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NEUROCOGNITION IN INDIVIDUALS AT HIGH FAMILIAL RISK FOR MAJOR DEPRESSIVE DISORDER

A dissertation submitted in partial fulfillment

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New York

by

Rachel Venezia

Date Submitted _____ Date Approved _____

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ABSTRACT

NEUROCOGNITION IN INDIVIDUALS AT HIGH FAMILIAL RISK FOR MAJOR DEPRESSIVE DISORDER

Rachel Venezia

Neurocognitive deficits may qualify as vulnerability markers in individuals at risk for developing MDD. We examined the extent to which characteristic neurocognitive difficulties in MDD may be apparent in early to late adolescence in the offspring of a parent with MDD, as well as the extent to which other factors, such as a history of comorbid diagnoses (e.g., ADHD), a history of MDD, and a current depressive episode, might confound to these differences.

Offspring of patients with MDD (n=184) and a healthy normative sample (n=88) were compared on measures assessing attention, working memory, impulse control, and visual memory. The two groups were compared using ANCOVA, including an estimate of intellectual ability as a covariate, examining the effect of offspring status on neuropsychological performance.

Offspring had significantly lower working memory and visual memory performance than did the normative sample, even after adjustment for IQ differences. Offspring with current depression, a history of comorbid ADHD or comorbid PTSD had significantly lower attention and working memory performance than did other unaffected offspring. Offspring with past depressive episodes and those who had never been depressed did not differ in current neuropsychological performance. When offspring with ADHD, PTSD, or current depression were removed from the analysis, however, and scores were adjusted for IQ differences, offspring of a parent with MDD continued to

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differ from individuals in the normative sample in working memory, at all levels of estimated intelligence.

Offspring of patients with MDD exhibited working memory weaknesses at all levels of basic estimated intellectual ability. Modest working memory deficiencies may be a risk factor for, or potential genetic marker of, susceptibility to MDD.

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DEDICATION

For my dad, Mark Venezia, who raised me in the life of the mind and inspired my doctoral pursuits.

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1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders worldwide. The lifetime prevalence is approximately 16% (Kessler et al. 2005). Furthermore, MDD is highly familial (Gershon, 1983), with relatives of those with MDD showing increased rates themselves (Gershon et al., 1982; Maier et al., 1993; Weissman et al., 1984, 1993, 2005). Twin studies demonstrate moderate heritability (Sullivan et al., 2000), with a much higher concordance rate for monozygotic, compared with dizygotic twins (McGuffin, 1984), whether they are raised together or apart (Price, 1968). Overall, there is a strong genetic influence on the aggregation of MDD within families (Bierut et al., 1999; Guffanti et al., 2016; Kendler et al., 1995; Kendler & Prescott, 1999; Lyons et al., 1998; McGuffin et al., 1996).

Research has also found support for the familial transmission of various neurobiological traits associated with depression (Bansal et al., 2016; Bruder et al., 2012; Dublin et al., 2011; Peterson et al., 2014; Posner et al., 2016). Biological descendants of individuals with depression have reduced frontal and parietal white matter volumes (Dublin et al., 2011), even when they are not themselves depressed. Moreover, the reduction in white matter volume is associated with severity of depressive symptoms (Dublin et al., 2011). Increased cortical thinning of the right frontal, parietal, posterior temporal, and occipital cortices has also been found in these descendants (Peterson et al., 2009). These neuroanatomical differences may represent stable traits that increase the risk of developing depression (Peterson et al., 2009).

Individuals at high familial risk for MDD also showed increased Default Mode Network connectivity, as well as decreased connectivity between the Default Mode

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Network and the Central Executive Network (Posner et al., 2016). This is the opposite of what is seen in individuals who are not depressed. Again, these findings, based upon resting-state functional connectivity MRI studies, were independent of individuals' current or lifetime history of depression.

Abnormal resting EEG measures of hemispheric activity have been found in both individuals with a depressive disorder (Davidson et al. 1987; Bruder et al. 1997; Reid et al. 1998; Kentgen et al. 2000) and their biological descendants (Weissman et al. 2005). These abnormal results have also been found in the offspring of depressed patients, regardless of whether they have had a diagnosis of depression (Bruder et al., 2012). In general, about 60% of the difference in EEG activity appears to be due to a latent trait that is stable across time (Hagemann et al. 2005).

MDD is also associated with a range of neurocognitive deficits (Schatzberg, 2002; Shenal, Harrison, & Demaree, 2003; Zakzanis, Leach, & Kaplan, 1999). These include deficits in processing speed (Nebes et al., 2000; Ravnkilde et al., 2002), attention and concentration (Kampf-Sherf et al., 2004; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Ravnkilde et al. (2002), working memory (Landro, Stiles & Sletvold, 2001), executive function (Harvey et al., 2004; Lee et al., 2012), and memory (Fossati, Amar, Raoux, Ergis, & Allilare, 1999). Overall, depression appears to cause a mild to moderate global-diffuse impairment of brain function during a depressive episode.

Neurocognitive deficits have also been observed in the unaffected relatives of patients with MDD, although the literature in this area is nascent. Papmeyer and colleagues (2015) found that individuals with a close family history of a mood disorder (i.e., individuals with a high risk of developing MDD) had reduced set-shifting ability

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when compared with healthy non-patients. Furthermore, a recent meta-analysis found that first-degree relatives of individuals with MDD had significantly lower full-scale IQ, verbal intelligence, perceptual intelligence, memory, academic performance, and language (MacKenzie, Uher, & Pavlova, 2019) than individuals without a family history of MDD. In short, they found that, similar to what has been found in patients with MDD, individuals at high risk of developing MDD appear to have mild global and diffuse deficits in neurocognition. No single one of these domains, though, stood out as being specifically impaired.

The presence of neurocognitive deficits in the relatives of individuals with MDD raises the possibility that these neurocognitive deficits may qualify as endophenotypes (Glahn, Bearden, Niendam, & Escamilla, 2004), which are stable, measurable traits along the pathway between disease and phenotype. Establishing a neurocognitive marker as a true endophenotype, however, is challenging. To qualify as an endophenotype, markers must (1) be associated with illness in the population, (2) be state-independent, (3) be heritable, (4) be associated with families, (5) co-segregate within families, and (6) be a measurable trait that is more strongly associated with the disease of interest than with other psychiatric conditions (Gottesman & Gold, 2005; Chan & Gottesman, 2008). Few differences meet all of these criteria.

There is a growing consensus that at least some neurocognitive deficits in MDD are state-independent, meaning that they are present both during depressive episodes and after those episodes have remitted (Beats et al., 1996; Hammar, Lund, & Hugdahl, 2003; Neu, et al., 2005; Papmeyer et al., 2015; Paradiso et al., 1997; Reischies and Neu, 2000; Shilyansky et al., 2017; Trichard et al., 1995). Hammar, Lund, and Hugdahl (2003)

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found that patients with MDD were deficient on an effortful visual search paradigm both at intake and when depressive symptoms had remitted at six-month follow-up sessions. Neu and colleagues (2005) found that depressed patients had verbal memory deficits during both the acute phase of a depressive episode as well as after they had been in a euthymic state for at least 6 months. This is consistent with other findings on the state-independence of these deficits (Fromm & Schopflocher, 1983; Kopelman, 1986; La Rue et al., 1986).

Papmeyer and colleagues (2015) examined the state-independence hypothesis in three groups: unaffected healthy participants, patients who were at a high-risk of developing MDD who were well at baseline and remained well, and high-risk patients who were well at baseline but developed MDD during the follow-up period. They found that both high-risk groups had reduced set-shifting ability when compared with healthy non-patients. Furthermore, they found no significant differences in neurocognitive performance between the two high-risk groups, indicating that the presence of a depressive episode is not necessary for the expression of neurocognitive deficits. Shilyansky and colleagues (2017) reached similar conclusions. They found that in MDD patients, deficits in attention, response inhibition, verbal memory, decision speed, and information processing remained at the end of eight weeks of antidepressant treatment, even in patients whose changes on clinical measures of depression indicated remission.

Neurocognitive deficits in MDD are highly heritable (Glahn et al., 2004). This includes memory (Bertisch, Hoptman, & DeLisi, 2010; Husted, Lim, Chow, Greenwood, & Bassett, 2009; Swan et al., 1999), processing speed (Posthuma, Neale, Boomsma, & de Geus, 2001), and aspects of attention and executive function (Glahn et al., 2007), such as

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executive control, reaction time (Kuntsi et al., 2006), working memory (Ando, Ono, & Wright, 2001; Blokland et al., 2011; Vogler et al., 2014), and sustained attention (Polderman et al., 2006). Our measures included the Stroop Test, which is one of the most widely used measures of attention control. Twin studies of the Stroop Test show moderate heritability, suggesting a significant genetic component (Nánási, Katonai, Sasvári-Székely, & Székely, 2012; Stins, van Baal, Polderman, Verhulst, & Boomsma, 2004; Taylor, 2007). Stins and colleagues (2004) found a moderate degree of heritability (49%) for the Stroop interference effect, which was the metric used in our analysis. Our measures also included the N-Back task, which is a continuous performance task commonly used to measure working memory. Twin studies of the N-Back show moderate heritability (Blokland et al., 2011; Vogler et al., 2014). Furthermore, working memory tasks like the N-Back task are associated with blood-oxygen-level dependent (BOLD) activation patterns, which have been found to be heritable (Blokland et al., 2011; Blokland et al., 2014; Blokland et al., 2017).

Research has yet to determine whether neurocognitive weaknesses associated with MDD may be markers of risk in unaffected family members. MDD is more common in the relatives of patients with MDD, compared to healthy comparison participants. However, it is unclear if specific deficits might be used to identify individuals who are at risk. In the present study, we investigated aspects of neurocognitive performance that may function as specific risk factors. On the basis of findings in heritability studies (Blokland et al., 2011; Vogler et al., 2014; Stins et al., 2004) and results from a study of offspring of depressed adults (Papmeyer et al., 2015), we hypothesized that the offspring of patients with MDD would have poorer attention, working memory, visual memory,

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and impulse control than would a normative sample. We also hypothesized that poorer performance in offspring of depressed parents will not be attributable to other factors, such as differences in overall intelligence, between the groups (Note: These hypotheses were formulated prior to the publication of MacKenzie et al.'s meta-analysis in 2019; they showed a global diffuse impairment in the offspring of individuals with MDD). Consistent with previous research (Papmeyer et al., 2015), we expect that these neurocognitive deficits will be present in offspring both with and without a current depressive episode and with and without a history of MDD. In exploratory analyses, we will examine the extent to which neurocognitive differences may be more strongly associated with other psychological disorders, such as ADHD. Lastly, we will determine the extent to which our measures can be used to predict vulnerability to MDD.

Data for this study was derived from the Familial Pathways study (Brent et al., 2002), a two-site developmental study examining clinical and neurocognitive factors associated with depression and suicidal behavior in both proband parents and their offspring. The study described here focuses on the late childhood to adolescent offspring of parents with a lifetime history of MDD. In parallel to the collection of the familial pathways data, data on attention, working memory, visual memory, and impulse control was also collected in a normative sample (88 individuals, aged 10-19, stratified by age band and sex) without a known history of parental MDD. The present study represents a unique opportunity to compare a large sample of offspring of patients with MDD to a general population sample of children and adolescents, to determine if there might be any systematic differences in their neurocognitive abilities.

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II. Methods

Participants

All participants were native English speakers. The offspring sample consisted of 184 offspring of 117 parents with MDD, and the normative sample consisted of a population sample of 88 participants. Exclusion criteria for the normative sample included a history of major medical conditions, learning disabilities, behavioral issues, and treatment for psychiatric disorders, assessed by parental report. At the time of assessment, none of the participants in the normative sample had current depression or other major psychiatric illnesses, by parental report.

Instruments

Clinical assessment

For Axis I disorders, offspring aged 10 to 17 years were assessed using the School Aged Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL: Kaufman et al., 1997). All participants older than 18 years were assessed for current and lifetime *DSM-IV* (American Psychiatric Association, 1994) psychiatric disorders using the Structured Clinical Interview for *DSM-IV* (SCID-I: First, Spitzer, Gibbon, & Williams, 1996). The Structured Clinical Interview for the *DSM-IV* Diagnosis of Personality Disorders (SCID-II: First, Gibbon, Spitzer, Williams, & Benjamin, 1997) was used to diagnose personality disorders in all participants older than 14 years. A history of physical and sexual abuse was assessed in participants older than 18 years from a series of screening questions in a demographic questionnaire.

The following psychopathology ratings were obtained in the offspring of depressed parents only: Current severity of depressive symptoms was established via the

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Hamilton Rating Scale for Depression (HRSD: Hamilton, 1960) in adults 18 and older, and with the Children's Depression Rating Scale, revised (CDRS-R: Poznanski, Freeman, Mokros, 1985), for those younger than age 18 years. Subjective depression was assessed via the Beck Depression Inventory (BDI: Beck, Ward, Mendelson, & Erbaugh, 1961) in participants age 14 years and older, and via the Children's Depression Inventory (CDI: Kovacs, 1992) in those younger than age 14 years.

Hopelessness was assessed with the Beck Hopelessness Scale (Beck, Weissman, Lester, & Trexler, 1974) for participants age 14 years and older, and with the Children's Hopelessness Scale (Kazdin, Rodgers, & Colbus, 1986) for participants under age 14 years. Suicidal ideation was assessed via the Beck Scale for Suicidal Ideation (Beck, Kovacs, & Weissman, 1979).

Impulsiveness was assessed with the Barratt Impulsiveness Scale (BIS: Barratt, 1965; Barratt, 1985) for participants age 18 years and older and with the Iowa Connors Parent Physical Report Impulsivity Subscale (Pelham, Milich, Murphy, Murphy, 1989) for participants under age 18. Hostility was assessed with the Buss-Durkee Hostility Inventory (BDHI: Buss & Durkee, 1957) for participants age 18 and older and Childrens Hostility Inventory (CHI: Kazdin, Rodgers, Colbus, & Siegel, 1987) for participants under aged 10 to 17. Aggressive Behavior was assessed using the 11-item Brown-Goodwin Lifetime History of Aggressive Behavior (BGLHA: Brown & Goodwin, 1986).

Estimated intellectual ability was assessed via the Peabody Picture Vocabulary Test, Third Revision (PPVT-III: Dunn & Dunn, 1997). The PPVT-III provides an estimate of receptive vocabulary, a strong correlate of overall intelligence. The examinee is presented with a series of pictures, four to a page. For each page, the examiner speaks a

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work describing the pictures and asks the examinee to identify the picture matching the word. The PPVT-III is highly correlated with more comprehensive measures of intelligence, such as the Wechsler Intelligence Scale for Children, third edition (Hodapp & Gerken, 1999).

Neurocognitive Assessment

The neuropsychological battery included measures of attention, working memory, impulse control, and visual memory. These tests cover a range of neurocognitive functions typically impacted by depression (Austin, Mitchell, & Goodwin, 2001; Keilp, et al., 2013). All computerized tasks were presented on a Macintosh PowerBook 1400c laptop computer, with responses recorded via an external keypad. Computer tasks were programmed in the PsyScope (v1.1) programming language (Cohen, MacWhinney, Flatt, & Provost, 1993).

Attentional capacity was assessed using the Continuous Performance Test (CPT: Rosvold et al., 1956). The Identical Pairs version (CPT-IP: Cornblatt and Erlenmeyer-Kimling 1985; Erlenmeyer-Kimling and Comblatt 1992) was used. Participants were presented with strings of numbers that were displayed one string at a time in the center of a visual display. They were instructed to respond by pressing a key whenever two identical strings of numbers were presented in a row. This task required participants to keep every stimulus presented in working memory until it could be compared with the one immediately following it, leading to a high information processing load (Cornblatt et al., 1988). The signal detection indices d' prime, which is a standardized hit rate adjusted for the standardized false alarm rate, and Log Beta, were computed as outcome measures (Cornblatt and Keilp, 1994).

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Interference processing/attentional control was assessed using a computerized Stroop task (Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008; Keilp, Sackeim, & Mann, 2005). The Stroop task was adapted from standard color/word versions of the task (MacLeod, 1991) using a single item presentation and a button press response. Percent interference (percent change in median reaction time to color/word vs. color responses) was used to summarize performance (see Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008). For analysis, internal normative data were used to convert raw interference scores to z-scores. In adults, this score is strongly associated with age (see Keilp, Sackeim, & Mann, 2005), with no known sex or education effects. In our adolescent normative data, however, the interference score appears to be relatively stable throughout the age range examined in this study, and unaffected by sex or education level.

Working memory was assessed using the A, Not B task and the N-Back task. The A, Not B task is a computerized version of a paper- and-pencil working memory and reasoning task developed by Baddeley (1968). It required participants to evaluate syllogisms based on the serial order of two letters. The critical variable was reaction time to correct responses. Total number correct was recorded as well.

The N-Back task, developed by Kirchner (1958), is a variant of a continuous performance task. Participants observed random sequences of letters appearing one at a time at the center of a visual display. They were instructed to respond by pressing a key whenever the stimulus matched one that they had seen just before (one back condition), two items before (two back condition) or three items before (three back condition) in each of three separate conditions. Stimuli were presented for 500 ms, with an interstimulus interval of 2,500 ms. Each condition of the task contained 60 stimuli, with

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12 targets in the one-back condition, and 10 each in the two- and three-back conditions. The signal detection index d' was used as the outcome measure.

Impulse control was measured using a Time Estimation task and a Go-No Go task. For the Time Estimation task, participants were presented with a time interval to estimate, heard a beep, and were asked to hit a computer key when that amount of time had passed. Participants were presented with three iterations of five intervals (10, 20, 40, 60, and 90 s) in a random order. Participants' performance was characterized as the percent difference between their estimates and the actual intervals. Impulsive individuals have been found to count faster, and thus produce shorter estimates of real time (Keilp et al., 2005).

Impulse control was also measured using a bimodal-matching Go No-Go procedure. An association between impulsiveness and the number of commission errors has been found previously (Keilp et al., 2005). The letter X appeared once per second for 50 ms in one of six locations on a computer screen. The X was accompanied by either a high tone (400 Hz) or a low tone (200 Hz). Participants were instructed to hit a response key only when the X appeared in the top half of the screen and was accompanied by the low tone. Most stimuli (64%) were targets. The remainder of the stimuli consisted of mismatches on one dimension (location or tone) or both. A total of 225 stimuli were presented, 144 of which were appropriate response trials. The commission error score was the total number of responses to the mismatch trials, adjusted for the total number of correct responses out of the total of 144.

Visual memory was assessed using the Benton Visual Retention Test (VRT) (Sivan, 1992). This was the only non-computerized paper-and-pencil task. Administration

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D, which includes a 15-second delay following the standard 10-second exposure, was used. This produces slightly higher error scores in mildly to moderately impaired populations and improves sensitivity, although normative data on this administration is limited. Analyses were conducted on normatively-corrected error scores, with scores corrected for age, age-squared, and sex, based on data from our normative comparison group (see Keilp, Sackeim, & Mann, 2005).

Procedure

The individuals with MDD who are the parents of the offspring included in our sample will be referred to as "probands," as they are the starting point for this neurocognitive study. Probands were recruited from the research inpatient and outpatient clinics at the New York State Psychiatric Institute and the Western Psychiatric Institute and Clinic, where they had been referred for evaluation of a mood disorder. Probands had no prior history of major medical or neurological illness. Probands provided contact information for offspring. All participants gave written informed consent, as required by the applicable institutional review boards.

All interviewers were at least Master's level clinicians who received extensive training in the administration of semi-structured interviews. Interviewers of probands were blind to the diagnoses of the offspring and interviewers of offspring were blind to the diagnoses of the probands. All diagnoses were defined according to *DSM-IV* (American Psychiatric Association, 1994) criteria.

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Statistical Analysis

Groups were compared via t-test (continuous variables) or chi square analysis (categorical variables) on demographic measures (e.g., age, sex, education), as well as estimated intelligence (PPVT-III). Neurocognitive data was transformed into standard scores, and the distribution was examined. In order to facilitate the comparison of neurocognitive abilities by domain, three composite variables were created, consistent with prior publications using these same measures (see Keilp et al., 2013): Attention Composite, consisting of an average of the CPT d' and Stroop Interference z-scores; Working Memory Composite, consisting of an average of the A, Not B response time to correct items and N-Back d' z-scores; and Impulsiveness Composite, consisting of an average of the Time Production Task and Go-No Go z-scores.

Neurocognitive performance in the offspring versus the control group was initially compared via t-test. Then, ten ANCOVAs (one for each neurocognitive measure as well as each neurocognitive composite) were performed in order to examine neurocognitive test performance between offspring and controls, while statistically controlling for the effects of covariates found to be statistically different across groups. When a significant group (offspring vs. control) main effect was found, data were graphed to determine the nature of the differential effect.

We then further explored psychopathological factors within the offspring sample that might be contributing to offspring/normative sample differences. We ran independent samples t-tests comparing offspring with and without current depression or any of the most prominent past psychiatric diagnoses among the offspring (MDD, Attention Deficit Hyperactivity Disorder [ADHD], Post-Traumatic Stress Disorder

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[PTSD], anxiety, alcohol abuse, substance abuse, mood disorder, oppositional defiant disorder [ODD]). Then, we removed offspring with disorders demonstrated to be associated with significantly lower neurocognitive performance, yielding a "restricted offspring group." We re-ran our ten ANCOVAs with the restricted offspring group, in order to determine whether other psychological risk factors was driving the observed differences between group. For each significant group effect (restricted offspring vs. normative group), data was graphed to determine the nature of the differential effect.

Neurocognitive performance in the currently depressed (based on clinical rating scales) offspring versus the currently not depressed offspring was also compared via t-test.

We then ran a series of exploratory stepwise logistic regressions in order to determine which neuropsychological measures were the strongest predictors of a) offspring versus normative group status, b) offspring with a history of MDD versus offspring without a history of MDD, c) offspring without MDD versus normative group, and d) offspring with current depression versus offspring without current depression.

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III. Results

Demographic and Clinical Characteristics

Normative Sample

Demographic and clinical characteristics of the offspring and normative samples are presented in Table 1. The average age of the normative sample was 14.4 years (SD = 2.9 years; Range = 10-19 years). There were slightly more females (n = 45, 51.1%) than males. Average educational attainment was 8.7 years (SD = 2.8 years; Range = 4-14 years), and the average PPVT-III score was 113.0 (SD = 11.7; Range = 85-142), which falls in a high-average range.

Offspring Sample

A total of 5 offspring, including 1 with a history of a psychotic disorder, 3 with a history of bipolar disorder, and 1 with a history of an eating disorder, were excluded from analysis in order not to bias any comparisons and because these groups were not large enough for any systematic statistical analysis. This yielded a total of 179 offspring included in our sample. The average age of the offspring was 13.9 years (SD = 2.7 years; Range = 10-19 years). There were slightly more males (n = 101, 56.4%) than females. The average educational attainment was 8.2 years (SD = 2.7 years; Range = 3-14 years), and the average PPVT-III score was 107.7 (SD = 13.4; Range = 85-143), a score at the upper end of the average range of estimated intelligence.

Within the offspring sample, 80 (44.7%) had no history of a prior diagnosis, and 99 (55.3%) had a history of 1 or more diagnosis. 61 offspring (34.1%) had a lifetime history of MDD, 43 (24%) had a lifetime history of an anxiety disorder, 10 (5.6%) had a lifetime history of post-traumatic stress disorder (PTSD), 30 (16.8%) had a lifetime

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history of ADHD, 16 (8.9%) had a lifetime history of oppositional defiant disorder (ODD), 3 (1.7%) had a lifetime history of alcohol abuse, 2 (1.7%) had a lifetime history of substance abuse, and 12 (6.7%) had a lifetime history of a suicide attempt.

Although, as mentioned previously, 61 (34.1%) of the offspring met *DSM-IV* criteria for lifetime history of MDD, on average, the offspring group had minimal/no current depression as measured by clinical rating scales. Secondary analyses were conducted using rating scale clinical cutoffs for depression that have been established in the literature. We used a BDI clinical cutoff of 20 (Kendall, Hollon, Beck, Hammen, & Ingram, 1987), which is equivalent to moderate depression; a CDI cut-off of 20 (Kovacs, 1992); a HDRS clinical cutoff of 17 (Hamilton, 1967); and a CDRSR clinical cutoff of 40 (Plener et al., 2012). Using these cutoffs, 16 offspring met criteria for current depression on the subjective rating scales (BDI and CDI) and 6 met criteria for current depression on the objective rating scales (HDRS and CDRSR). Of these, 5 offspring met criteria on both the subjective and the objective measures, 9 offspring met criteria on the subjective measures but not the objective measures, 2 offspring met criteria on the subjective measures but were not administered the objective measures, and 1 offspring met criteria on the objective measures but not the subjective measures, yielding a total of 17 offspring who met criteria for current depression on any scale(s).

Demographic and Clinical Differences Between Groups

The offspring group (mean = 107.88, SD = 13.40) had significantly lower PPVT-III scores (p = .002) than the normative group (mean = 113.03, SD = 11.65). The offspring and normative groups were comparable in age and education level, and the two groups had comparable sex ratios. The currently depressed and the currently not

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depressed offspring groups were comparable in age, education, and PPVT-III test scores. Mean group differences for demographic characteristics of offspring and normative groups are presented in Table 1, and mean group differences for demographic characteristics of currently depressed and currently not depressed offspring are presented in Table 4.

Neuropsychological Test Scores

Offspring vs. Normative

Before analyses, test scores were adjusted for normative effects on performance, based on significant values of various demographic factors (age, age-squared, sex, or education) in the normative group, tested via stepwise regression, with any factor contributing at greater than $p \leq .15$ retained in the model. The CPT d' and A, Not B response time scores were adjusted for age. N-Back and Go No-Go were adjusted for age and age-squared (due to an accelerated improvement in performance with age). BVRT was adjusted for age, age-squared, and sex. The Stroop interference score and Time Estimation percent deviation score were not affected by these demographic factors through the age range assessed.

Mean demographically-adjusted scores on individual test measures and test composites are presented for each group in Table 2. The offspring sample scored significantly worse ($p < 0.05$) than the normative sample on the Stroop Interference; A, Not B; N-Back; and Benton VRT measures; as well as the Attention Composite and the Working Memory Composite. In contrast, there were no statistically significant differences between the offspring sample and the normative group on the CPT, Time Production, or Go No-Go tasks. However, the Impulsiveness Composite (p=0.057)

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approached statistical significance when Time Production and Go No-Go scores were combined in a single metric.

Given that the offspring group had significantly lower PPVT-III scores than the normative group, a repeated measures Analysis of Covariance (ANCOVA) was run including PPVT-III scores as a covariate. This data is presented in Table 3 and in Figure 1. In this model, significant effects for offspring status remained for A, Not B ($F[1,257]=9.49$ $p= 0.002$); N-Back ($F[1,256]=11.56$, $p= 0.001$), and Benton VRT ($F[1,263]=4.32$, $p= 0.039$) scores, respectively. However, Stroop Interference ($F[1,255]=3.05$, $p= 0.082$) became marginally significant, and Time Production ($F[1,256]=1.10$, $p= 0.296$), Go No-Go ($F[1,260]=1.21$, $p= 0.273$), and CPT ($F[1,254]=0.40$, $p= 0.526$) scores remained statistically non-significant. In terms of composite variables, a statistically significant main effect for offspring status remained for the Working Memory Composite ($F[1,253]=18.32$ $p < 0.001$), but the Attention Composite became marginally significant ($F[1,254]=2.90$, $p= 0.090$), and the Impulsiveness Composite remained statistically non-significant ($F[1,255]=1.87$, $p= 0.173$).

Currently Depressed Offspring vs. Currently Not Depressed Offspring

We next examined the extent to which offspring with current depression might differ from offspring without current depression. The currently depressed offspring group scored significantly worse ($p < 0.05$) than the not currently depressed offspring group on the A, Not B and Time Production, and Benton VRT tasks. In contrast, there were no statistically significant differences between these two groups on the CPT, Stroop Interference, N-Back, or the Go No-Go task, nor was there a statistically significant

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difference for any of the composites, although the Working Memory Composite approached significance ($p = 0.055$). Mean demographically-adjusted scores on individual test measures and test composites are presented for the currently depressed offspring group and the currently not depressed offspring group are presented in Table 4

Offspring with Diagnoses vs. Offspring without Diagnoses

We next examined the extent to which offspring diagnoses might be contributing to differences between the offspring and the normative sample, given that subgroups of the offspring sample already had received diagnoses of disorders such as MDD, ADHD, and PTSD. We then ran an independent samples t-test comparing the offspring with a history of any psychological disorder to offspring with no history of any psychological disorder. Compared with the group of offspring without a history of any psychological disorder, the group of offspring with a history of one or more psychological disorder(s) had significantly worse (p <0.05) CPT, Stroop Interference, and N-Back scores, as well as well as significantly worse Attention and Working Memory composite scores. There were no significant differences on any other neuropsychological variable, and these two groups had comparable PPVT-III scores. This data is presented in Table 5. When we compared offspring with and without specific diagnoses, only offspring with ADHD and offspring with PTSD had lower neurocognitive scores than the overall offspring group. Notably, there was no statistically significant difference between offspring with versus without a history of MDD.

The ADHD group had significantly lower educational attainment (p<0.05), as well as significantly worse CPT, N-Back, and Go No-Go test performances (p<0.05). Furthermore, they had significantly worse Attention, Working Memory, and

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Impulsiveness composites (p <0.05). They showed no differences for any other demographic or neuropsychological variables. This data is presented in Table 6. We also specifically compared offspring with and without a history of PTSD. The PTSD group had significantly lower PPVT-III scores (p<0.05), and the CPT test performance difference was marginally significant (p =0.060). They showed no differences for any other demographic or neuropsychological variables. This data is presented in Table 7.

Restricted Offspring Group vs. Normative Group

Given the significant neurocognitive differences between offspring with and without current depression, a history of ADHD, or a history of PTSD, we wondered to what extent this was what was driving the differences between the offspring and the normative sample. When we removed offspring with current depression (9.5% of the offspring sample, 17 total), ADHD (16.8% of the offspring sample, 30 total), or PTSD (5.6% of the offspring sample, 10 total) from analysis, yielding a "restricted offspring group," there was still a significant main effect of offspring status and A, Not B (F[1,194]=7.86, p= 0.006) and N-Back (F[1,194]=7.20, p= 0.008) scores, respectively. Benton VRT scores (F[1,198]=0.l88, p= 0.350), however, were no longer statistically significant, and Stroop Interference scores (F[1,194]=1.33, p= 0.250) became statistically non-significant. Time Production (F[1,192]=0.14, p= 0.708), Go No-Go (F[1,196]=0.36, p= 0.550), and CPT (F[1,193]=0.001, p= 0.980) scores remained statistically non-significant. In terms of composite variables, the Working Memory Composite (F[1,191]=12.06, p= 0.001) remained statistically significant, but the Attention Composite (F[1,193]=0.70, p= 0.407) became statistically non-significant. Finally, the Impulsiveness Composite (F[1,191]=0.34, p= 0.533) remained statistically non-

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significant. In sum, when offspring with current depression, a history of ADHD, or a history of PTSD were excluded, only the working memory measures remained statistically significant. This data is presented in Table 8.

Exploratory Analyses

Given the neurocognitive deficits we observed in individuals at risk for developing depression, we wondered how well neuropsychological test performance could predict those at risk for depression. We also wondered which of our neuropsychological tests was the best predictor of depression. In order to determine this, we performed exploratory analyses in order to determine which measures were the strongest predictors of a) offspring versus normative group status, b) offspring with a history of MDD versus offspring without a history of MDD, c) offspring without MDD versus normative group, and d) offspring with current depression versus offspring without current depression.

Predicting Offspring vs. the Normative Group

Stepwise logistic regression using neuropsychological test scores was implemented in order to determine which measures contributed most strongly to the classification of offspring versus normative group status. N-Back and A, Not B emerged as significant predictors ($p<0.05$) of offspring status. This analysis revealed that 87.9% of offspring but only 29.9% of normative group could be identified (overall 67.2% correct classification; $\chi^2 = 25.43$, df = 2, $p = .000$).

In general, this analysis classified people with poorer working memory as offspring, and led to accurate classification of participants into the offspring group, but inaccurate classification of the normative sample as offspring. Poorer working memory

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was sensitive, but not specific.

Predicting Offspring with a History of MDD vs. Offspring without a History of MDD

Stepwise logistic regression using neuropsychological test scores and demographic variables was also implemented to determine which measures and variables contributed most strongly to the classification of offspring with a history of MDD versus offspring without a history of MDD. Age (p=0.000) and Go No-Go (p=0.006) emerged as statistically significant predictors of offspring with a history of MDD. Furthermore, Time Estimation (p=0.066) emerged as a marginally significant predictor of offspring with a history of MDD. This analysis accurately classified 26.9% of MDD offspring as MDD and 86.4% of offspring without MDD as non-MDD (overall 66.5% correct classification; $\chi^2 = 20.35$, df = 3, $p = 000$).

This analysis classified most people as not depressed. Specifically, it classified people who were younger and had better impulse control as not depressed, and led to a significant misclassification of those in the MDD group. Of the 52 people with MDD, it correctly identified only 14 of them.

Predicting Offspring without a History of MDD vs. the Normative Group

Stepwise logistic regression using neuropsychological test scores was also implemented to determine which measures contributed most strongly to the identification of offspring without a history of MDD. N-Back and A, Not B emerged as significant predictors (p<0.05) of those without a history of MDD. This analysis revealed that 70.9% of offspring with no history of MDD and 59.8% of the normative group could be correctly classified (overall 65.8% correct classification; $\chi^2 = 17.61$, df = 2, $p = 000$).

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To some degree, this is an overly stringent classification analysis, since one would expect that, within a risk group, there would be some individuals who would have the disorder they are at risk for (i.e. some individuals who had already converted to the diagnosis). Thus, this analysis is restricted to those who have not yet converted, as well as those who never will. Working memory measures were again the best predictor of those within this restricted risk group.

Predicting Offspring with Current Depression vs. Offspring without Current Depression

We also conducted exploratory analysis in order to try to classify which offspring were experiencing current depression. Stepwise logistic regression using neuropsychological test scores was implemented to determine which measures contributed most strongly to the classification of current depression (as measured by clinical rating scales). Worse A, Not B scores; better Go No-Go scores, and faster Time Estimation ($p<0.05$) emerged as significant predictors of current depression. This analysis revealed that 100% of not currently depressed offspring but only 7.1% of currently depressed offspring (a single individual) could be identified (overall 91.2% correct classification; $\chi^2 = 13.15$, df = 3, $p = .004$). Overall, this classification model was very specific, but not at all sensitive, since it simply classified virtually all offspring (except one) as not depressed.

Predicting Restricted Offspring Group vs. Normative Group

Given our findings that ADHD, PTSD, and current depression were each independently associated with lower neurocognitive performance, we also wanted to see whether we could predict offspring (versus normative group) status if we removed

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participants with these diagnoses from analysis.

Stepwise logistic regression using neuropsychological test scores was implemented in order to determine which measures contributed most strongly to the classification of the restricted offspring group (i.e., excluding offspring with ADHD, PTSD, and current depression). For this analysis, N-Back and A, Not B, two measures of working memory, emerged as significant predictors ($p<0.05$) of restricted offspring status. This analysis revealed that 60.9% of the normative group and 68.7% of the offspring group could be identified (overall 65.1% correct classification; $\chi^2 = 14.29$, df = 2, $p = .001$).

In general, similar to our classification analysis that included the entire offspring group, this analysis classified people with poorer working memory as members of the restricted offspring group. For this analysis, poorer working memory had roughly equal sensitivity and specificity, although neither was very high.

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IV. Discussion

The present study compared a relatively large sample of the offspring of parents with a lifetime history of MDD to a population sample of children and adolescents. The offspring sample (n=179) ranged in age from 10 to 19, had an average age of 14 years, an average of 8 years of education, an average level of estimated IQ, and were roughly half male and half female.

We sought to determine whether the neurocognitive difficulties characteristic in MDD are apparent in early to late adolescence in a high-risk sample, before the onset of illness in the majority of at-risk individuals. Specifically, we compared the two groups on measures of attention, working memory, impulse control, and visual memory. We examined the extent to which other factors, such as a history of psychological disorder(s) or current depression, were driving these differences. Lastly, we analyzed the extent to which neurocognitive measures could be used to predict current depression, history of MDD, and offspring status, respectively.

In a straightforward comparison of the offspring and normative samples, the groups differed on a number of cognitive performance tasks, including the Stroop; A, Not B; N-Back; and the Benton VRT. Furthermore, they differed on the Attention and Working Memory Composites and were close to different on the Impulsiveness Composite. Even though they were comparable for age, sex, and educational attainment, however, their estimated intelligence (as measured by PPVT-III scores) was significantly different (by about 5 Standard Score points). After adjusting for PPVT-III scores, univariate differences in Stroop performance and the Attention Composite became

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marginal. But differences in the working memory measures (A, Not B and N-Back), the Working Memory Composite, and Benton VRT scores remained significant.

Next, we examined whether these neurocognitive difficulties were present in and out of depressive episodes. The currently depressed offspring group scored significantly worse than the currently not depressed group on the A, Not B and Time Production; and Benton VRT tasks; but not on any of the other tasks; or on the composite variables. The small sample size of the currently depressed group (n = 17), however, raises significant questions about the adequacy of statistical power for this comparison.

In contrast, we found no differences in neurocognitive performance between offspring with a history of MDD and offspring with no history of MDD. The latter group, however, remains a risk group, and – to the extent that these neurocognitive difficulties are a component of risk – would not necessarily perform more poorly.

The offspring sample carried a number of comorbid diagnoses. The two that were associated with lower neurocognitive performance were ADHD and PTSD. Offspring with ADHD, consistent with previous findings on this diagnosis, performed more poorly on each of the attention measures (CPT and Stroop) and on the Attention Composite. They also performed more poorly on the N-Back task and the Working Memory Composite, as well as on the Go-No-Go task and on the Impulsiveness Composite. There were no major neurocognitive differences between offspring with and without PTSD; offspring with PTSD only had marginally poorer performance on the CPT. To insure that we were not including a separate diagnosis in our offspring risk group, however, we ran an additional analysis excluding these individuals as well.

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The goal of our study was to determine whether there are familial neurocognitive deficits specific to having a parent with MDD. We wanted to determine whether this risk was present in offspring who were not neurocognitively impacted by other psychological disorders. Therefore, we removed offspring with other psychological risk factors that we found to be associated with lower neurocognitive performance (i.e., current depression, ADHD, and PTSD), yielding a restricted offspring group. When we then re-ran our analysis with this restricted offspring group, differences in Benton VRT scores became non-significant. But differences in Working Memory measures and on the Working Memory Composite remained significant.

Lastly, we analyzed the extent to which neurocognitive measures could be used to classify offspring status, history of MDD, current depression, and restricted offspring group membership, respectively. Unfortunately, these analyses were hampered by the unbalanced nature of the samples being compared. There were significantly more participants in our offspring group (n = 179) than in our normative group (n = 88), leaving it possible in a logistic regression to get accurate classification merely by assigning most or all participants to the larger group. In general, equations, though significant, either lacked sufficient sensitivity, or specificity, or both, to be useful.

A recent literature review of first-degree relatives of individuals with MDD found that a general impairment in cognition was a feature of familial disposition for MDD (MacKenzie et al., 2019). After adjusting for differences in estimated IQ (a measure of general impairment in cognition), we found that differences in working memory remained. In sum, our results indicate that the offspring of patients with MDD carry

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weaknesses in working memory abilities that are above and beyond the general impairment in cognition that has been demonstrated in the literature.

The only other article that we found that examined neurocognitive difficulties in individuals at high risk of developing MDD found differences in set-shifting ability, but no differences in working memory (Papmeyer et al., 2015). They may not have found differences in working memory, however, because their measures were less sensitive. This study used the A, Not B and N-Back tasks; two measures of working memory that are at least partially dependent on processing speed. The outcome measure for A, Not B is response time to correct responses, and N-Back is paced against time. Papmeyer et al. (2015), by contrast, used the Digit Span backwards condition of the Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS: Wechsler, 1955); a common clinical measure of working memory, but one which does not have any timing component.

Working memory has been defined as "a temporary storage system under attentional control that underpins our capacity for complex thought" (Baddeley, 2007, p. 1). It stores information despite distractions, shifts in attention, and simultaneous information processing (Baddeley & Hitch, 1974; Engle, Tuholski, et al., 1999; Miyake & Shah, 1999). The extent to which a task requires access to stored information--information that could otherwise be lost from the focus of attention due to interference or decay--determines working memory capacity (Conway, et al., 2005). This capacity can be conceptualized as a general neurocognitive resource that contributes to performance in any domain that demands this type of information processing (Cowan, 1995; Engle, Tuholski, et al., 1999; Lovett, Reder, & Lebiere, 1999).

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Cognitive research psychologists and clinical psychologists tend to agree on this conceptualization of working memory, but often use different measures to assess it. While research psychologists use laboratory tasks that attempt to distinguish specific components of working memory, clinical psychologists often use standard psychometric indices, such as the working memory subscales from the WAIS (Shelton, Elliott, Hill, Calamia, & Gouview, 2009). The use of these indices is based on the assumption that they accurately represent the working memory construct defined by cognitive psychologists (Shelton, Elliott, Hill, Calamia, & Gouview, 2009). This assumption, however, has not been fully tested. Simple span tests, such as the WAIS Digits backwards subtest used by Papmeyer et al. (2015), are weak measures of working memory because they lack a processing component and thereby do not demand sufficient attentional control (Shelton, et al., 2009). A, Not B, and N-Back may be more demanding due to their link to response timing, and the need for sustaining attention for three minutes or more per condition.

Results overall suggest, however, that offspring of patients with MDD have a mild working memory deficit independent of any general cognitive deficiency. Previous research has demonstrated that working memory deficits are associated with MDD (Landro, Stiles & Sletvold, 2001) and are heritable (Ando, Ono, & Wright, 2001; Blokland et al., 2011; Vogler et al., 2014). Our results demonstrate that working memory deficits are associated with families, and are more strongly associated with MDD than with many other common psychiatric disorders (such as ADHD). In sum, our findings increase the empirical support for working memory as an endophenotype for MDD. This suggests that, rather than expending resources to administer full neurocognitive batteries

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on participants with MDD, researchers completing genetic studies need only administer working memory measures.

Identifying neurocognitive risk factors prior to illness onset is critical to identifying who would benefit from early intervention. It may also assist with the selection of differential treatments. Previous studies suggest that neurocognitive features of depression have predictive value for differential therapeutics. For example, deficient performance on tests of psychomotor speed has been associated with poorer response to antidepressants (Kalayam & Alexopoulos, 1999; Taylor et al., 2006; Bruder et al., 2014), but paradoxically good response to bupropion, a norepinephrine/dopamine reuptake inhibitor (Bruder et al., 2014). Poor performance on the A, Not B task, in particular, has been found to be related to poor response to specific serotonin reuptake inhibitors (SSRI's; Gorlyn et al., 2008).

Future neurocognitive research should determine whether working memory deficits in MDD co-segregate within families—that is, do family members who will ultimately convert to MDD have worse working memory deficits than those who pass through the ages of risk without ever developing MDD. Unfortunately, answering this question requires very extensive long-term follow-up of these risk samples. Future research should also investigate to what degree these working memory deficits are associated with MDD rather than other psychiatric disorders not included in our sample, such as schizophrenia, which has also been found to be associated with working memory deficits as well (Lett, Voineskos, Kennedy, Levine, & Daskalakis, 2014). This would help to determine whether working memory deficits are specific to MDD, or whether they are simply risk factors for a general vulnerability to psychiatric disorders.

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Our findings pave the way for future genetic studies, which can use genetic linkage and association strategies to identify genes associated with MDD and working memory (Flint & Munafo, 2007). Previous researchers have posited that endophenotypes are more appropriate than psychiatric diagnostic categories for genetic dissection (Gottesman & Gould, 2003). The genetic basis of endophenotypes is assumed to be less complicated than that of their associated psychiatric illness, and their genetic determination is therefore thought to be more straightforward. Through filling in the gap between gene and disease process, endophenotypes are posited to improve the chances of molecular level detection of genetic variants that contribute to disease susceptibility (Freimer & Sabatti, 2003, 2004).

The present study had a number of limitations. First, and importantly, the healthy comparison group was collected as a population-based normative sample with limited screening. Since they were not assessed with the same rigor as the offspring sample, there is a possibility that they included some individuals with psychiatric symptomatology that was hidden from examiners. Another limitation was our cross-sectional design. A longitudinal design, such as that which was used by Papmeyer et al. (2015), would help to establish the time course of cognitive deficits and depressive episodes. Furthermore, our offspring participants were children or adolescents at the time of our data collection. Those who had no current depression or history of MDD were still at risk of developing depression in the future. A longitudinal design that included assessment of depression status at later offspring age would capture more depressive episodes and better characterize offspring vulnerability.

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Another limitation was that the estimate of intelligence (PPVT-III) for the normative sample was significantly better than average (it fell in the high average range). Though we were able to demonstrate that working memory deficits were evident across the range of estimated ability, there may have been other factors associated with higher intelligence (e.g. higher socio-economic status, better educational opportunities) that boosted performance. In addition, sample sizes in the normative sample and the offspring sample were different.

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Tables

Table 1

Group Differences for Demographic Characteristics Between Offspring and Normative Groups, Clinical Characteristics of Offspring

	Offspring (n = 179)		Normative (n = 88)				
Variable	$\bar{x}$ *(M)*	*SD*	$\bar{x}$	*SD*	*df*	*t*	*p*
Age	13.87	2.74	14.35	2.86	265	1.33	0.185
Education	8.19	2.66	8.72	2.79	264	1.51	0.134
PPVT-III	107.88	13.40	113.03	11.65	265	3.08	0.002*
Rating Scale							
BDI	3.3 (3)	5.7	-	-	-	-	-
CDI	6.6 (4)	7.3	-	-	-	-	-
HRSD	3.3 (1)	4.4	-	-	-	-	-
CDRSR	21.6 (20)	7.1	-	-	-	-	-
Variable	*N*	*%*	*N*	*%*	*df*	χ^2	*p*
Male Sex	101	56.4	43	48.9	1	1.36	0.244
Past Diagnoses							
No Diagnosis	80	44.7	-	-	-	-	-
Any Diagnosis	99	55.3	-	-	-	-	-
MDD	61	34.1	-	-	-	-	-
Anxiety	43	24.0	-	-	-	-	-
PTSD	10	5.6	-	-	-	-	-
ADHD	30	1.7	-	-	-	-	-
ODD	16	1.1	-	-	-	-	-
Alc. Abuse	3	16.8	-	-	-	-	-
Sub. Abuse	2	8.9	-	-	-	-	-
Sui. Attempt	12	6.7	-	-	-	-	-

Note. * $p < .05$; $\bar{x}$ = Mean; M = Median; SD = Standard Deviation; BDI = Beck Depression Inventory; CBDI = Children's Beck Depression Inventory; CDI = Children's Depression Inventory; HRSD = Hamilton Rating Scale for Depression; CDSRS = Children's Depression Rating Scale, Revised; Past Diagnoses = History of psychiatric disorder(s); No Diagnosis = No history of any psychiatric disorder; Any Diagnosis = History of one or more psychiatric disorder(s); MDD = Major Depressive Disorder; Anxiety = Any anxiety disorder other than PTSD; PTSD = Post-Traumatic Stress Disorder; ADHD = Attention-Deficit/Hyperactivity Disorder; ODD = Oppositional Defiant Disorder; Alc. Abuse = Alcohol Abuse; Sub. Abuse = Substance Abuse; Sui. Attempt = History of one or more suicide attempt(s).

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Table 2

Group Differences for Individual Neuropsychological Test Scores Between Offspring and Normative Groups

	Offspring (n = 179)		Normative (n = 88)				
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*	*p*
CPT	-0.19	0.98	-0.1	0.99	255	1.36	0.174
Stroop Interference	-0.36	1.26	<0.01	1.00	256	-2.33	0.021*
A, Not B	-0.59	1.23	<-0.01	0.98	258	-3.85	0.000*
N-Back	-0.56	1.10	<-0.01	0.98	257	4.01	0.000*
Time Production	-0.24	1.03	<0.01	1.00	257	1.79	0.075
Go No-Go	-0.23	1.02	-0.07	1.11	261	-1.18	0.238
Benton VRT	-0.50	1.49	-0.01	0.96	246.46	-03.23	0.001*
Attn. Composite	-0.28	0.84	<-0.01	0.77	255	2.53	0.012*
WM Composite	-0.56	0.88	0.01	0.82	254	5.04	0.000*
Imp. Composite	-0.24	0.82	-0.04	0.75	256	1.92	0.057

Note. * $p < .05$. In Group, offspring group is coded as 1 and normative group is coded as 0. All scores were standardized for analyses.

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Table 3

Analysis of Covariance Results for Main Effect of Group on Neuropsychological Test Scores After Adjusting for Differences in PPVT-III Scores

Variable	*df*	*F*	*p*
CPT			
PPVT-III	1	20.10	<0.001*
Group	1	0.40	0.526
Error	254	-	-
Stroop Interference			
PPVT-III	1	13.21	<0.001*
Group	1	3.05	0.082
Error	255	-	-
A, Not B			
PPVT-III	1	19.89	<0.001*
Group	1	9.49	0.002*
Error	257	-	-
N-Back			
PPVT-III	1	13.52	<0.001*
Group	1	11.56	0.001*
Error	256	-	-
Time Production			
PPVT-III	1	14.98	<0.001*
Group	1	1.10	0.296
Error	256	-	-
Go No-Go			
PPVT-III	1	0.10	0.749
Group	1	1.21	0.273
Error	260	-	-
Benton VRT			
PPVT-III	1	16.87	<0.001*
Group	1	4.32	0.039*
Error	263	-	-
Attn. Composite			
PPVT-III	1	29.86	<0.001*
Group	1	2.90	0.090
Error	254	-	-
WM Composite			
PPVT-III	1	25.54	<0.001*
Group	1	.18.32	<0.001*
Error	253	-	-

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Imp. Composite			
PPVT-III	1	6.98	0.009*
Group	1	1.87	.173
Error	255	-	-

Note. * $p < .05$. In Group, offspring group is coded as 1 and normative group is coded as 0. All scores were standardized for analyses.

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Table 4

Group Differences for Individual Neuropsychological Test Scores Between Currently Depressed Offspring and Offspring Not Currently Depressed, Based on Clinical Rating Scales

	Offspring Currently Depressed (n = 17)		Offspring Not Currently Depressed (n = 150)				
Variables	$\bar{x}$	*SD*	$\bar{x}$	*SD*	*df*	*t*	*p*
Demographic							
Age	14.24	3.11	13.90	2.72	165	-0.48	0.636
Education	8.12	2.80	8.27	2.67	164	0.22	0.827
PPVT-III	103.88	11.86	108.69	13.51	165	1.41	0.162
Neuropsychological							
CPT	-0.46	0.72	-0.19	0.99	158	1.06	0.293
Stroop Interference	-0.38	1.22	-0.37	1.30	159	-0.02	0.983
A, Not B	-1.42	1.72	-0.53	1.14	16.47	-2.02	0.006*
N-Back	-0.63	0.80	-0.56	1.15	158	0.23	0.818
Time Production	-0.81	0.97	-0.18	1.04	158	2.37	0.019*
Go No-Go	-0.19	1.06	-0.28	1.01	163	0.33	0.742
Benton VRT	-0.61	0.69	-0.43	1.54	38.28	-0.90	0.038*
Attn. Composite	-0.42	0.69	-0.28	0.86	158	0.61	0.542
WM Composite	-1.00	1.01	-0.54	0.86	156	1.93	0.055
Imp. Composite	-0.50	0.73	-0.24	0.83	158	1.27	0.207

Note. * $p < .05$, $\bar{x}$ = Mean, SD = Standard Deviation. All scores were standardized for analyses.

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Table 5

Group Differences for Individual Neuropsychological Test Scores Between Offspring without and with Diagnoses

	No Diagnosis (n = 80)		Any Diagnoses (n = 99)				
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*	*p*
PPVT-III	107.35	13.52	107.53	13.90	108	-0.06	0.950
CPT	-0.10	0.88	-0.56	1.18	102	2.16	0.033*
Stroop Interference	-0.24	1.09	-0.82	1.80	103	-2.02	0.046*
A, Not B	-0.56	1.13	-0.90	1.73	37.24	-1.00	0.329
N-Back	-0.41	1.05	-0.87	0.94	102	2.05	0.043*
Time Production	-0.37	1.03	-0.37	0.89	104	-0.01	0.994
Go No-Go	-0.19	0.97	-0.61	1.18	106	-1.88	0.063
Benton VRT	-0.45	1.83	-0.66	1.15	107	-0.57	0.568
Attn. Composite	-0.17	0.72	-0.69	1.14	102	2.76	0.007*
WM Composite	-0.46	0.81	-0.86	0.88	102	2.18	0.032*
Imp. Composite	-0.29	0.83	-0.49	0.79	104	1.12	0.250

Note. * $p < .05$, $\bar{x}$ = Mean, SD = Standard Deviation. All scores were standardized for analyses. Diagnoses = MDD, anxiety, PTSD, alcohol abuse, substance abuse, ADHD, mood disorder, ODD.

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Table 6

Group Differences for Individual Neuropsychological Test Scores Between Offspring without and with ADHD

	Without ADHD (n = 154)		With ADHD (n = 30)				
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*	*p*
Age	13.87	2.56	12.91	2.48	171	1.93	0.056
Education	8.26	2.53	7.06	2.58	170	2.40	0.017*
PPVT-III	108.70	13.22	107.28	13.53	171	0.55	0.585
CPT	-0.08	0.90	-0.55	1.15	162	2.50	0.013*
Stroop Interference	-0.24	1.09	-0.81	1.75	37.02	-1.76	0.087
A, Not B	-0.55	1.12	-0.90	1.68	36.30	-1.11	0.272
N-Back	-0.48	1.04	-0.91	0.93	164	2.10	0.037*
Time Production	-0.18	1.03	-0.39	0.87	164	1.05	0.294
Go No-Go	-0.17	0.97	-0.65	1.16	169	-2.42	0.016*
Benton VRT	-0.39	1.34	-0.87	1.42	171	-1.82	0.070
Attn. Composite	-0.16	0.72	-0.68	1.11	162	3.27	0.001*
WM Composite	-0.51	0.86	-0.88	0.86	162	2.12	0.032*
Imp. Composite	-0.18	0.79	-0.52	0.78	164	2.18	0.030*

Note. * $p < .05$, $\bar{x}$ = Mean, SD = Standard Deviation. All scores were standardized for analyses.

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Table 7

Group Differences for Individual Neuropsychological Test Scores Between Offspring without and with PTSD

	Without PTSD (n = 174)		With PTSD (n = 10)				
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*	*p*
Age	13.80	2.65	14.90	3.28	180	-1.26	0.210
Education	8.13	2.60	9.10	3.25	179	-1.13	0.258
PPVT-III	108.43	13.30	99.60	8.91	180	2.07	0.040*
CPT	-0.15	0.98	-0.75	0.79	170	1.90	0.060
Stroop Interference	-0.35	1.25	-0.50	1.37	171	-0.35	0.751
A, Not B	-0.58	1.24	-0.73	1.15	174	-0.36	0.721
N-Back	-0.56	1.10	-0.79	0.98	172	0.63	0.529
Time Production	-0.22	1.02	-0.44	1.03	172	0.68	0.496
Go No-Go	-0.24	1.04	-0.48	0.90	177	-0.72	0.470
Benton VRT	-0.58	1.57	-0.22	1.53	179	0.70	0.487
Attn. Composite	-0.25	0.84	-0.62	0.66	170	1.37	0.173
WM Composite	-0.56	0.88	-0.76	0.78	170	0.68	0.497
Imp. Composite	-0.23	0.82	-0.46	0.79	172	0.87	0.388

Note. * $p < .05$, $\bar{x}$ = Mean, SD = Standard Deviation. All scores were standardized for analyses.

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Table 8

Analysis of Covariance Results for Main Effect of Group (excluding current depression, ADHD, and PTSD) on Neuropsychological Test Scores After Adjusting for Differences in PPVT-III Scores

Variable	*df*	*F*	*p*
CPT			
PPVT-III	1	17.956	<0.001*
Group	1	0.001*	0.980
Error	193	-	-
Stroop Interference			
PPVT-III	1	9.93	0.002*
Group	1	1.33	0.250
Error	194	-	-
A, Not B			
PPVT-III	1	31.65	<0.001*
Group	1	7.86	0.006*
Error	194	-	-
N-Back			
PPVT-III	1	11.34	0.001*
Group	1	7.20	0.008*
Error	194	-	-
Time Production			
PPVT-III	1	8.14	0.005*
Group	1	0.14	0.708
Error	192	-	-
Go No-Go			
PPVT-III	1	0.09	0.768
Group	1	0.36	0.550
Error	196	-	-
Benton VRT			
PPVT-III	1	9.50	0.002
Group	1	0.88	0.350
Error	198	-	-
Attn. Composite			
PPVT-III	1	25.37	<0.001*
Group	1	0.70	0.407
Error	193	-	-
WM Composite			
PPVT-III	1	27.09	<0.001*
Group	1	12.06	0.001*
Error	191	-	-

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Imp. Composite			
PPVT-III	1	4.15	0.043*
Group	1	0.34	0.533
Error	191	-	-

Note. * $p < .05$. In Group, offspring group is coded as 1 and normative group is coded as 0. All scores were standardized for analyses.

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Figures

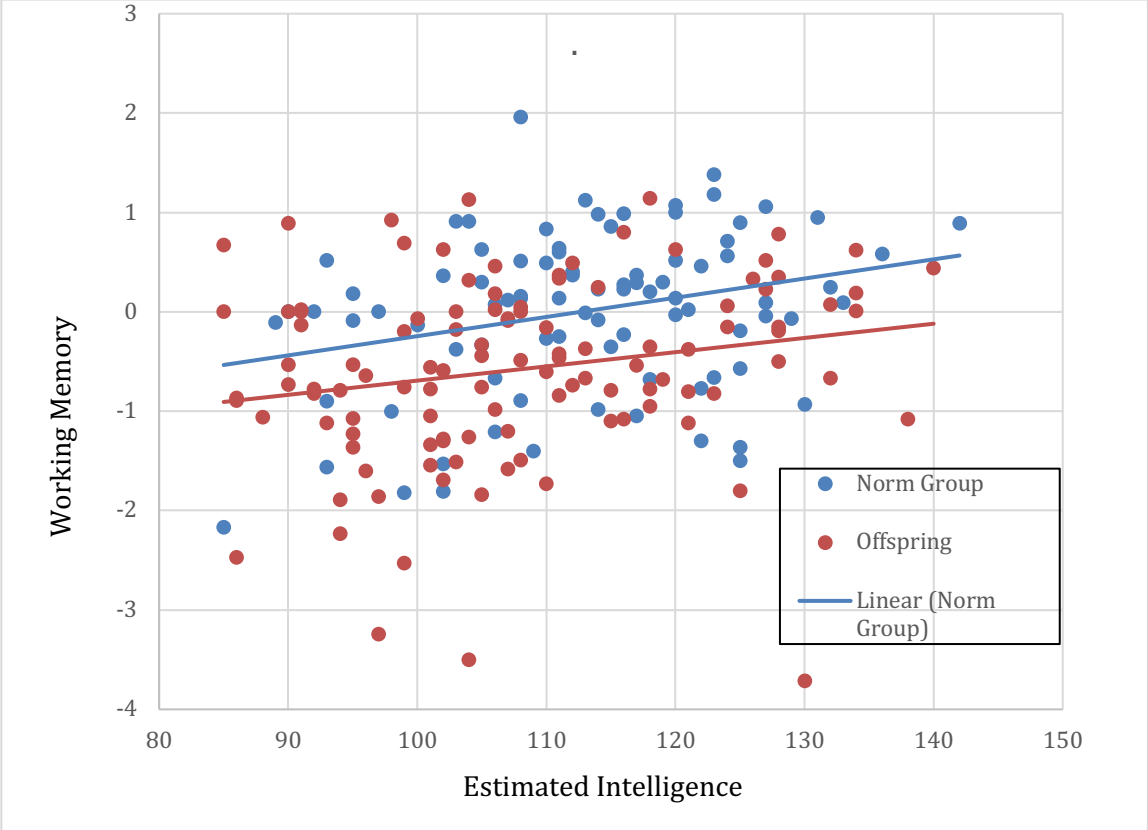

Figure 1. This table compares the entire offspring group to the normative group. It presents working memory as a function of estimated intelligence, by group. Estimated intelligence was measured using the PPVT-III, and data are presenting using standard scores. Working memory is a composite variable consisting of A, Not B and N-Back scores; presented as z-scores.

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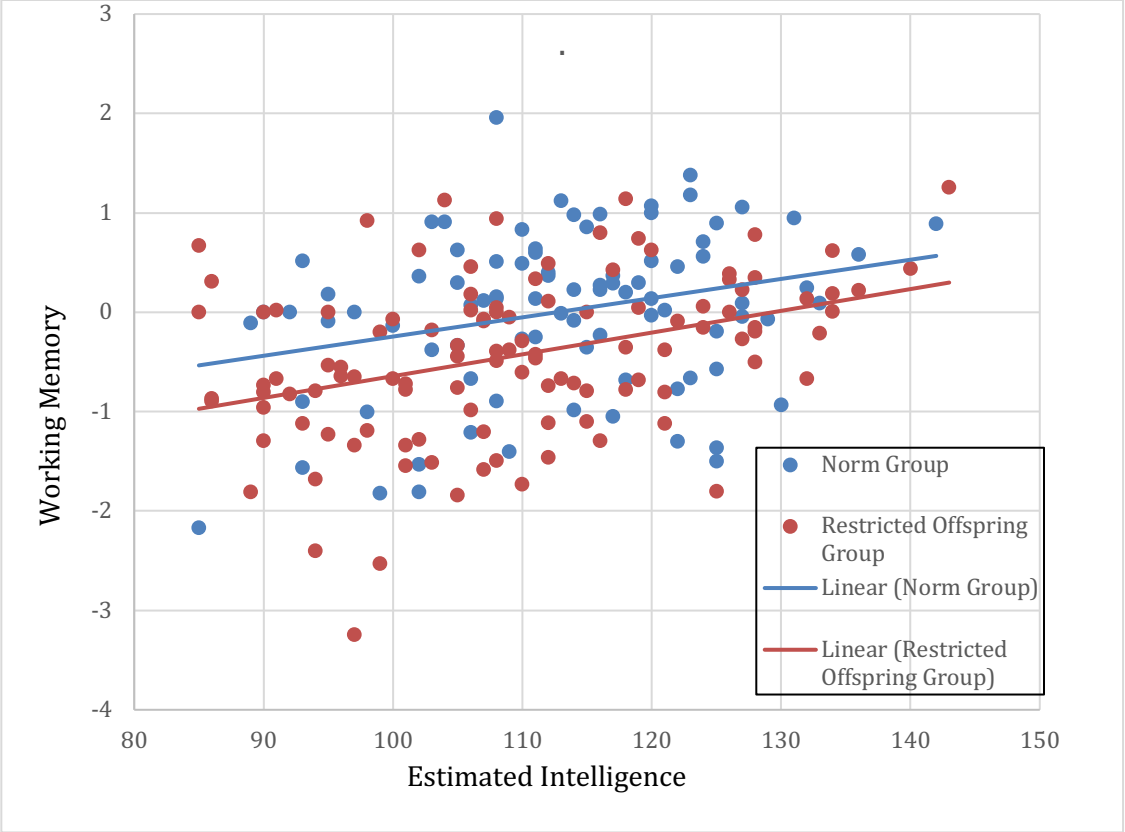

Figure 2. This table compares a restricted offspring group (excluding offspring with ADHD, PTSD, or current depression) to the normative group. It presents working memory as a function of estimated intelligence, by group. Estimated intelligence was measured using the PPVT-III, and data are presenting using standard scores. Working memory is a composite variable consisting of A, Not B and N-Back scores; presented as z-scores.

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