Trait and State Effects of Depression Severity on Neurocognition:

Evidence from a Longitudinal Study

BY

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THESIS

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<td>1.</td>
<td>ATTENTION/PROCESSING SPEED, VERBAL FLUENCY, COGNITIVE FLEXIBILITY, AND VERBAL MEMORY PERFORMANCE AMONG INDIVIDUALS WITH UNIPOLAR AND BIPOLAR DEPRESSION</td>
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LIST OF ABBREVIATIONS

BDNF  Brain-derived neurotrophic factor
CFUS  Chicago Follow-Up Study
CVLT  California Verbal Learning Test
DSM   Diagnostic and Statistical Manual of Mental Disorders
IQ    Intelligence Quotient
KAS   Katz Adjustment Scales
SADS  Schedule for Affective Disorders and Schizophrenia
SCL-90 Symptom Checklist 90
Trails A Trail Making Test part A
Trails B Trail Making Test part B
Trails B-A Trail Making Test part B time minus Trail Making Test part A time
WAIS  Wechsler Adult Intelligence Scale
WCST  Wisconsin Card Sorting Test
SUMMARY

Unipolar and bipolar depression are associated with neurocognitive impairment. However, both the specific pattern of deficits and whether unipolar and bipolar individuals differ on neurocognition remain unclear. Furthermore, neurocognition is related to current depression severity, but it is unknown whether this association stems from between-individual trait differences in disorder severity or from within-individual state variation in symptom severity. We addressed these questions in 43 unipolar and 51 bipolar participants drawn from a 25-year longitudinal study of severe mental illness. We assessed (1) differences among unipolar and bipolar individuals and the general population in attention/processing speed, verbal fluency, cognitive flexibility, and verbal memory; (2) the extent to which current symptom severity, overall trait disorder severity, and within-participant changes in symptom severity predicted neurocognition; and (3) the stability of neurocognitive measures over six years. Both groups showed generalized impairment relative to population norms. Bipolar participants performed more poorly than unipolar participants on measures of attention/processing speed; this may be attributable to differences in medication. Trait disorder severity predicted performance on attention/processing speed, cognitive flexibility, and long-term verbal memory. In contrast, within-participant state changes in depressive symptoms predicted change in only one non-specific cognitive measure. Most measures were stable over six years. Findings are consistent with previous evidence of generalized cognitive impairment in severe mood disorders. Associations of attention/processing speed, cognitive flexibility, and long-term memory with trait depression severity suggest these measures may be dimensional risk markers for severity of depressive illness.
1. INTRODUCTION

It is well established that both unipolar depression and bipolar disorder are associated with varying degrees of cognitive impairment. Indeed, some investigations have reported levels of decrement in depression comparable to neurological populations such as Huntington’s disease (Wolfe et al., 1987). Research has also suggested that some degree of impairment persists into euthymia (Austin et al., 2001; Olley et al., 2005). However, findings have differed widely on the time-course, severity, and specificity of impairments in unipolar depression and bipolar disorder, as well as on neuropsychological differences between these two populations. Moreover, few studies have considered the relationship between cognition and overall course of depressive illness.

1.1 Neurocognition in Mood Disorders

1.1.1 Unipolar Depression

Studies on neuropsychological deficits during unipolar depression have yielded inconsistent results. Many investigators have reported impairments across a broad range of neuropsychological domains (Reppermund et al., 2009). Others have found more specific deficits, but in different domains. For example, some studies reported deficits in memory, but not executive functions (Basso & Bornstein, 1999; Sweeney et al., 2000), while others reported deficits in executive functions, but not memory (Fossati et al., 1999). There have been several meta-analytic investigations comparing unipolar depressed to healthy individuals, but these have yielded similarly conflicting results. Specifically, different meta-analyses have reported the largest impairments in cognitive flexibility (Veiel, 1997), attention (Christensen et al., 1997), or episodic memory (Zakzanis et al., 1998). These conflicts may result from collapsing effects for individual tests into composite domains (as both Veiel and Christensen et al. did) or from
differences in study selection (Henry & Crawford, 2005). Nonetheless, meta-analyses have generally agreed that most domains are impaired to some degree.

In contrast, studies testing whether unipolar individuals remain impaired (relative to healthy controls) after recovering from mood episodes have conflicted on virtually every domain studied (including processing speed, attention, cognitive flexibility, fluency, and verbal memory; e.g., Biringer et al., 2005; Paelecke-Habermann et al., 2005; Preiss et al., 2009; Trichard et al., 1995).

1.1.2 Bipolar Depression

In comparison to neuropsychological studies of unipolar depression, a smaller literature exists on neuropsychological performance during the depressive phase of bipolar disorder. A recent meta-analysis comparing currently depressed bipolar individuals to healthy controls found impairments in all domains analyzed, with the largest effect size impairments in verbal memory, followed by phonemic fluency, attention, and attentional set-shifting (Kurtz & Gerraty, 2009). The results of a slightly older meta-analysis by Goodwin and Jamison (2007) were generally similar, although they found executive function to be the most impaired domain. Notably, only three to five studies of bipolar depression (depending on domain) were included in the Kurtz and Gerraty meta-analysis, and only one to three studies were included in the Goodwin and Jamison meta-analysis. Thus, preliminary evidence suggests broad neurocognitive impairment in the depressed phase of bipolar disorder. However, the specific profile of deficits remains unclear, due in part to a paucity of studies.

A much larger literature has compared healthy controls to currently euthymic individuals with bipolar disorder. Several meta-analyses of these results have consistently shown that individuals with bipolar disorder continue to exhibit broad cognitive deficits during euthymia
(Arts et al., 2008; Bora et al., 2009; Goodwin & Jamison, 2007; Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007). Verbal and non-verbal memory, cognitive flexibility, and category fluency are the most severely impaired domains.

1.1.3 **Unipolar Versus Bipolar Depression**

Studies that have directly compared currently depressed unipolar and bipolar individuals on neurocognition have yielded mixed results. Some studies have indicated poorer performance in bipolar depression on memory and executive tasks (Borkowska & Rybakowski, 2001; Wolfe et al., 1987), whereas several others have found no differences between unipolar and bipolar depression (Abrams & Taylor, 1980; Bearden et al., 2006; Sweeney et al., 2000). Further complicating matters, one study reported poorer executive function in unipolar than bipolar depression (Taylor Tavares et al., 2007). Similarly, of two studies comparing euthymic unipolar and bipolar participants on cognitive measures, one reported poorer performance in the bipolar group (Tham et al., 1997) while the other found poorer performance among unipolar individuals (Paradiso et al., 1997). Studies to date therefore do not allow clear conclusions to be drawn about differences in cognition between individuals with unipolar depression versus bipolar disorder.

1.2 **Effects of Depressive Symptom Severity**

One possible explanation for these conflicting findings is that, given the heterogeneity of mood disorders (Clark et al., 1995), neurocognitive deficits are unlikely to be uniform across all individuals with mood disorders. One factor that may parse the heterogeneity of mood disorders is the severity of depressive symptoms (McClintock et al., 2010)—that is, more severe symptoms may be associated with greater decrements in cognitive functioning. Indeed, two meta-analyses have found that this is the case (Christensen et al., 1997; McDermott & Ebmeier, 2009).
However, previous research on the relationship between depression severity and cognition presents interpretive challenges, and specifically has not revealed whether the deficits associated with depression severity are state-related and transient, or trait-related and persistent. Most studies have been cross-sectional (i.e., testing whether there is a rank-order relationship between differences in cognitive performance and depressive symptom severity at the time of testing), and therefore confound neurocognitive effects of within-individual symptom variation with between-individual trait differences in disorder severity. For instance, suppose one finds that verbal fluency is poorer in more severely depressed individuals (e.g., Henry & Crawford, 2005). This may be due to a within-individual state effect, in that individuals perform more poorly on fluency tests when depressed than when not, for instance due to fatigue associated with current depressive episodes. If this is the case, fluency in severely depressed individuals would improve when depressive symptoms improve. Alternatively, this finding may be due to a between-individual trait effect, in that individuals prone to experience more severe, recurrent, or chronic symptoms have poorer trait verbal fluency ability than those who experience milder or more infrequent depression. A corollary to this hypothesis is that those with a more severe illness would show poorer performance than those with a less severe illness regardless of their clinical state at the time of testing. Because most previous studies have assessed depression and cognition at just one time point, rather than considering the overall time-course of depression, they have been unable to distinguish between these two alternative explanations. However, several lines of evidence have suggested that there may be within-person state effects of depression on cognition, and a small number of studies provide indirect evidence for the trait effects hypothesis.

1.2.1 State Effects of Current Symptom Severity on Neurocognition
Most of these studies bear on the state effects hypothesis (i.e., that cognitive performance covaries with the course of current mood symptoms over time), but have yielded mixed results. For instance, studies that have induced depressed mood or rumination have found that healthy individuals show poorer phonemic fluency but better figural fluency after mood induction (Bartolic et al., 1999), or that induced depressive symptoms have no effect on cognitive performance (Clark et al., 2000). Philoppot and Brutoux (2008) reported that induced rumination led to poorer inhibition among dysphoric, but not non-dysphoric, college students. Experimental efforts to understand state effects of depressive symptoms on cognition are therefore inconclusive.

Another line of evidence relevant to the state effects hypothesis comes from studies that have assessed cognition in the same individuals twice—once during depressive episodes and again during euthymia. If current depressive symptoms affect test performance, the “removal” of these symptoms during euthymia should be associated with milder (or no) cognitive deficits. In unipolar depression, studies have generally found that performance in some areas does improve after recovery from depressive episodes; these studies nonetheless conflict regarding which specific domains are impaired by depressive symptoms (e.g., Beats et al., 1996; Neu et al., 2005). However, Reischies & Neu (2000) reported that impairments in verbal and non-verbal memory, fluency, and processing speed did not improve upon recovery from depression after controlling for practice effects (that is, any improvements observed in the depressed group at retesting did not exceed those observed in healthy controls). This calls into question results from other within-subjects studies, which have not controlled for practice effects.

We are only aware of one study that has examined within-subject changes in neurocognition across phases of illness in bipolar disorder. This study found poorer verbal recall
when subjects were depressed compared to when they were euthymic (Malhi et al., 2007). In addition to not controlling for practice effects, the very small sample size for this comparison (n = 6) limits the interpretability of these results. Kurtz and Gerraty (2009) meta-analytically compared separate studies of cognition during the depressive and euthymic phases of bipolar disorder and found significantly higher effect size impairments for verbal memory and phonemic fluency (but not processing speed or set-shifting) during depression than euthymia. This conclusion was limited by the small number of studies of bipolar depression available, and was not based on evaluation of the same individuals across phases of illness.

Thus, although limited evidence suggests that within-individual variation in depressive symptom severity may affect cognitive functioning, conflicting results and methodological limitations make this conclusion tentative at best. These studies of euthymic individuals are further limited by widely variable definitions of “euthymia” from study to study (e.g., various cutoffs on symptom measures, not meeting full DSM criteria for a depressive episode), and by the fact that not all individuals with mood disorders experience completely symptom-free periods (Judd et al., 1998; 2002; 2003). Unsurprisingly, individuals with more chronic or recurrent depression are particularly unlikely to experience periods of complete remission (Judd et al., 1998). Therefore, studies of euthymia may under-represent individuals with severe mood disorders.

Therefore, rather than relying on problematic definitions of euthymia, a better method of assessing the influence of depressive symptoms on performance may be to include participants with a full range of symptoms in the sample and model symptoms as a continuous variable. This approach is externally valid, as it captures the realities that mood symptoms vary in severity (both between individuals and within the same individual over time) and that there may not be a
clear boundary where “euthymia” begins. To date, no study has examined whether the degree of change in a continuous measure of depressive symptom severity predicts change in cognitive measures. This approach would allow a more fine-grained analysis of the state effects hypothesis than is possible with the dichotomous depressed/euthymic comparisons that have been utilized in previous studies.

1.2.2  **Trait Effects of Mood Disorder Severity on Neurocognition**

There is little evidence available to evaluate whether trait disorder severity is related to cognitive functioning. Basso and Bornstein (1999) reported poorer verbal memory in individuals with recurrent depression than in those experiencing a first depressive episode, who did not differ from population norms. Kessing (1998) found similar results among euthymic unipolar and bipolar individuals with regard to general cognitive functioning, but did not report domain-specific results. Insofar as recurrence is a proxy for “disorder severity” (Sullivan et al., 2000), this result provides some support for the trait effects hypothesis, albeit only in one domain.

If cognitive deficits in mood disorders are due to trait differences in disorder severity (rather than to state variations in current symptoms), these deficits should be stable over time. Several studies have investigated the longitudinal stability of neurocognitive dysfunction in mood disorders using subsets of the dataset used in the present study. Bonner-Jackson and colleagues (2010) reported that processing speed remained stable among individuals with non-psychotic depression over the course of twenty years. Burdick and colleagues (2006) found that, in 16 bipolar participants, measures of attention were stable over five years, but executive functioning and verbal memory were not. However, neither of these studies evaluated the effects of either within-individual changes in depressive symptoms or of between-individual differences in disorder severity.
Very little evidence relevant to the trait effects hypothesis exists. In fact, to the best of our knowledge, no study has directly evaluated the impact of trait disorder severity on neurocognitive function in mood disorders. It also is not clear what factors should be taken into account when determining “trait severity” of a mood disorder (McClintock et al., 2010). Most theorists have focused on symptom severity during depressive episodes (i.e., those who experience the most severe symptoms during episodes have the greatest “trait depression”). As Klein (2008) points out, although episode severity is one important factor to consider in classification of mood disorders, previous course is an equally important factor. For example, chronic depression is associated with greater functional impairment, higher rates of comorbidity, and increased risk for suicide compared to nonchronic depression (Gilmer et al., 2005; Holm-Denoma et al., 2006).

A valid operationalization of “trait depression severity” should therefore tap both episode severity and disorder chronicity. One way of achieving this is to average current symptom severity ratings taken across a number of prospective observations. This has the added advantage of avoiding biases inherent in retrospective report of symptoms and illness course (Ben-Zeev et al., 2009).

1.3 **Aims and Hypotheses**

Using data from a twenty five year longitudinal study of severe psychopathology (the Chicago Follow-Up Study [CFUS]; Burdick et al., 2006; Harrow et al., 1997; 2000; 2004), the current study evaluated attention/processing speed, verbal fluency, cognitive flexibility, and verbal memory in individuals with unipolar depression and bipolar disorder relative to each other and the normal population. Given that this is a severe sample (all participants were recruited during a psychiatric hospitalization), we predicted that mood disordered individuals would show
impairment on most measures relative to population norms. Some studies suggest that bipolar
participants perform more poorly than unipolar participants (Borkowska & Rybakowski, 2001;
Wolfe et al., 1987); however, due to conflicting findings (Sweeney et al., 2000; Taylor Tavares
et al., 2007), we did not make strong hypotheses for the effects of polarity.

Additionally, we examined effects of depression severity on cognitive performance. We
predicted that more severe current depressive symptoms will predict poorer performance across
domains (McDermott & Ebmeier, 2009). Because this cross-sectional analysis confounds state
and trait effects of depression severity on cognition, we also tested two competing hypotheses
regarding the source of this effect. Data from the CFUS are well-suited to independently
assessing state and trait effects of depression on cognitive ability, as they include
neuropsychological data from multiple time points, and twenty five years of longitudinal data on
depression severity (from which a measure of trait “disorder severity” can be derived). We
evaluated the state effects hypothesis by examining whether neurocognitive dysfunction is
longitudinally stable, and, if not, whether within-individual changes in depressive symptom
severity predict within-individual changes in cognitive functioning. We evaluated the trait effects
hypothesis by examining whether disorder severity over twenty-five years is as strong or
stronger a predictor of cognitive functioning than current symptom severity.

We evaluated the generalizability of these findings by testing whether polarity moderates
relationships between depression severity and cognition. Given that prior studies comparing
unipolar and bipolar depression on neuropsychological functioning have yielded mixed results as
described above, we did not make any specific hypotheses as to whether the effects will differ
based on diagnostic group.
2. METHODS

2.1 Participants

The present sample is drawn from the Chicago Follow-Up Study (CFUS), a 25-year prospective research program based at the University of Illinois College of Medicine studying psychotic and affective disorders (Burdick et al., 2006; Harrow et al., 1997; 2000; 2004). All participants in the present sample were recruited from inpatient hospital psychiatric units and initially diagnosed by Research Diagnostic Criteria (Spitzer et al., 1978) for an acute depressive or manic episode. Research diagnoses were made by a consensus team of senior research psychologists and clinical investigators based on information obtained from the Schedule for Affective Disorders and Schizophrenia, a semi-structured diagnostic interview (SADS; Endicott & Spitzer, 1978), or another semi-structured interview at the baseline hospital assessment.

The sample used for primary cross-sectional analyses consists of 94 participants, 43 with unipolar and 51 with bipolar affective disorders. Of the 51 bipolar participants, 16 had been diagnosed as unipolar at baseline hospitalization, but met criteria for a past year hypomanic or manic episode at one or more later follow-up points, and are therefore classified as bipolar in the present analyses. Participants were initially evaluated at the time of their baseline hospitalization and reassessed seven times, at approximately 2, 4.5, 7.5, 10, 15, 20, and 25 year points. Not all participants have neuropsychological data from more than one time point; therefore, the sample size for within-participant analyses is 45 (19 unipolar and 26 bipolar participants).

2.2 Measures

2.2.1 Diagnostic Assessment

Depressive symptoms were assessed at each follow-up using the composite depressed mood and behavior score (subscale 12) from the Katz Adjustment Scales (KAS; Katz and
Lyerly, 1963). The KAS is a 55-item self-report instrument that assesses various domains of distress, depressive symptoms, and adjustment during the previous few weeks and was the precursor to the Symptom Checklist 90 (SCL-90; Derogatis et al., 1973). Because participants completed the KAS at each follow-up, we were also able to use each participant’s mean KAS depression severity over all follow-ups as a measure of trait depressive illness severity (as opposed to current depressive symptom severity).

Manic and psychotic symptoms were also rated at each follow-up using the SADS. Participants who were psychotic or who had more than two SADS manic symptoms at the time of neuropsychological assessment were excluded from analyses.

2.2.2 **Neuropsychological Battery**

The follow-up assessments conducted during the first 10 years focused on psychopathologic symptoms and psychosocial functioning. Beginning at the 15 year time point, a neuropsychological battery was administered, which included measures of the following cognitive domains:

2.2.2.1 **Attention / Processing Speed**

- *Trail Making Test (Trails) part A* (Reitan, 1979). A test of attention and processing speed in which participants are timed while drawing lines consecutively between targets numbered from 1 through 25 as quickly as possible.

- *Digit Symbol.* In this processing speed subtest from the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955), participants are required to write symbols corresponding to a list of numerals based on a key.
2.2.2.2 **Fluency**

- *Verbal fluency* (Benton & Hamsher, 1976). A test of phonemic fluency in which participants are required to say as many words as they can starting with three different letters within 60 seconds per letter.

2.2.2.3 **Cognitive Flexibility**

- *Trails part B*. A measure of attentional set-shifting in which participants are timed while drawing lines alternating between numbered and lettered targets (i.e., from 1 to A to 2 to B and so on). As recommended by Lezak (1995), Trails B time minus Trails A time was used as a measure of cognitive flexibility, as it adjusts for psychomotor speed.

- *Wisconsin Card Sorting Test* (WCST; Heaton et al., 1993). A test of set-shifting and rule detection in which participants are required to sort cards based on an unstated rule which changes periodically. Participants must ascertain the rule, detect when the rule has changed, and change their sorting strategy accordingly based on feedback from the test administrator. Analyses included two WCST measures of set-shifting–categories completed and percent perseverative errors–along with percent non-perseverative errors.

2.2.2.4 **Verbal Learning and Memory**

- *California Verbal Learning Test* (CVLT; Delis et al., 1987). A test of verbal learning and memory. Participants hear five presentations of a list of words and recall as many words as they can after each presentation. Recall of the word list is tested again after administration of an interference list. Recall and recognition are tested after a 20 minute delay period. Trials 1 - 5 total learning, short delay and long delay free recall, and discriminability (i.e., recognition performance taking into account both hits and false positives) were included in analyses.
2.2.2.5 **Premorbid Intellectual Functioning**

- **Information.** This verbal subtest from the *WAIS* assesses crystallized general knowledge and has been shown to correlate with full scale IQ (Gold & Harvey, 1993).

2.3 **Analyses**

Due to the lack of a healthy control group, we compared the sample’s performance to published population norms for each test using z-scores and single sample *t*-tests. To identify possible covariates for the remaining analyses, bivariate correlations were employed to find clinical and demographic variables which are significantly correlated with neurocognitive measures. To test whether polarity, current depressive symptoms, or past average depressive illness severity predicted neurocognitive performance, we then conducted three sets of regression analyses. These each included neurocognitive measures as dependent variables and either polarity, current KAS depression severity, or past average KAS depression severity, along with covariates, as predictors. To determine whether effects of current and past depressive symptoms were uniform across diagnostic groups, we ran models testing for interactions between depressive symptoms (centered) and polarity. Significant interactions were followed up using analyses of simple slopes (Aiken & West, 1991; Holmbeck, 2002).

As a prerequisite to analyses of within-participant relationships between depressive symptoms and cognition, we assessed the longitudinal stability of KAS depression and each cognitive measure. A measure was deemed stable if it did not show significant rank-order or mean-level changes between the two time points, as evidenced by a significant Pearson correlation from the first to the second time point and a non-significant paired-samples *t*-test, respectively. To test whether changes in current symptom severity were associated with changes in neurocognition, we computed change scores from the first to the second time point for current
KAS depression severity and for neuropsychological measures which were not stable over time.

We then regressed the change scores for these measures on centered covariates and the centered change score for current KAS depression. We also examined whether these effects were moderated by polarity.
3. RESULTS

3.1 Demographic and Clinical Characteristics

Characteristics of the sample are presented in Table 1. Unipolar and bipolar participants did not differ on demographic variables, current or past average depression severity, or intellectual functioning. Bipolar participants were more likely to have a history of psychosis and to be taking lithium or antipsychotics at the time of neuropsychological testing. Groups did not differ on proportion taking antidepressants or psychiatric medications in general.

3.2 Group Differences in Neurocognition

The first aim of this study was to examine whether unipolar and bipolar depressed individuals show poorer neuropsychological performance than the general population, and whether these two groups differed from each other on performance. First, to identify differences between the sample and the normal population, we computed $z$-scores based on norming data for each measure; $z$-scores for both the unipolar and bipolar groups were then compared to published population means using single sample t-tests. These analyses revealed that both groups of participants performed more poorly than the general population on most measures, across all four cognitive domains (Figure 1). The one exception to this pattern is for Digit Symbol—unipolar (and, at trend, bipolar) participants performed better than the population on this measure.

We used linear regression to determine whether unipolar and bipolar participants showed different levels of cognitive performance. Because age, gender, and educational level were correlated with several neurocognitive measures, these were included as covariates in this and the following analyses. This set of analyses revealed that bipolar participants performed more...
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<td><strong>Demographics</strong></td>
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<tr>
<td>Age at Assessment (SD)</td>
<td>40.3 (5.4)</td>
<td>40.0 (5.3)</td>
<td>$t(90) = 0.28, ns$</td>
</tr>
<tr>
<td>% Female</td>
<td>60.5%</td>
<td>51.0%</td>
<td>$\chi^2(1) = 0.85, ns$</td>
</tr>
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<td>% Caucasian</td>
<td>65.1%</td>
<td>74.5%</td>
<td>$\chi^2(1) = 0.98, ns$</td>
</tr>
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<td>Years of Education (SD)</td>
<td>13.7 (1.8)</td>
<td>13.6 (1.9)</td>
<td>$t(91) = 0.36, ns$</td>
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<td><strong>Clinical Variables</strong></td>
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<tr>
<td>KAS Current Depression$^a$ (SD)</td>
<td>14.5 (5.2)</td>
<td>16.0 (5.2)</td>
<td>$t(90) = -1.40, ns$</td>
</tr>
<tr>
<td>KAS Average Past Depression$^b$ (SD)</td>
<td>14.6 (3.7)</td>
<td>15.4 (3.7)</td>
<td>$t(90) = -1.05, ns$</td>
</tr>
<tr>
<td>% with History of Psychosis</td>
<td>23.3%</td>
<td>51.0%</td>
<td>$\chi^2(1) = 7.59, p &lt; .01$</td>
</tr>
<tr>
<td><strong>Current Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Taking Antidepressant</td>
<td>27.9%</td>
<td>23.5%</td>
<td>$\chi^2(1) = 0.24, ns$</td>
</tr>
<tr>
<td>% Taking Lithium</td>
<td>7.0%</td>
<td>25.5%</td>
<td>$\chi^2(1) = 5.65, p &lt; .05$</td>
</tr>
<tr>
<td>% Taking Antipsychotic</td>
<td>4.7%</td>
<td>21.6%</td>
<td>$\chi^2(1) = 5.60, p &lt; .05$</td>
</tr>
<tr>
<td>% Taking Any Psychotropic</td>
<td>44.2%</td>
<td>60.0%</td>
<td>$\chi^2(1) = 2.32, ns$</td>
</tr>
<tr>
<td><strong>Premorbid Intellectual Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS$^c$ Information, Scaled (SD)</td>
<td>12.0 (3.0)</td>
<td>11.9 (2.6)</td>
<td>$t(90) = 0.17, ns$</td>
</tr>
</tbody>
</table>

$^a$ KAS current depression = Katz Adjustment Scales, subscale 12 (depressed mood and behavior), administered at time of neuropsychological testing

$^b$ KAS average past depression = average of KAS subscale 12 from all follow-ups, for individuals with KAS data from at least 3 follow-ups

$^c$ WAIS = Wechsler Adult Intelligence Scale
Figure 1. Attention/processing speed, verbal fluency, cognitive flexibility, and verbal memory performance among individuals with unipolar and bipolar depression. Graphed values are z-scores representing performance compared to published norms; lower scores represent poorer performance. Error bars represent standard errors. Asterisks over bars denote significant differences from population norms; asterisks over brackets denote significant differences between unipolar and bipolar individuals. \( ^{+} p < .10 \). \( * p < .05 \). \( ** p < .01 \), \( *** p < .001 \).
poorly than unipolar participants on both measures of attention/processing speed—Trails A and (at trend) Digit Symbol (Figure 1 and Table 2).\(^1\)

### 3.3 Effects of Current Depressive Symptoms

The second aim of this study was to determine whether current depressive symptoms affected neurocognition among individuals with mood disorders. To accomplish this, we regressed each measure on current KAS depression (along with covariates). Higher current depressive symptoms predicted significantly poorer performance on Digit Symbol, Trails B-A, CVLT long delay recall and, at trend, short delay recall.\(^2\)

### 3.4 Evaluating Trait Versus State Sources of Cognitive Impairment

The third and final aim of the study was to test two competing hypotheses regarding the course of cognitive deficits in mood disorders—the “trait effects” and “state effects” hypotheses.

---

\(^1\) Bipolar participants were more likely to have a history of psychosis and to be taking lithium or antipsychotics than unipolar participants. It is therefore possible that these results were due to these variables status rather than polarity. Interestingly, however, history of psychosis did not predict performance on any neuropsychological measure besides Digit Symbol (at trend). When history of psychosis was entered as a covariate, the effect of polarity dropped to non-significance, \(\beta = -.17, t(85) = -1.64, ns\). In contrast, use of antipsychotics did predict poorer performance on a number of measures, including both Trails A and Digit Symbol, while lithium use also predicted poorer Digit Symbol performance. When analyses were run controlling for antipsychotic use, unipolar and bipolar participants no longer differed on Trails A, \(\beta = .16, t(83) = 1.54, ns\), or Digit Symbol, \(\beta = -.13, t(85) = -1.33, ns\). Similarly, when lithium use was entered as a covariate, groups no longer differed on Digit Symbol, \(\beta = -.15, t(83) = -1.40, ns\). Controlling for medications in this way may be an overly conservative approach, as it removed variance due to the independent variable (insofar as medication use and polarity are correlated; Miller & Chapman, 2001). Nonetheless, the differences between unipolar and bipolar participants on Trails A and Digit Symbol may be due to the greater medication use in the bipolar group, and these results should be interpreted with caution.

\(^2\) Use of lithium was significantly associated with current depressive symptoms and with performance on Digit Symbol; however, the effect of current depression on Digit Symbol remained significant even when lithium use was entered as a covariate, \(\beta = -.28, t(81) = -2.72, p < .01\). Antidepressant and antipsychotic medications were not significantly associated with current depression severity; when these were included in analyses as covariates, the pattern of results was identical to that reported in Table 2.
TABLE II

EFFECTS OF DIAGNOSTIC GROUP AND CURRENT AND AVERAGE DEPRESSION
SYMPTOMS ON COGNITIVE PERFORMANCE\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Polarity</th>
<th>Current Depression\textsuperscript{b}</th>
<th>Past Average Depression\textsuperscript{c}</th>
<th>Current Depression X Polarity</th>
<th>Past Average Depression X Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention / Processing Speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A</td>
<td>.21*</td>
<td>.16</td>
<td>.24*</td>
<td>-.01</td>
<td>.05</td>
</tr>
<tr>
<td>WAIS\textsuperscript{d} Digit Symbol</td>
<td>-.20\textsuperscript{+}</td>
<td>-.26*</td>
<td>-.40**</td>
<td>.22</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonemic Fluency</td>
<td>.08</td>
<td>-.03</td>
<td>-.16</td>
<td>.08</td>
<td>-.08</td>
</tr>
<tr>
<td><strong>Cognitive Flexibility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B - A</td>
<td>.07</td>
<td>.34**</td>
<td>.30**</td>
<td>&lt; .01</td>
<td>-.05</td>
</tr>
<tr>
<td>WCST\textsuperscript{e} Categories Completed</td>
<td>-.03</td>
<td>-.13</td>
<td>-.18\textsuperscript{+}</td>
<td>.04</td>
<td>.11</td>
</tr>
<tr>
<td>WCST % Perseverative Errors</td>
<td>.02</td>
<td>.15</td>
<td>.30**</td>
<td>-.27\textsuperscript{+}</td>
<td>-.32*</td>
</tr>
<tr>
<td>WCST % Non-Persev. Errors</td>
<td>.14</td>
<td>-.05</td>
<td>-.06</td>
<td>.07</td>
<td>&lt; .01</td>
</tr>
<tr>
<td><strong>Verbal Learning (CVLT)\textsuperscript{f}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials 1-5 Total Recall</td>
<td>-.13</td>
<td>-.17</td>
<td>-.18</td>
<td>.07</td>
<td>.05</td>
</tr>
<tr>
<td>Short Delay Free Recall</td>
<td>-.15</td>
<td>-.18\textsuperscript{+}</td>
<td>-.17</td>
<td>.15</td>
<td>.07</td>
</tr>
<tr>
<td>Long Delay Free Recall</td>
<td>-.13</td>
<td>-.26*</td>
<td>-.22*</td>
<td>.05</td>
<td>-.01</td>
</tr>
<tr>
<td>Discriminability</td>
<td>-.13</td>
<td>-.05</td>
<td>-.17</td>
<td>.15</td>
<td>-.08</td>
</tr>
</tbody>
</table>

\textsuperscript{+}p < .10. *p < .05. **p < .01. ***p < .001

\textsuperscript{a} All values are $\beta$ coefficients from linear regression

\textsuperscript{b} Current depression = KAS depressed mood and behavior scale administered at time of neuropsychological testing

\textsuperscript{c} Past average depression = average of KAS depressed mood and behavior ratings from all follow-ups, for individuals with KAS data from at least 3 follow-ups

\textsuperscript{d} WAIS = Wechsler Adult Intelligence Scale

\textsuperscript{e} WCST = Wisconsin Card Sorting Test

\textsuperscript{f} CVLT = California Verbal Learning Test
3.4.1 **Trait Effects of Overall Depressive Illness Severity**

To test the trait effects hypothesis, we regressed each neuropsychological measure on past average KAS depression severity (and covariates). More severe past average depression predicted significantly poorer performance on five measures (plus one at trend). These included both measures of attention/processing speed: Trails A and Digit Symbol; all three measures of cognitive flexibility: Trails B-A, WCST percent perseverative errors, and (at trend) WCST categories completed; and one measure of verbal memory: CVLT long delay recall.3

3.4.2 **Longitudinal Stability of Neurocognitive Measures**

Next, we conducted analyses to test the state effects hypothesis in a subset of participants for whom we had neuropsychological data at two time points. The mean time between assessments was 6.4 years (SD = 2.4 years). As a prerequisite to these analyses, we assessed the longitudinal stability of KAS depression and each cognitive measure. A measure was deemed stable if it did not show significant rank-order or mean-level changes between the two time points. The former was established by a significant Pearson correlation from the first to the second time point, and the latter by a non-significant paired-samples \( t \)-test. These analyses revealed that both depression severity and most cognitive measures were stable over time (Table 3). The few exceptions were Trails B-A and WCST percent non-perseverative errors, neither of which were significantly correlated between the two time points, and CVLT long delay recall and (at trend) WCST percent perseverative errors, which rose significantly between the two time points.

---

3 Use of antidepressants was significantly associated with past average depressive symptoms and with WCST percent perseverative errors; however, the effect of past average depression on percent perseverative errors remained significant even when antidepressant use was entered as a covariate, \( \beta = .23, t(84) = 2.17, p < .05 \). Lithium and antipsychotic medications were not significantly associated with past average depression. When these were included in analyses as covariates, the pattern of results was similar to that reported in Table 2, though slightly weaker.
### TABLE III

LONGITUDINAL STABILITY OF NEUROCOGNITIVE MEASURES AND DEPRESSIVE SYMPTOMS

<table>
<thead>
<tr>
<th></th>
<th>Rank Order Stability: Correlation T1 - T2</th>
<th>Mean Level Stability: Paired Samples $t$-test T1 - T2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention / Processing Speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A</td>
<td>$r(40) = .32, p &lt; .05^a$</td>
<td>$t(41) = 1.19, ns$</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>$r(40) = .72, p &lt; .001$</td>
<td>$t(41) = -1.54, ns$</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonemic Fluency</td>
<td>$r(39) = .75, p &lt; .001$</td>
<td>$t(40) = -1.49, ns$</td>
</tr>
<tr>
<td><strong>Cognitive Flexibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B - A</td>
<td>$r(38) = .13, ns$</td>
<td>$t(39) = 0.70, ns$</td>
</tr>
<tr>
<td>WCST Categories Completed</td>
<td>$r(37) = .35, p &lt; .05$</td>
<td>$t(38) = -1.52, ns$</td>
</tr>
<tr>
<td>WCST % Perseverative Errors</td>
<td>$r(37) = .40, p &lt; .05$</td>
<td>$t(38) = 1.72, p &lt; .10$</td>
</tr>
<tr>
<td>WCST % Non-Persev. Errors</td>
<td>$r(37) = .24, ns$</td>
<td>$t(38) = 1.13, ns$</td>
</tr>
<tr>
<td><strong>Verbal Learning (CVLT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials 1-5 Total Recall</td>
<td>$r(40) = .61, p &lt; .001$</td>
<td>$t(41) = -1.07, ns$</td>
</tr>
<tr>
<td>Short Delay Free Recall</td>
<td>$r(40) = .56, p &lt; .001$</td>
<td>$t(41) = -1.15, ns$</td>
</tr>
<tr>
<td>Long Delay Free Recall</td>
<td>$r(39) = .73, p &lt; .001$</td>
<td>$t(40) = -2.30, p &lt; .05$</td>
</tr>
<tr>
<td>Discriminability</td>
<td>$r(36) = .68, p &lt; .001$</td>
<td>$t(37) = -1.22, ns$</td>
</tr>
<tr>
<td><strong>Depressive Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KAS Subscale 12</td>
<td>$r(43) = .61, p &lt; .001$</td>
<td>$t(44) = 0.63, ns$</td>
</tr>
</tbody>
</table>

^a **Boldface** values are consistent with longitudinal stability of that measure.
3.4.3 **State Effects of Within-Participant Symptom Variation**

To test whether changes in current symptom severity were associated with changes in neurocognition, we computed change scores from the first to the second time point for current KAS depression severity and for these four neuropsychological measures. We then regressed the change score for each neuropsychological measure on the change score for KAS depression and covariates (gender, education, and change in age from time one to time two). These analyses revealed that longitudinal change in depressive symptoms predicted significant change in percent non-perseverative errors, \( \beta = .37, t(34) = 2.31, p < .05 \). Individuals made more errors when more severely depressed than when they were less depressed. Change in depressive symptoms did not predict change in Trails B-A, \( \beta = .14, t(35) = 0.84, ns \); percent perseverative errors, \( \beta = .14, t(34) = .81, ns \); or CVLT long delay free recall, \( \beta = .03, t(34) = 0.20, ns \).

3.5 **Moderating Effects of Polarity**

To assess whether these effects were uniform across diagnostic groups, we conducted moderated regression analyses examining the interaction of polarity with current symptoms, past average symptoms, and change in symptoms in predicting neurocognition. With one exception, polarity did not significantly moderate the effects of current or average depressive symptoms, indicating that the effects of depression severity held for both unipolar and bipolar participants on most measures. However, for WCST percent perseverative errors, analyses did reveal a polarity by average past depression interaction as well as a trend interaction for polarity by current depression. Analyses of simple slopes of average depression severity at each level of polarity revealed that average depression predicted percent perseverative errors among unipolar, \( \beta = .36, t(81) = 3.48, p < .001 \), but not bipolar participants, \( \beta = .08, t(81) = 0.75, ns \). Taken together with the fact that both groups showed some impairment relative to the general
population (Figure 1), this appears to suggest that while bipolar participants show impairment on this measure regardless of disorder severity, only unipolar participants with more severe depressive illness made an elevated number of perseverative errors. Follow-up analyses of the trend-level polarity by current depression interaction revealed a pattern similar to that just described for past average depression.

Finally, the significant effect of within-individual change in depressive symptoms on change in WCST percent perseverative errors was qualified by a symptom by polarity interaction, $\beta = .81$, $t(32) = 2.16$, $p < .05$. Follow-up analyses of simple slopes of change in depressive symptoms at each level of polarity revealed that increases in depressive symptoms predicted more non-perseverative errors among bipolar, $\beta = .46$, $t(32) = 3.00$, $p < .01$, but not unipolar participants, $\beta = -.16$, $t(32) = -1.04$, $ns$. 

4. DISCUSSION

Although there is a growing literature on neurocognitive function in mood disorders, research to date has not yielded clear conclusions on the specific domains, time course, or source of cognitive deficits. The present study investigated these questions using measures of attention, processing speed, fluency, cognitive flexibility, and verbal memory from a twenty five year longitudinal study of individuals with unipolar depression and bipolar disorder. We found evidence of generalized cognitive impairment in both unipolar and bipolar depression. Additionally, more severe trait depressive illness predicted greater decrements in attention/processing speed, cognitive flexibility, and long-term verbal memory, while within-individual symptom fluctuation was not related to performance on most measures.

The first aim of the present study was to evaluate cognitive performance among unipolar and bipolar depressed individuals relative to the normal population and to each other. Relative to population norms, both unipolar and bipolar participants showed generalized impairment across all four cognitive domains investigated. This is largely consistent with prior research on cognition in both unipolar (Christensen et al., 1997; Reppermund et al., 2009) and bipolar depression (Bora et al., 2009; Kurtz & Gerraty, 2009). For unipolar participants, the largest effect size decrements were observed for long-term verbal retrieval, as reported by one previous meta-analysis (Zakzanis et al., 1998). Given the role of the hippocampus in long-term verbal memory (Squire, 1992) and the severity of this sample, this is consistent with the finding of reduced hippocampal volume in severe major depression (Campbell et al., 2004). Bipolar participants also performed most poorly on short- and long-term retrieval, in addition to a measure of attention/processing speed.
Surprisingly, participants (and in particular unipolar participants) performed above the population average on Digit Symbol, another measure of attention/processing speed. This measure was administered at each follow-up point after the index hospitalization; in contrast, all other measures in the battery presented here were administered starting around the 15 year follow-up. It is therefore possible that the performance of the sample on Digit Symbol was inflated by practice effects. This unexpected result may also be partially explained by the Flynn effect (the tendency of the population’s performance on IQ tasks to improve over time; Flynn, 1984; 1998), as 1981 norms for this test were used, but tests were actually administered in the 1990s and 2000s.

Direct comparisons of unipolar and bipolar participants on cognitive ability initially revealed poorer performance on both measures of attention/speed in the bipolar group, consistent with some previous studies showing poorer cognitive performance among bipolar than unipolar individuals (Borkowska & Rybakowski, 2001; Tham et al., 1997; Wolfe et al., 1987). This may be related to a greater prevalence of psychomotor retardation in bipolar than unipolar depression (Sobin & Sackeim, 1997). However, the difference found in the present study may be accounted for by sedative or slowing effects of antipsychotic drugs or lithium (Goldberg & Chengappa, 2009), both of which were more common among bipolar participants in the present sample (see footnote 1). The present results therefore may be more in line with previous findings of no cognitive differences between unipolar and bipolar depression (Abrams & Taylor, 1980; Bearden et al., 2006; Sweeney et al., 2000). Nonetheless, it is difficult to draw clear conclusions when groups differ on covariates such as medication use (Miller & Chapman, 2001), and more research is needed to tease apart cognitive effects of medications and polarity.
These findings are relevant to the relation between unipolar and bipolar disorder—a controversial topic (Klein et al., 2006). Some theorists argue that the differences between these disorders are largely quantitative rather than qualitative (i.e., they differ by degree rather than by kind), with bipolar disorder being more severe. For instance, based on rates of familial aggregation, Gershon et al. (1982) argue that risk for major depression, bipolar disorders, and schizoaffective disorder lie along a unitary dimension. Additionally, a recent meta-analysis of genome-wide association studies identified a locus on chromosome 3 conferring approximately equal risk for bipolar disorder and major depression (McMahon et al., 2010; but see comment and re-analysis by Breen et al., 2011). Consistent with this conceptualization, the present study did not find evidence of qualitative differences between unipolar and bipolar depression (i.e., impairments in separate domains) and found only equivocal evidence of quantitative differences (i.e., greater impairment among bipolar participants in attention/processing speed). The lack of robust quantitative differences may be attributable to the use of a relatively severe sample, with groups not differing on current or lifetime depressive symptom severity.

Nonetheless, many argue that bipolar and unipolar mood disorders are qualitatively different disorders. Some studies have found different symptom profiles during depressive episodes among unipolar versus bipolar individuals (Cuellar et al., 2005; Perris, 1992). Moreover, although data from twin studies suggest that most of the genetic variance underlying unipolar and bipolar depressive episodes is shared, most of the genetic risk for manic episodes is distinct from that for depression (McGuffin et al., 2003). Consistent with this, rates of bipolar disorder are elevated among relatives of bipolar, but not unipolar, probands (Winokur et al., 1995). It is therefore possible that qualitative differences between unipolar and bipolar participants may have been found in the current study if currently manic individuals had been
included as well. However, previous meta-analytic (Goodwin & Jamison, 2007; Kurtz & Gerraty, 2009) and direct within-subject comparisons (Malhi et al., 2007) have not found that cognitive deficits are more severe or widespread during mania than during bipolar depression. Together with the current findings, this suggests that severe unipolar and bipolar individuals do not show qualitative differences in neurocognition.

The second aim of the study was to assess the effects of depression severity on cognition. Current depressive symptom severity predicted poorer performance on three measures (one each of attention/processing speed, cognitive flexibility, and verbal learning). These results are generally consistent with prior studies (McDermott & Ebmeier, 2009). However, these cross-sectional effects are difficult to interpret, as they may stem from either state effects of symptom severity (i.e., individuals perform more poorly when depressed than when not) or trait effects of disorder severity (i.e., individuals with more severe mood disorders show greater cognitive decrement than individuals with less severe disorders, regardless of current clinical state). Indeed, this has been an important confound of previous cross-sectional studies of the relationship between depression severity and neurocognition.

The current study therefore evaluated these two competing explanations for the effects of depression severity. We found little support for within-individual state effects of depressive symptoms—most neurocognitive measures were stable over approximately six years, and longitudinal changes in depressive symptoms predicted change in only one measure, and then only among bipolar participants. In contrast, we found considerable support for between-individual trait effects of disorder severity. Trait disorder severity—operationalized as the average depression severity at several observation points over the previous twenty years—predicted poorer performance on both measures of attention/processing speed, all three measures of
cognitive flexibility, and a measure of long-term verbal memory. Notably, this included all three measures that were associated with current symptom severity, in addition to several others. In this sample, then, overall mood disorder severity accounted for a much greater share of neuropsychological impairment than within-individual fluctuations in symptom severity. Individuals who experience more severe or chronic symptoms showed impaired functioning across several domains of cognitive functioning. Additionally, these deficits appeared relatively persistent, and did not appear to covary with clinical state. These results are therefore consistent with findings that some individuals with unipolar depression (Reppermund et al., 2009) and bipolar disorder (Bora et al., 2009; Kurtz & Gerraty, 2009) show cognitive impairments even during periods of euthymia. Moreover, the results identify an important source of heterogeneity in mood disorders—average depression severity over time—which may help explain why not all samples have shown impaired performance during euthymia (e.g., Bulbena & Berrios, 1993).

These findings appear to be consistent among both unipolar and bipolar individuals. The only exception to this is that mood disorder severity predicted performance on one measure of cognitive flexibility (WCST percent perseverative errors) among unipolar but not bipolar participants. This may reflect that bipolar depressed individuals show similarly impaired flexibility regardless of disorder severity, whereas individuals with more severe unipolar depression perseverate more than those with less severe depression. Interestingly, a previous study found that longer duration of depressive illness predicted poorer performance on four measures of cognitive flexibility among unipolar, but not bipolar, participants, providing additional evidence of a specific effect of disorder severity on this aspect of cognition (Borkowska & Rybakowski, 2001). On the other hand, the present study found this moderating effect of polarity for only one of three measures of flexibility (i.e., WCST percent perseverative
errors but not categories completed or Trails B-A); additional replication is needed to fully understand this result.

Given their relation to trait mood disorder severity, impaired attention/processing speed, cognitive flexibility, and long-term verbal memory may be dimensional risk markers for more severe mood disorders. Deficits in these domains may be an indicator of other factors predisposing to mood disorders (e.g., frontostriatal dysfunction), or may themselves play a role in the etiology or maintenance of disorder. Although there is a larger literature on neurocognition as a risk marker for schizophrenia (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009), there is growing interest in candidate cognitive endophenotypes for bipolar disorder (Balanzá-Martínez et al., 2008; Glahn et al., 2004). For instance, first-degree relatives of bipolar probands show deficits in executive functions (including inhibition and set-shifting), verbal memory, and attention (Bora et al., 2009), supporting the role of cognition as a trait risk marker for mood disorder. In contrast, few studies have examined cognition among relatives of individuals with unipolar depression, although one study reported even broader impairment in this population than that found in relatives of bipolar individuals (Christensen et al., 2006). Cognition among healthy individuals at risk for unipolar depression is a promising area for future study.

In addition to representing pre-existing, potentially heritable risk markers, some trait cognitive deficits in mood disorder might be enduring “scars” of mood episodes. This would be consistent with the present finding that individuals with more chronic, highly recurrent, or severe mood episodes show more severe deficits in speed, flexibility, and memory. That is, there may be a dose-response relationship between total time depressed or lifetime symptom severity and cognitive impairment (Grant et al., 2001). A meta-analysis by Lin (2009) found that brain-derived neurotrophic factor (BDNF) levels were significantly lower in bipolar individuals during
both manic and depressive episodes than during euthymia, and levels of neurotrophic factors are similarly lower during depression than euthymia in unipolar individuals (Otsuki et al., 2008); these findings suggest one possible mechanism for a “scar” effect. Similarly, cortisol levels are higher during depressive episodes in the course of both unipolar (Rao & Poland, 2008; Steiger & Holsboer, 1997) and bipolar depression (Maj et al., 1984), and these elevations appear to contribute to cognitive deficits (Egeland et al., 2005; Gomez et al., 2009). Both these and other physiological sequelae of depressive episodes may help explain why individuals with greater lifetime illness severity manifest greater cognitive deficits.

The current results are consistent with findings of greater functional impairment among individuals with more chronic (Gilmer et al., 2005; Holm-Denoma et al., 2006) and/or severe (Evans et al., 1996; Kiosses & Alexopoulos, 2005; Simon et al., 2007) depression. Neurocognitive ability may be particularly relevant for adaptive functioning. Indeed, several studies have found that poorer cognition predicts greater functional impairment in depression (Baune et al., 2010; Jaeger et al., 2006; Kiosses & Alexopoulos, 2005). The findings of the current study therefore suggest that neurocognition may mediate the relationship between depression severity and life functioning. To date, however, no study has formally tested this mediational hypothesis.

Several limitations should be taken into account in interpreting this study. First, the independent variables (i.e., polarity, current and trait symptom severity) were related to potentially confounding factors such as history of psychosis and medication use. Covariate analyses suggest that the significant effects of symptom severity on cognition were not due to these factors; nonetheless, performing such analyses when the independent variable and covariate are correlated is not ideal (Miller & Chapman, 2001). Second, the fact that KAS
depression severity was stable over the two neuropsychological follow-up points may help explain why this variable did not predict change in most cognitive measures in the within-participant analyses. Nonetheless, change in depressive symptoms was associated with change in one cognitive measure, suggesting that other effects of within-person symptom fluctuation would have been detectable had they existed.

The study also had a number of strengths, stemming from the use of a 25-year prospective dataset with multiple assessments of symptomatology and neuropsychology. First, this allowed us to derive a measure of trait depression severity based on multiple current observations of depressive symptoms. This measure is therefore sensitive to both symptom severity and chronicity/recurrence, and is likely more valid than a one-time retrospective report (Ben-Zeev, Young, & Madsen, 2009). Second, we were able to assess the stability of cognitive measures, and the relationship between within-individual changes in depression and changes in cognition, over multiple assessments. We were therefore uniquely able to compare trait and state effects of depression severity on neurocognition in the same sample. Third, we were able to reclassify 16 individuals diagnosed as having unipolar depression at the index hospitalization as bipolar, based on identification of hypomanic or manic episodes at a later follow-up point. This stands in contrast to cross-sectional studies of unipolar depression, which cannot assess whether individuals diagnosed as “unipolar” go on to develop manic symptoms—a “conversion” which occurs in approximately 10% of apparently unipolar individuals (Coryell et al., 1995). A fourth strength was the use of multiple measures of most neuropsychological domains (e.g., Trails B, WCST categories completed, and perseverative errors for cognitive flexibility), which provided more robust evidence for effects in these domains than a single measure would have.
This study replicated previous findings of broad cognitive impairment associated with severe unipolar and bipolar depression. We found that these two groups showed generally similar levels of decrement, with bipolar individuals possibly having poorer attention/processing speed. Using longitudinal data on the course of mood disorders over twenty five years, we demonstrated that trait severity of mood disorder predicts level of impairment in attention/processing speed, cognitive flexibility, and long-term verbal memory. In contrast, within-individual symptom variation did not appear to predict substantial changes in neurocognition.
CITED LITERATURE


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