely utilized screening instrument of impairment in neuropsychological functioning (Reitan, 1992). The research suggests that the TMT-B offers sensitivity in detecting neurological impairment and provides information on overall cerebral capabilities (Reitan, 1992). The TMT-B assesses cognitive flexibility, which is measured by the examinee's ability to shift mental sets in integrating numerical and alphabetical series (Reitan, 1992). The test stimulus consists of letters and numbers scattered across a page, in which the examinee is required to draw a line connecting the numbers and letters in alternating sequence as quickly as possible. For example, the examinee begins at the number 1, and draws a line from 1 to A…A to 2…2 to B…B to 3…, and so on in order until reaching the location marked "end." When an error is made in the sequence, the examinee is immediately redirected to the previous letter or number and is instructed to continue from that point.

Examinee scores are based on the amount of time taken to complete the task, producing a raw time score. Raw scores are converted to z scores and comparisons are made to normative data (Sherman, Spreen, & Strauss, 2006) based on medically healthy,

age-matched individuals. Two versions of the TMT-B have been developed for assessing both youth and adults. The Adult version is comprised of 25 numbers and letters and is appropriate for individuals 15 years of age and older. The Children's version includes a total of 15 numbers and letter and is used for individuals between the ages of 9 through 14 years.

Woodcock- Johnson III Tests of Cognitive Abilities (WJ-III COG)

The WJ III COG is one of two assessment instruments comprising the Woodcock-Johnson III (WJ-III; Woodcock, McGrew, & Mather, 2001). The WJ-III is a comprehensive measure of intellectual abilities and academic achievement. Normative data are available on most subtests for individuals between 2 and 90 years of age (Mather & Woodcock, 2001). The WJ- III COG is comprised of 20 subtests that assess specific components of three general domains of cognitive functioning including verbal ability, thinking ability, and cognitive efficiency (Mather & Woodcock, 2001).

Cognitive abilities are represented by cluster scores that are based on the Cattell-Horn-Carroll theory of cognitive abilities (Mather & Woodcock, 2001). Cluster scores yield higher reliability compared to the individual subtests and are useful in the interpretation of test results (Mather & Woodcock, 2001). For the purpose of the current study, the Executive Processes cluster (EPC) was used to obtain information on EF. Additionally, each of the three subtests comprising the EPC, including Concept Formation, Planning and Pair Cancellation were examined individually.

The EPC is a reliable measure of EF, with correlations of .93 and .95 reported across two age groups of 5 to 19 year olds, and adults , respectively (Mather &

Woodcock, 2001). Each of the three subtests comprising the EPC, specifically Concept Formation, Planning and Pair Cancellation, measure specific components of EF (Mather & Woodcock, 2001). For example, the Concept Formation subtest is a measure of mental flexibility. In this task, the individual is presented with a stimulus set consisting of pairs of drawings and is required to determine the rule that differentiates the two drawings. Differences are based on four characteristics of shape, color, size and quantity. The examinee is given immediate feedback on the correctness of each response for the first 35 of 40 items and no feedback is given for the last 5 items. Additionally, the examinee is not required to remember what has occurred over a series of items, which is a requirement in many other tests of concept formation (Mather & Woodcock, 2001). Median reliabilities of the Concept Formation are .94 for examinees aged 5 through 19 years and .96 for adults (Mather & Woodcock, 2001).

The Planning subtest is a measure of mental control and forethought, specifically those processes involved in problem-solving (Mather & Woodcock, 2001). The Planning task requires that the examinee trace a design without lifting the pencil from the paper and without retracing any lines. The examinee is asked to finish as much of each design as possible and is counted off for segments of the design left incomplete or for retraced segments. Median reliabilities for the Planning subtest are .75 for individuals between the ages of 5 and 19 years and .74 for adults (Mather & Woodcock, 2001).

Pair Cancellation is a measure of interference control, attention and concentration, and processing speed abilities (Mather & Woodcock, 2001). In this task, examinees are given 3 minutes to identify and mark a repeated pattern as quickly as possible. For the Pair Cancellation subtest, median reliabilities include .80 for the 5 to 19

year age group and .85 in the adult range (Mather & Woodcock, 2001). Additionally, Pair Cancellation Time is reported in raw time scores of seconds required to complete the task, of which higher scores indicate a slower performance.

Estimated age- and grade-equivalent scores are available in the scoring manual and can be obtained from raw scores on each subtest. All other scoring is completed with the Compuscore and Profiles Program (Mather & Woodcock, 2001). These computerized scoring programs convert raw scores into standard scores for each of the subtests and individual clusters (Mather & Woodcock, 2001).

Statistical Analyses

All data were analyzed with the Statistical Package for the Social Sciences for Windows, version 18 (SPSS, 2009). Of the 146 participants enrolled in the study, data for 105 of those participants were used in the current analyses. Five cases were excluded from data analyses due to missing data points. Additionally, data were excluded on 36 participants due to scores falling at or above 3 standard deviations from the mean score. The following statistical analyses were conducted to investigate the research question and hypotheses proposed.

Chi square analyses were used to determine possible race and gender differences between the groups (e.g., adolescents vs. adults, or controls vs. depressed). Additionally, t- tests were run to investigate possible age differences between the adolescent groups (depressed vs. control) and adult groups (depressed vs. control).

In order to address the primary research question of the current study, on the nature of the relationship between adolescents/adults and depressive illness status on EF, hierarchical regressions were run on each of the ten outcome variables. Adolescent/adult and depression status were entered in the first step, and the interaction term of adolescent/adult and depression status was entered in the second step. This statistical method was chosen in order to provide information on the extent to which each of these variables, (i.e., adolescent/adult and depression status) and the interaction between adolescent/adult and depressive illness status may correlate with outcomes on EF.

In addressing each of the three hypotheses, an analysis of variance (ANOVA) was performed for each of the ten outcome variables for group comparisons, including potential covariates when applicable. Secondly, post-hoc tests were run utilizing the Fisher's least significant difference (LSD) statistic in order to identify differences among the four groups. This investigation chose to use the LSD statistic due to the exploratory nature and to have greater sensitivity in identifying possible differences between these groups.

CHAPTER FOUR
Results

Sample Characteristics

Descriptive information for the sample is provided in Table 1. A total of 105 participants (27 adolescent controls, 21 adolescents with depression, 27 adult controls and 30 adults with depression) who met inclusion criteria and completed neuropsychological testing were included in the study. The adolescent groups did not differ significantly with respect to age, gender and ethnicity/race. Additionally, there was no significant age or ethnic differences between the adult groups, however a significant difference was observed for gender.

Mean values of the estimated IQ, TMT-B and executive cluster scores for WCST and WJ-III tests are given in Table 2. Overall, the performance of all four groups fell within the average range on all ten outcome measures. Additionally, no significant difference was observed between the adolescent groups (depressed vs. controls) or adult groups (depressed vs. controls) for IQ. In terms of group differences on the outcome measures, no differences emerged on the TMT-B or the WCST. However, group differences were observed on several WJ-III outcomes, including a decreased performance among adolescents on the WJ-III EPC, Planning and Pair Cancellation Time, and a decreased performance among the depressed groups (adults and adolescents) on WJ-III Planning.

Primary Analyses

Overall findings utilizing the hierarchical regression indicated no significant interaction effects of age and depressive illness status on the TMT-B, WCST or WJ-III (see Table 3). However, main effects for age and depressive illness status were found on several of the outcomes. For example, main effects for age were observed on the WJ-III EPC ($\beta = .24$, $p = .01$) and the WJ-III Pair Cancellation subtest ($\beta = .25$, $p = .01$), with a lower performance demonstrated on both measures among adolescents compared to adults. Additionally, main effects for depression were observed on the WJ-III Planning subtest ($\beta = -.22$, $p = .02$), with a lower performance observed among the depressed groups (adolescents and adults) compared to healthy participants. In terms of the WCST, main effects for age were observed on Perseverative Errors ($\beta = -.37$, $p = .000$) and Total Errors ($\beta = -.36$, $p = .000$), with a lower performance exhibited among adults compared to adolescents.

Post-hoc Analyses

Analysis of variance (ANOVA) was used to further explore between group differences in outcomes from the primary analyses. No significant group differences were found on the WCST or WJ-III Pair Cancellation. However, significant group differences were observed on the WJ-III EPC and WJ-III Planning. Additionally, group differences emerged on WJ-III Pair Cancellation Time.

In terms of the WJ-III EPC, both adolescent groups exhibited a lower performance compared to the adult control group. On WJ-III Planning, both adolescent groups exhibited a lower performance compared to the adult control group, and the adult depressed group exhibited a decreased performance compared to the adult control group. Additionally, on WJ-III Pair Cancellation Time, the adolescent depressed group exhibited a lower performance compared to both the adult depressed and adult control groups, and a trend ($p = .053$) was observed suggesting a lower performance among the adolescent control group compared to the adult control group.

Hypotheses

In addressing the specific hypotheses, analysis of covariance (ANCOVA) was used to control for significant gender differences among the adult groups in investigating between group differences (depressed vs. controls) on each of the ten outcome variables. Additionally, ANOVA was used to compare performance between the adolescent groups (depressed vs. controls) on each of the ten outcomes.

Hypothesis 1 stated that both the adolescent depressed and adult depressed groups would exhibit greater impairment in EF than their healthy counterparts as assessed by the WJ-III. In terms of adults, results revealed significant differences on WJ-III Planning, $F (1, 55) = 4.41$, $p = .017$, with the adult depressed group exhibiting a lower performance compared to the adult control group. No significant differences emerged between the adolescent groups (depressed vs. controls) on any of the WJ-III outcomes.

Hypothesis 2 stated that the adult depressed group would exhibit greater impairment in EF than the adult control group on the WCST, and that no differences would be observed in outcomes on the WCST between the adolescent groups (depressed vs. controls). No differences in performance were observed on any of the WCST outcomes among the adult groups (depressed vs. controls) or the adolescent groups (depressed vs. controls).

Finally, hypothesis 3 stated that adult depressed group would exhibit greater impairment in EF than the adult control group on the TMT-B, and that no difference would be observed in outcomes on the TMT-B between the adolescent groups (depressed vs. controls). No difference was observed in performance on the TMT-B between the adult groups (depressed vs. controls), or between the adolescent groups (depressed vs. controls).

CHAPTER FIVE
Conclusions and Recommendations

All of the hypotheses in the current study were partially supported, with significant differences observed between the adult groups on one of the WJ-III outcomes, and no differences revealed on the WCST or TMT-B between the adolescent (depressed vs. controls) or adult (depressed vs. controls) groups. Additionally, in terms of the primary research question addressed in the current study, on the possible presence of developmental differences in EF in depressive illness, results revealed subtle differences between the age groups (adolescents vs. adults), as well as between the depressed and non-depressed groups on several outcomes. Furthermore, depression status had a significant effect and a trend emerged for age effects on Pair Cancellation Time. In spite of the group differences on several EF measures, the performance in all four groups was within the normal range. Hence, developmental (or depression-related) differences between the groups in the following sections are indicative of only relative group differences.

Developmental Differences Demonstrated in EF

In the current investigation, depressed adolescents exhibited a significantly slower performance on WJ-III Pair Cancellation Time compared to both of the adult groups. Also, there was a non-significant trend for a slower performance in healthy adolescents compared to their adult counterparts. This task involves interference control, processing

speed and the ability to sustain attention (Mather & Woodcock, 2001). In terms of these EFs, the majority of them appear to reach mature levels during adolescence (Anderson et al., 2008), with the exception of sustained attention ability (Silver & Feldman, 2005). Additionally, the developmental trajectory of sustained attention appears to follow a course similar to WM (Silver & Feldman, 2005), and WM does not reach full maturational levels until adulthood (Anderson et al., 2008). Hence, it may be that this slower performance demonstrated in depressed adolescents could be explained by developmental differences in sustained attention ability, which could have been further compromised by depressive illness.

Effects of Age on EF

In terms of the effects of age (adolescents vs. adults) on EF performance in the current study, the primary analyses explained only a small portion of the variance on several outcomes. It is possible that these results were due to the modest sample sizes. Additionally, these results could have been influenced by the age of the adolescent sample (mid-adolescence) in the current study, as the majority of EFs involved on the outcome measures have reached developmental maturity by this age, and greater differences may have been observed with a younger sample.

Regarding the WJ-III, healthy adolescents exhibited a lower performance compared to their adult counterparts on the EPC and Planning. In explaining these findings, one possibility points to the EFs under investigation. For example, the EPC involves multiple EFs, including planning or problem-solving ability, interference control, and mental flexibility. Additionally, Planning involves problem-solving skills.

The EFs involved in both the EPC and Planning have been shown to reach full maturational levels during adolescence (Anderson et al., 2008), and results from the current study support this notion because performance in both adolescent groups fell within the average range. However, in terms of the relatively decreased performance demonstrated among healthy adolescents compared to healthy adults on these measures, it could be that although developmentally mature, these EFs may gain greater proficiency with age, and therefore may be less efficient in youth compared to adults.

Effects of Depressive Illness on EF

In terms of the influence of depressive illness on EF, primary analyses in the current study explained only a small portion of the variance, and only on WJ-III Planning. In terms of secondary analyses, however, significant between-group differences emerged between the depressed and non-depressed groups on WJ-III EPC, WJ-III Planning, and WJ-III Pair Cancellation Time. Additionally, depression status did not differentiate between the groups on the WCST or TMT-B. In terms of the WJ-III, depressed adults exhibited a lower performance compared to healthy adults on Planning, which involves problem-solving skills. It is likely, however, that this finding is due to the high average performance demonstrated by healthy adults in comparison to the average performance among depressed adults. Additionally, these results are not consistent with prior reports of deficits in problem-solving or planning skills in adult depression (Naismith et al., 2003; Rogers et al., 2004).

Among adolescents, depression did not show a significant effect on neuropsychological performance, although there was a non-significant trend for the

depressed group to have lower performance across the majority of outcome measures compared to their healthy counterparts. These findings may suggest developmental differences in EF in depressive illness, with subtle disturbances beginning to manifest in the context of adolescents.

The Utility of the WJ-III in Detecting Developmental Differences in EF

In regards to the current study's findings, significant between group differences for age and depressive illness status emerged only on the WJ-III. Based on these findings, it appears that the WJ-III is sensitive in detecting subtle changes associated with depression across adolescent and adult groups.

Limitations

There were a number of limitations to the current study. The main limitation of this study concerns the modest sample sizes, with inadequate power to detect potential group differences. Based on the observed effect sizes, a total of 180 adolescent and adult participants will be required in order to detect significant group differences. Future studies should consider larger sample sizes in order to examine the interactions between age and depressive disorder status on neuropsychological performance.

A second limitation of the current study involves the lack of information on depression severity in participants at the time of neuropsychological testing. Although the status of depression severity was known for each participant at the time of enrollment

into the larger study, depression measures were not administered at the time of neuropsychological testing, and it is possible that depression status may have changed for some participants from the time of enrollment until the time of neuropsychological testing. Additionally, three depressed adults and one depressed adolescent began treatment with bupropion prior to neuropsychological testing, and it is possible that the medication may have affected performance in these individuals. Furthermore, the inclusion of individuals whose depressive illness was in remission may have had an effect on outcomes, because it is likely that EF performance in such individuals may be more similar to healthy participants in comparison to depressed participants.

A third limitation of this study includes the generalizability of the current results. The participants were volunteers (self-selected) and had stringent inclusion and exclusion criteria for the larger study of neurobiological assessments. Hence, these results will not be generalizable to the community samples. Additionally, all participants were financially compensated for their participation in the current study. Although it may be common practice to compensate individuals for participation in investigational research, it is possible that such participants have increased levels of motivation compared to other individuals, which may have resulted in an increased performance.

Conclusions

The purpose of this study was to explore the extent to which developmental differences are evidenced in EF in depressive illness, and to investigate the possible presence of EF impairment in adolescents with depression. This investigation was conducted using three

neuropsychological instruments, with the additional purpose of providing information on possible advantages of utilizing age-appropriate measures in the assessment of EF.

In general, all groups performed within the normal range on all ten outcome measures. However, significant group differences emerged on several measures of the WJ-III, suggestive of possible developmental differences in EF and their possible interaction with depressive illness (albeit not statistically significant). Specifically, healthy adolescents showed a trend for lower performance compared with their adult counterparts on a task involving processing speed, interference control, and sustained attention, and depressed adolescents demonstrated a lower performance compared to both depressed and non-depressed adults. Implications of these findings suggest that depressive illness during early life may have mild effects on select EFs, such as those EFs that remain underdeveloped in youth. Additionally, adolescents as a whole exhibited a decreased performance compared to healthy adults on tasks involving planning ability, interference control or inhibition, and mental flexibility. It is possible that although these EFs may be developmentally mature in youngsters, EF may be less reliable in youth due to the ongoing maturation of this system in youngsters, and may increase in proficiency with age.

In summary, the results of this study contribute to the literature in that there are no published reports utilizing the WJ-III COG in examining EF in depressed samples. Additionally, this study may be the first to compare executive functioning abilities among youth and adults with depressive illness, and provides a good base from which to compare future studies on the interactions between developmental effects and depressive illness on EF.

Implications for Future Research

The conclusions drawn from this investigation underscore the importance of utilizing measures that offer adequate sensitivity in assessing EF among depressed youth in both clinical and research settings. The WJ-III COG appears to be one such measure since subtle developmental differences in EF were detected on this measure but not on other measures. Additionally, the extent to which impairment in EF is evidenced in youth with depression remains unclear, and future research is warranted. Results from the current study, however, suggest that depressive illness may influence EF performance in youth, although these differences may remain subtle within this age group. Additionally, these results provide sufficient evidence to suggest that further research be conducted on the developmental effects of depressive illness on EF performance in youngsters, and researchers should consider using larger samples in future investigations.

TABLE 1.

Descriptive Information on Demographic Variables of the Sample

	Control Adolescents (n=27)	Depressed Adolescents (n=21)	*t*	Control Adults (n=27)	Depressed Adults (n=30)	*t*	Total Sample Adolescents (n=48)		Total Sample Adults (n=57)		Total Adults and Adolescents (n=105)	
	M SD	M SD		M SD	M SD		M SD	-----	M SD	---	M SD	---
Age	14.26 1.77	14.14 1.32	.25	28.96 9.56	25.10 7.88	1.67	14.21 1.57		26.93 8.85		21.11 9.16	
								χ^2		χ^2		χ^2
Gender												
Male	13 (48.1%)	8 (38.1%)		12 (44.4%)	7 (23.3%)		21 (43.8%)	.75	19 (33.3%)	6.33*	40 (38.1%)	5.95*
Female	14 (51.9%)	13 (61.9%)		15 (55.6%)	23 (76.7%)		27 (56.3%)		38 (66.7%)		65 (61.9%)	
Race												
Caucasian	11 (40.7%)	10 (47.6%)		9 (33.3%)	14 (46.7%)		21 (43.8%)	.23	23 (40.4%)	2.12	44 (41.9%)	2.75
Non-Caucasian	16 (59.3%)	11 (52.4%)		18 (66.7%)	16 (53.3%)		27 (56.3%)		34 (59.6%)		61 (58.1%)	

*p<.05

TABLE 2.

Mean Scores for Neuropsychological Variables and Group Comparisons

	Depressed Adolescents	Control Adolescents		Depressed Adults	Control Adults		
	M (SD)	*M* (SD)	*t*	*M* (SD)	*M* (SD)	*t*	*F*
IQ	96.81 (10.81)	99.85 (10.44)	.64	108.77 (13.97)	113.41 (14.51)	1.23	
Trails B	.18 (.86)	-.04 (1.35)		.11 (1.11)	.10 (1.15)		.16
WJ-III EPC	98.33 (9.27)	100.74 (11.93)		102.47 (10.71)	107.44 (10.42)		3.22*
WJ-III Planning	104.95 (7.12)	106.11 (9.91)		104.70 (7.04)	111.81 (.70)		3.77*
WJ-III Concept Formation	101.67 (12.50)	103.19 (12.07)		103.57 (11.03)	108.85 (9.90)		1.95
WJ-III Pair Cancellation	95.29 (7.89)	96.85 (10.84)		100.03 (12.39)	102.30 (10.88)		2.10
WJ-III Pair Cancellation Time[1]	159.62 (16.36)	153.48 (20.77)		145.13 (24.51)	142.37 (19.61)		3.46*
WCST categories completed[2]	5.19 (1.54)	5.37 (1.21)		5.60 (1.20)	5.30 (1.46)		.44
WCST total errors	52.57 (9.73)	54.93 (11.89)		50.57 (10.08)	47.56 (8.85)		2.50
WCST perseverative errors	52.62 (10.88)	56.59 (11.27)		51.77 (12.54)	48.59 (9.53)		2.35
WCST failure to maintain set[2]	1.00 (1.38)	.63 (1.18)		.70 (1.02)	1.04 (1.29)		.77

Note: 1= in seconds; higher number indicates slower performance. 2 = raw scores. All other scores are standard, *z*, or *T* scores unless otherwise indicated. *$p < .05$.

TABLE 3.

Hierarchical Regression Analyses Predicting Performance on EF from Age and Depressive Illness Status

	Executive Functioning Outcome Measures																					
	WJ-III EPC		WJ-III Planning		WJ-III Concept Formation		WJ-III Pair Cancellation		WJ-III Pair Cancellation Time		WCST Perseverative Errors		WCST Total Errors		WCST Categories Completed		WCST Failure to Maintain Set		TMT-B	
Predictor	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1	.08		.06		.04		.07		.03		.13		.13		.01		.03		.01	
Age		.24*		.08		.15		.25*		-.14		-.37*		-.36*		-.11		.18		.09
MDD Dx		-.14		-.22*		-.13		-.05		.07		-.04		-.01		.03		.01		.05
Step 2	.01		.00		.00		.01		.00		.00		.00		.01		.00		.00	
Interaction Term[a]		-.52		-.35		-.41		-.60		.04		.22		-.01		-.60		-.29		-.24
Total R^2	.09		.06		.05		.08		.03		.14		.13		.02		.03		.01	
n	105																			

[a]Interaction term = age & depression status. *$p < .05$.

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VITAE

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