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Neurocognitive deficits and disability in major depressive disorder

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Abstract

Disability in life functioning is an important and poorly understood consequence of major depressive disorder (MDD). Mood symptoms do not account for the magnitude of disability resulting from MDD. Impairments in several domains of neurocognitive (NC) functioning have been shown to interfere with functionality in other psychiatric populations. These deficits, also present in MDD, may play a significant role in disability experienced by many with this disorder. The aim of this study was to examine the degree to which NC deficits, independent of affective and psychotic symptoms, explain functional outcome 6 months following hospitalization for a major depressive episode. Participants with an MDD diagnosis ($N=48$) received NC testing and symptom ratings while in the hospital. These procedures were repeated, along with functionality ratings, 6 months later. Six-month NC performance was strongly associated with functionality ratings after covariation for residual depression. Selected NC domains tested at baseline were predictive of functionality at 6 months. These data indicate that NC deficits, at least for some MDD sufferers, play an important role in functional recovery. New treatments, whether pharmacologic or rehabilitative, may be required to help affected patients accommodate neurocognitively based performance deficits at work, at home and in the community.

Keywords: Major depressive disorder; Neurocognitive deficits; Disability; Cognitive function; Neuropsychological tests; Functional recovery

1. Introduction

Disability in life functioning (LF) is one of the most important and least understood consequences of major depressive disorder (MDD). Many MDD sufferers struggle or even fail in their careers; they have trouble maintaining a household, managing their finances and sustaining family relations, friendships and community ties. Historically managed as an episodic condition, MDD is now widely regarded as a chronic, disabling disease affecting a range of LF domains (Keller and Hanks, 1994; Andrews, 2001; Judd, 1997). Twenty percent of patients are permanently incapacitated, while only another 20% permanently recover both clinically and functionally (Andrews, 2001; Lee and Murray, 1988; Judd et al., 1998). Judd et al. (2002) have shown that full inter-episode recovery is less common than had previously been assumed, with the typical course of MDD characterized by substantial periods of intermittent sub-threshold depressive symptoms. Severity of depression does not appear to fully explain level of disability: subsyndromal depression is associ-

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ated with a disability level comparable to that seen during major depression (Judd et al., 1996). Strikingly, few studies have sought to determine what accounts for this enormous disability.

Neurocognitive (NC) impairments in MDD have been reported on measures of executive functioning (Merriam et al., 1999; Schatzberg et al., 2000; Trichard et al., 1995; Paradiso et al., 1997), sustained vigilance (Cornblatt et al., 1989; Schatzberg et al., 2000; Dunkin et al., 2000; Sheline, 2000; Landro et al., 2001), visuomotor attention (Brown et al., 1994; Albus et al., 1996; Porter et al., 2003), ideational fluency (Dunkin et al., 2000; Fossati et al., 1999), short-term and working memory (Purcell et al., 1997; Basso and Bornstein, 1999), visuospatial processing (Coello et al., 1990; Henriques and Davidson, 1997; Bulbena and Berrios, 1993; Porter et al., 2003), verbal and non-verbal learning (Basso and Bornstein, 1999) and motor functioning (Landro et al., 2001; Hirschfeld et al., 1997; Borkowska and Rybakowski, 2001; Swann et al., 1999; Popescu et al., 1991) and general intelligence (Kluger and Goldberg, 1990). Not all studies have consistently found deficits in each of these domains. For example, a few studies found no significant differences between MDD patients and healthy controls in short-term and working memory (Purcell et al., 1997, 1998), and attention (Albus et al., 1996; Sweeney et al., 2000). Discrepancies may be due in part to different populations of MDD patients sampled (e.g., with or without psychotic features (Albus et al., 1996; Jeste et al., 1996). More likely to have significant NC deficits are patients with a younger younger onset age (Burt et al., 1995; Jovic, 1997), recurrent episodes (Basso and Bornstein, 1999), history of psychotic depression (Andreasen, 1997), poor response to pharmacotherapy (Dunkin et al., 2000) and higher residual symptom severity (Williams et al., 2000). Differences in test difficulty across test batteries may also impact sensitivity to group differences. Bremner et al. (2004) reported no significant difference between 18 MDD subjects and 9 healthy controls on verbal memory encoding performance; however, they found that depressed subjects failed to activate right hippocampus and anterior cingulate regions during task performance as did controls.

Unfortunately, most studies seeking to profile NC deficit in MDD have used small test batteries of varied composition, limiting comparison among them. Nevertheless, available meta-analyses reveal that NC deficits are reliably observed on tasks requiring mental flexibility/control, visual-spatial abilities, visual scanning/visuo-motor tracking, verbal fluency (especially phonemic fluency), and verbal and nonverbal learning and retention (Burt et al., 1995; Veiel, 1997). Recent longitudinal studies, albeit still with relatively small samples, have shown that specific declarative memory deficits present during the depressed state may improve with symptom remission (Vythilingam et al., 2004) while measures of attention continue to show deficits even with full remission and after correction for residual mood symptoms (Weiland-Fiedler et al., 2004). Researchers seeking to uncover abnormalities in the neural systems underlying cognitive deficits in affective disorders have begun to focus on the dynamic relationship between cognition and affect. Early observations suggest that "hot" cognitive tasks, i.e., those involving conflict or cognitive challenge under conditions of negative feedback, may be the most discriminatory (see reviews by Chamberlain and Sahakian, 2004; Tavares et al., 2003).

The role of NC deficits in producing disability in LF has not previously been studied in MDD. In other psychiatric populations, NC deficits have been shown to interfere with LF in a variety of ways such as getting and keeping a job, educational and career advancement, maintaining a household, and community and family relationships (Gold et al., 2002; Green and Nuechterlein, 1999; Velligan et al., 1997; Addington and Addington, 1993). NC deficits also directly impair problem solving, a coping method critical to ameliorating the disabling effects of any disease (Folkman and Lazarus, 1988; Wilder-Willis et al., 2002; Manly et al., 1997). Further, impaired coping and persistent LF disability have been shown to burden families, friends and coworkers (Judd et al., 1998) who, over time, diminish or withdraw their support, increasing the patient's reliance on compromised problem-solving ability to maintain LF roles and thus increasing exposure to stress. We hypothesize that NC deficits, known to be present in MDD, play an important causative role in persistent disability experienced by many with this disorder.

2. Methods

2.1. Participants

Participants were 48 SCID-DSM-IV confirmed MDD patients hospitalized at the Zucker Hillside Hospital. All participants provided written informed consent and underwent a battery of NC tests and clinical and functional ratings in the hospital and again 6 months later. Inclusion required at least one prior hospitalization for MDD, illness duration greater than 1 year, English fluency, and age between 18 and 59 at the time of the baseline assessment. Potential participants

were excluded from the study if they had a primary neurological disorder, mental retardation, or significant medical disability (including pregnancy), of their primary treatment target for the present admission was substance use, and if they had electro-convulsive therapy (ECT) planned during baseline inpatient stay or ECT within the 2-month period prior to recruitment. See Table 1 for demographic and clinical descriptive information.

Table 1
Sample demographics ($N=48$)

Gender	Female=67%
Ethnicity	Caucasian=81.3%
	African-American=8.3%
	Hispanic=6.3%
	Asian=4.2%
Age (years)	Mean=39.6 (S.D.=12.7)
Education (years)	Mean=14.5 (S.D.=2.2)
Years since first hospitalization	Mean=6.9 (S.D.=10.3)
Presence of psychosis	20.8% ($n=10$)
Medications at baseline	Mean number=2.69 (S.D.=1.35)
	62.6% antidepressant
	35.4% neuroleptic
	29.2% anti-convulsant
	18.8% anxiolytic
	6.3% anti-manic
	6.3% sedative

2.2. Procedure

Lifetime MDD diagnosis was confirmed using the Structured Clinical Interview for DSM-IV, review of all obtainable hospital records (including all previous hospitalizations), and consultation with available family members and treatment providers. These data were then assembled into a case summary, and presented and discussed at a weekly diagnosis consensus conference, where experts review cases enrolled in different studies involving a range of diagnoses. Experts were blind to NC testing results. Since this process can take time, recruitment and baseline evaluations are typically completed well before the consensus diagnosis is assigned. Only cases having completed the diagnostic consensus process and receiving an MDD consensus diagnosis were included in these analyses.

After patients were deemed sufficiently stabilized for assessment (mean Hamilton Depression Scale-17 score=16.47, S.D.=7.06) and typically while still in hospital,[1] they received a comprehensive NC test battery, clinical ratings including the Hamilton Depression Scale (HAM-D) and the Positive and Negative Symptom Scale (PANSS) (psychosis factor derived from the Brief Psychiatric Rating Scale items within the PANSS), and family and medical history interviews. Clinical, family and medical history information was also obtained from all available clinical records and collateral interviews. Where there were discrepancies, information judged to be the most reliable, based on all available sources, was entered into the database. NC testing and symptom ratings were repeated 6 months later. In addition, at the 6-month follow-up point, LF disability was assessed using the Multidimensional Scale of Independent Functioning (MSIF) (Jaeger et al., 2003a). The MSIF consists of a semi-structured interview and detailed rating anchors (ranging from 1=essentially normal, to 7=severely disabled) with demonstrated reliability and validity (Jaeger et al., 2003a). The MSIF differs from other disability rating scales by distinguishing the presence and level of support from both role responsibility and performance quality in three different instrumental role environments (work, education and residential), which are then incorporated into global ratings of disability that take all three factors into account. Table 2 provides a summary of the anchors for the MSIF overall global rating.

Obviously, some non-psychiatric medical conditions can also produce disability. Patients having such medical conditions were excluded from the sample as their inclusion would obscure the sought-after relationships between MDD factors (depressive symptoms, NC deficits) and disability. Although patients with known medical disabilities were excluded from recruitment, the possibility could not be ruled out that medical conditions would develop or become exacerbated over the 6-month follow-up period. Thus, at the time of the MSIF interview, participants were also asked to rate on a five-point Likert scale the degree to which they believed any chronic (non-neuropsychiatric) physical/medical disorders with which they had been diagnosed, contributed to functional disability. Ten (21%) of the 48 patients assessed at follow-up had developed medical disabilities they rated as moderately disabling (a rating of 3) or worse and were hence excluded from analysis.

The NC test battery, designed to test a wide range of cognitive domains, was typically administered over two to four sessions with frequent rest breaks, determined by the wishes of the study participant. For data analysis purposes, a subset of NC measures was selected a priori from each test in our battery and grouped into cognitive domains. In most cases, global summary measures for

[1] Most assessments took place toward the end of the hospital stay. A handful of participants were discharged before assessments could be conducted and returned to for this purpose within a week after discharge.

Table 2
Overall global ratings on the MSIF at follow-up

Rating	Anchors	Percent of sample
1	*Essentially normal* role functioning	26.3
2	*Very mild disability*–(could be at low end of normal range) somewhat below normal functioning with no or minimal support; functioning normally with some support	10.5
3	*Somewhat disabled*–performing adequately with regular support in mainstream environments; performing with some difficulty with no supports in mainstream environments	2.6
4	*Moderately disabled*–performing well in non-mainstream, specialized environments; performing with some difficulty in spite of regular supports in mainstream environment; performing with significant difficulty with no supports in mainstream environments	2.6
5	*Significantly disabled*–generally unable to function at all without supports; performing with some difficulty in non-mainstream, specialized environments; performing with significant difficulty even with significant supports in mainstream environments	18.4
6	*Extremely disabled*–generally unable to function in mainstream environments, even with supports; performing with significant difficulty or at extremely limited capacity in non-mainstream, specialized environments; performing well and showing some independent functioning in comprehensive care environments	18.4
7	*Totally disabled*–virtually total care provided in institutional or specialized environments with no independent functioning	21.1

each test in the battery were used; however, in some cases, alternate methods for examining summary measures were used to better reflect specific cognitive attributes (e.g., instead of combining digits forward and backward as is done in the original test, these were examined separately) or to preserve our ability to study asymmetries, which are of interest in MDD (e.g., for motor measures, dominant and non-dominant hands were not combined). These variables and their cognitive domain groupings are shown in Table 3. Since the sample size was too small to reliably employ available NC test data reduction methods (e.g., Jaeger et al., 2003b), an alternative approach was adopted. Similar to clinical decision making in neuropsychology, we reasoned that large effect sizes in single measures, or more modest effect sizes in groups of redundant measures within a single cognitive domain, could be interpreted as suggestive of a domain-specific finding.

2.3. Data analysis

We examined associations between NC deficits and functional outcome, measured by the overall global MSIF rating after a 6-month recovery period following a major depressive episode requiring hospitalization. We examined whether NC measures at baseline (during the episode) predicted functional outcome 6 months later, and whether NC measures collected 6 months post-baseline were associated with degree of functional recovery at that point. Finally, change in NC measures over the 6-month post-hospital period was examined.

The generalized linear model was used for polychotomous responses to explain the dependent variable (6-month rating on the Overall Global [OG] rating from the MSIF). The independent variable for each model is the NC test score. Covariates for each included the HAMD-17, PANSS positive symptoms (for psychosis) and the self-report rating of medical disability.

Throughout these analyses, we employed the Hochberg step-down method for correcting "familywise" multiplicity (e.g., within each cognitive domain) (Hochberg, 1988). This is a widely accepted alternative to the Bonferroni method for multiplicity correction and more appropriate for the present analyses. After rank ordering all the P-values in a group of variables, critical P-values are "stepped down" such that for the highest (least significant) observed value of P, the critical value equals 0.05. Critical values for subsequent tests are equal to 0.05 divided by the rank. (Thus, in a family of five analyses, critical P-values for highest to lowest observed values of P are, respectively, 0.05, 0.025, 0.0167, 0.0125, and 0.01.) Correction was applied before rounding of P-values.

3. Results

The sample was of average intelligence relative to published age-corrected norms (Verbal IQ = 98.1, S.D. = 14.7; Performance IQ = 95.0, S.D. = 12.0, Full Scale IQ = 96.6, S.D. = 13.2). There were no patterns of selective deficit in the group as a whole, with age-corrected scaled scores for each of the WAIS-R subtests ranging between 9 and 11. Depressive symptoms were mild to moderate at baseline testing (HAM-D 17 item version mean = 16.18, S.D. = 6.58) and significantly improved 6 months later (mean = 11.68, S.D. = 7.91, $t = 3.96$, $P < 0.001$, confidence limits = 2.21–6.79). With regard to functionality, as shown in Fig. 1 (and making refer-

Table 3
Results from two sets of analyses: (1) generalized linear model for polychotomous responses to explain the dependent variable (6-month rating on the overall global [OG] from the Multidimensional Scale of Independent Functioning [MSIF][a]) and (2) repeated-measures MANOVA to examine change in NC functioning between study baseline and 6 months

NC domains/measures		1. Relationship of NC to functionality[a,b]						2. Change in NC: Baseline to 6 months	
		Predictive models (baseline NC, 6 months MSIF ratings)			Associative models (NC and MSIF concurrent at 6 months)			MANOVA	
								Main effect for time	Time × Measure interaction
		×[b]	OR	*P*	×[b]	OR	*P*	*F* (*P*)	*F* (*P*)
Attention/ Processing Speed	D2 Errors				***10.57***	***6.52***	***0.001***	25.21 (<0.0001)	22.25 (<0.0001)
	Stroop Words				***7.25***	***4.19***	***0.007***		
	Stroop Colors	4.76	2.91	0.03 NS[c]	***9.80***	***6.70***	***0.002***		
	Trails A Time				5.62	4.30	0.02 NS		
	WAIS Digit Symb Raw	5.88	4.89	0.02 NS	***18.63***	***19.95***	***<0.0001***		
Working memory	D2 Fluctuation							5.62 (0.028)	NS
	WAIS Digit Span Forw				4.42	3.70	0.04 NS		
	LNS Total Correct				5.65	4.02	0.02 NS		
	LNS-Long Item				***6.83***	***5.97***	***0.009***		
	WAIS Arithmetic Raw								
	WAIS Digit Span Back	4.44	3.05	0.03 NS	5.48	3.98	0.02 NS		
	WMS LogicalMemory1	4.46	3.69	0.04 NS	5.08	3.72	0.02 NS		
Ideational fluency/ Executive Fx	WCST Persev Errors	4.65	5.06	0.03 NS				7.67 (<0.01)	2.89(0.04)
	RFFT Unique Designs				***8.12***	***5.87***	***0.004***		
	COWAT Correct				***12.32***	***9.51***	***0.0004***		
	Animal Naming				***14.75***	***35.90***	***0.0001***		
Verbal knowlg	WAIS Vocabulary Raw							12.33 (<0.002)	3.25(0.046)
	WAIS Compreh Raw								
	WAIS Similarities Raw								
Non-verb Fx	WAIS Block Des Raw				***6.34***	***3.84***	***0.01***	NS	NS
	WAIS Pict Comp Raw	5.72	3.67	0.017 NS	***7.74***	***8.77***	***0.005***		
	WAIS Pict Arrang Raw	***5.15***	***4.26***	***0.02***	4.86	5.02	0.03 NS		
Learning	WMS Verbal Paired I				***17.59***	***20.37***	***<0.0001***	NS	NS
	WMS Verbal Paired II	4.65	5.99	0.03 NS	***9.15***	***14.85***	***0.003***		
	WMS Visual Paired I	***7.05***	***4.15***	***0.008***	***14.30***	***9.94***	***0.0002***		
	WMS Visual Paired II								
Motor	Finger Tap Prefer'd							NS	NS
	Finger Tap Non-Pref								
	Grooved Peg Prefer'd								
	Grooved Peg Non-Pref	***6.92***	***0.21***	***0.009***	4.41	0.25	0.04 NS		

Guide to abbreviations in the table: *NC Domains*: Attn Proc Spd = Attention Processing Speed; Fx = Functioning. *Measures*: WAIS = Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981); D2 = Concentration–Endurance Test (Brickenkamp, 1981); WCST = Wisconsin Card Sorting Test (Grant and Berg, 1995); COWAT = Controlled Oral Word Association Test (Benton et al., 1978); WMS = Wechsler Memory Scale Revised (Wechsler, 1987); RFFT = Ruff Figural Fluency Test (Ruff et al., 1987). *Terms*: Persev Errors = perseverative errors; I = immediate; II = delayed; Mem = memory; Paired = paired associates; Rep = reproduction.

[a]Covariates for both predictive and cross-sectional models include concurrent HAMD-17, Psychosis and Medical disability (see text). OR = odds ratio (determined for 1 S.D. unit change in each NC var).

[b]Bolded/italicised analyses survive Hochberg step-down multicipality procedure (Hochberg, 1988). See text for description.

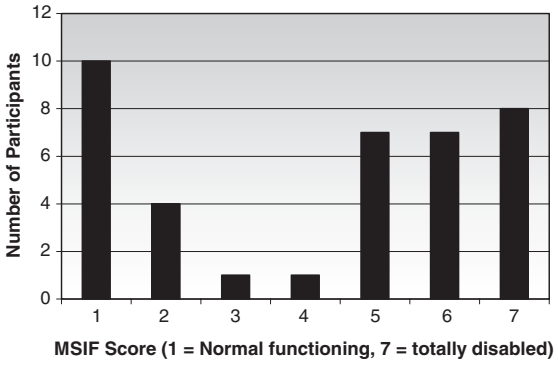

Fig. 1. MSIF distribution at follow-up (excluding cases having co-morbid disability).

ence to anchors shown in Table 2), excluding those having medical disabilities, nearly 60% of the sample rated as significantly, severely, or totally functionally disabled 6 months after baseline assessment. The MSIF global rating was significantly correlated to lifetime number of hospitalizations ($r=4.61$ $P=0.005$) but not age at first psychiatric hospitalization. Lifetime history of substance dependence was not associated with 6-month global MSIF rating.

Eighty-seven percent (87.5%) of the sample was taking a psychoactive medication (including all classes of antidepressants, anxiolytics, neuroleptics and mood stabilizers) at 6 months. The modal patient was taking three medications at baseline and two medications at 6 months. The mean number of psychoactive medications was 2.7 (S.D. =1.35) and 2.1 (S.D. =1.41) at baseline and 6 months, respectively. Since the study was naturalistic and medications were prescribed ad libitum, no causal inferences can be made regarding associations between medications and clinical or functional state. Nevertheless, it is interesting to note that global disability (MSIF global rating) was not different as a function of whether or not the patient was taking a neuroleptic; however, the 12 patients taking a benzodiazepine at 6 months had significantly worse functioning (mean=5.25, S.D. =2.26) than those not taking a benzodiazepine (3.50, S.D. =2.32) ($F=4.48$, $P=0.042$).

Few baseline NC measures were significantly predictive of 6-month functional outcome, although significant associations were found among nonverbal (visuo-spatial functions), learning and motor measures after correction for multiplicity using the Hochberg method (see above). Results of these analyses are shown in section 1 of Table 3 (the columns under the heading “Relationship of NC to functionality”).

Five out of seven cognitive domains showed significant findings in models of concurrent associations at the 6-month time point, e.g., the degree to which NC deficits present at the 6-month time point are associated with level of functional recovery at that point. Most measures within Attention, Ideational Fluency, Non-Verbal (visuo-spatial) and Learning domains were strongly associated with LF disability. Effect sizes are large to very large as reflected in the odds ratios (OR) (scaled in the table to standard deviation units). Thus, after accounting for the effect of residual depression and psychosis as well as presence of disabling medical comorbidities at follow-up, NC deficits were strongly associated with LF disability 6 months after hospital discharge.

Overall, concurrent associations were more consistent and reflect a broader representation of NC domains than predictive relationships. Only two of the seven NC domains studied were both predictive and concurrently associated with LF.

As shown in section 2 of Table 3 (the columns under the heading “Change in NC: baseline to 6 months”), significant main effects indicate improvement in four out of the seven NC domains. Three of these domains (attention, working memory and ideational fluency/executive functions) were not predictive, but were among those associated with LF recovery at 6 months. Thus, NC domains that remain stable from baseline to 6 months are associated with LF recovery regardless of when they are measured. On the other hand, NC domains that show improvement at 6 months are poor predictors if they are tested while the patient is in episode, but track with functional recovery independent of residual symptom levels at 6 months. (Note that symptoms were co-varied in both predictive and concurrent relationship models.) Further, symptoms at the time of NC testing are uncorrelated with NC measures at both baseline and 6 months: Of 120 correlation coefficients (30 NC variables correlated with two symptom variables–HAMD-17 and PANSS Psychosis factor–at two time points), four were statistically significant at the 0.05 level, with no pattern emerging among those four.

A close examination of individual data points for those variables that were correlated with disability at follow-up but did not predict disability suggested that patients who either failed to improve or worsened on neuropsychological test performance between baseline and follow-up were predominantly patients rated as significantly to totally disabled (ratings of 5–7) on the MSIF. Those improving on NP measures were more likely to be among those achieving higher levels of functional recovery.

When patients taking (vs. not taking) a neuroleptic or benzodiazepine at follow-up were compared, neither

class of drug was associated with differences on any individual neurocognitive measure studied.

4. Discussion

Nearly 60% of our sample remained significantly disabled or worse at the time of follow up, supporting other reports of high rates of persisting functional disability in this population (e.g., Andrews, 2001; Lee and Murray, 1988; Judd et al., 1998). Results additionally support the view that persistent NC deficits are, for some MDD sufferers, an important factor in functional recovery. Selected domains of NC functioning did not improve over the 6-month post-hospital period, and measures within these domains were predictive of level of functional recovery 6 months later. Among domains that did improve, all but one were associated with functionality at 6 months, consistent with our observation from individual scatter plots that NC improvement over time is associated with a higher likelihood of functional recovery. Also, there were patients for whom NC test performance worsened from baseline to follow-up, and these were almost exclusively patients who remained significantly to totally disabled at 6 months. Thus, it may be that patients who experience an improvement in NC performance are those who experience better functional recovery and both of these features are indicators of a more benign form of MDD. Conversely, 'residual' NC deficits at the time of follow-up are associated with greater disability and may be a marker of a more severe and disabling form of the illness associated with more frequent hospitalizations.

It is often assumed that NC deficits are secondary to depression-related decreases in motivational capacity or ability to exert sustained effort during testing. Two distinct lines of evidence indicate that this is not the case. First, motivation enhancement using monetary rewards results in significant (and similar) reinforcement-related improvement in both normal and MDD performance on a simple cognitive speed task but does not ameliorate deficits on visuo-spatial and verbal memory and learning tasks, which remain significantly worse in MDD patients than healthy controls (Richards and Ruff, 1989). Second, NC deficits are present during symptom remission (Neu et al., 2001; Paradiso et al., 1997; Tham et al., 1997), suggesting that deficits persist independent of mood state and are not secondary to depression-induced diminution in motivation. We note one study reporting minimal NC deficits in a mild–moderately depressed clinic sample that is in disagreement with these reports (Grant et al., 2001). However, the sample studied was unique and not representative of the substantial proportion of patients having a recurrent course, and a high rate of LF disability: the sample was highly educated (over 15 years), unmedicated, selected to have no psychotic features or comorbidities, and had an index episode lasting less than 2 years (non-chronic). In addition, relatively simple NC tasks were studied potentially producing a floor effect in this sample.

Little is known about how NC deficits arise in MDD. Current theories suggest that neuroanatomic changes in the brains of MDD patients may be the cause of observed deficits. Neuroimaging studies have shown enduring physical changes affecting hippocampus, amygdala, caudate nucleus, putamen and frontal cortex regions (Sheline, 2000), and postmortem studies show reduction in glia, neural size and/or synaptic proteins in subgenual, orbital and dorsolateral prefrontal cortex and amygdala (reviewed by Rogers et al., 1998; Davidson et al., 2002). Consistent with reports that NC deficits persist during remission of mood episode are findings of hippocampal volume reduction (associated with deficits in explicit memory; Sapolsky, 2000), reported to be present in MDD patients after an average of 31 weeks of symptom remission (Bremner et al., 2000). Reduced hippocampal size is hypothesized to occur in depression as a result of chronic stress-related hypercortisolemia (e.g., Sheline et al., 1996, 1999; Steffens et al., 2001), which itself has been associated with cognitive deficits (Belanoff et al., 2001). Whether caused by neuroanatomical change or chronic increase of stress-related glucocorticoid activity, to the degree that NC deficits interfere with LF recovery in MDD, these deficits must be targeted by MDD treatments.

A limitation in the current analyses is the number of comparisons, multicollinearity, and the need for data reduction procedures, which require a larger sample size than is currently available. Nevertheless, a substantial proportion of these MDD cases were significantly disabled 6 months after baseline, and convergent findings suggest that residual NC deficits, particularly in attention, ideational fluency, learning and nonverbal functions, were associated with level of functional recovery. The lack of an age-, gender- and education-matched healthy control group prevents us from estimating the level of NC deficit, both at baseline and after 6 months, although based on normative data, verbal, performance and full-scale IQ were all in the normal range, and age-corrected scaled scores for all subtests averaged between 9 and 11 for all subtests, suggesting that as a group there was no clinically significant global cognitive impairment. In spite of these limitations, the data reported here constitute (to our knowledge) the

largest longitudinal study to date examining the relationship between NC performance and disability in MDD.

With respect to illness chronicity variables, lifetime number of hospitalizations, but not age of illness onset, was significantly correlated with disability at 6 months. Those having co-morbid substance dependence were not significantly more disabled than those not carrying this diagnosis.

The ultimate goal of this work is to establish an empirical foundation for the development of interventions and services that more effectively target LF disability in MDD. The current follow-up period of 6 months may not be adequate to our purpose given the relatively long recovery course of MDD. Future studies will need to follow patients for a minimum of 2 years. Longitudinal studies inform us that, respectively, 1 and 2 years following an MDD episode 50% and 80% of patients achieve full symptomatic recovery. We do not at this point know the time course of NC and functional recovery. If, as our findings suggest, NC deficits play a critical role, this and future work in this area will inform evidence-based procedures for treating or accommodating NC-based performance deficits in the workplace, home and community, thus ameliorating the challenges patients now face to successfully return to work and other critical life roles.

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References

Addington, J., Addington, D., 1993. Premorbid functioning, cognitive functioning, symptoms and outcome in schizophrenia. Journal of Psychiatry and Neuroscience 18, 18–23.

Albus, M., Hubmann, W., Wahlheim, C., Sobizack, N., Franz, U., Mohr, F., 1996. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatrica Scandinavica 94, 87–93.

Andreasen, N.C., 1997. Linking mind and brain in the study of mental illnesses: a project for a scientific psychopathology. Science 275, 1586–1593.

Andrews, G., 2001. Should depression be managed as a chronic disease? British Medical Journal 322, 419–421.

Basso, M.R., Bornstein, R.A., 1999. Relative memory deficits in recurrent vs. first-episode major depression on a word-list learning task. Neuropsychology 13, 557–563.

Belanoff, J.K., Gross, K., Yager, A., Schatzberg, A.F., 2001. Corticosteroids and cognition. Journal of Psychiatric Research 35, 127–145.

Benton, A.L., Varney, N.R., Hamsher, K.D., 1978. Visuospatial judgment. A clinical test. Archives of Neurology 35, 364–367.

Borkowska, A., Rybakowski, J.K., 2001. Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. Bipolar Disorders 3, 88–94.

Bremner, J.D., Narayan, M., Anderson, E.R., Staib, L.H., Miller, H.L., Charney, D.S., 2000. Hippocampal volume reduction in major depression. American Journal of Psychiatry 157, 115–118.

Bremner, J.D., Vythilingam, M., Vermetten, E., Vaccarino, V., Charney, D.S., 2004. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. American Journal of Psychiatry 161, 637–645.

Brickenkamp, R., 1981. Concentration–Endurance Test Manual, vol. 5. Verlag fur Psychologie, Gottingen.

Brown, R.G., Scott, L.C., Bench, C.J., Dolan, R.J., 1994. Cognitive function in depression: its relationship to the presence and severity of intellectual decline. Psychological Medicine 24, 829–847.

Bulbena, A., Berrios, G.E., 1993. Cognitive function in the affective disorders: a prospective study. Psychopathology 26, 6–12.

Burt, D.B., Zembar, M.J., Niederehe, G., 1995. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychological Bulletin 117, 285–305.

Chamberlain, S.R., Sahakian, B.J., 2004. Cognition in mania and depression: psychological models and clinical implications. Current Psychiatry Report 6, 451–458.

Coello, E., Ardila, A., Rosselli, M., 1990. Is there a cognitive marker in major depression? International Journal of Neuroscience 50, 137–145.

Cornblatt, B.A., Lenzenweger, M.F., Erlenmeyer-Kimling, L., 1989. The continuous performance test, identical pairs version: II. Contrasting attentional profiles in schizophrenic and depressed patients. Psychiatry Research 29, 65–85.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: perspectives from affective neuroscience. Annual Review of Psychology 53, 545–574.

Dunkin, J.J., Leuchter, A.F., Cook, I.A., Kasl-Godley, J.E., Abrams, M., Rosenberg-Thompson, S., 2000. Executive dysfunction predicts nonresponse to fluoxetine in major depression. Journal of Affective Disorders 60, 13–23.

Folkman, S., Lazarus, R.S., 1988. Coping as a mediator of emotion. Journal of Personality and Social Psychology 54, 466–475.

Fossati, P., Amar, G., Raoux, N., Ergis, A.M., Allilaire, J.F., 1999. Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. Psychiatry Research 89, 171–187.

Gold, J.M., Goldberg, R.W., McNary, S.W., Dixon, L.B., Lehman, A.F., 2002. Cognitive correlates of job tenure among patients with severe mental illness. American Journal of Psychiatry 159, 1395–1402.

Grant, D., Berg, E., 1995. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. Journal of Experimental Psychology 38, 404–411.

Grant, M.M., Thase, M.E., Sweeney, J.A., 2001. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. Biological Psychiatry 50, 35–43.

Green, M.F., Nuechterlein, K.H., 1999. Should schizophrenia be treated as a neurocognitive disorder? Schizophrenia Bulletin 25, 309–319.

Henriques, J.B., Davidson, R.J., 1997. Brain electrical asymmetries during cognitive task performance in depressed and nondepressed subjects. Biological Psychiatry 42, 1039–1050.

Hirschfeld, R.M., Keller, M.B., Panico, S., Arons, B.S., Barlow, D., Davidoff, F., Endicott, J., Froom, J., Goldstein, M., Gorman, J.M., Marek, R.G., Maurer, T.A., Meyer, R., Phillips, K., Ross, J., Schwenk, T.L., Sharfstein, S.S., Thase, M.E., Wyatt, R.J., 1997. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. Journal of the American Medical Association 277, 333–340.

Hochberg, Y., 1988. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 75, 800–802.

Jaeger, J., Berns, S., Czobor, P., 2003a. The multidimensional scale for independent functioning: a new instrument for measuring functional disability in psychiatric populations. Schizophrenia Bulletin 29, 153–168.

Jaeger, J., Czobor, P., Berns, S., 2003b. Basic neuropsychological dimensions in schizophrenia. Schizophrenia Research 65, 105–116.

Jeste, D.V., Heaton, S.C., Paulsen, J.S., Ercoli, L., Harris, J., Heaton, R.K., 1996. Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. American Journal of Psychiatry 153, 490–496.

Jovic, N.I., 1997. Delusions, misidentifications and hallucinations in Alzheimer's disease. Croatian Medical Journal 38, 228–232.

Judd, L.L., 1997. The clinical course of unipolar major depressive disorders. Archives of General Psychiatry 54, 989–991.

Judd, L.L., Paulus, M.P., Wells, K.B., Rapaport, M.H., 1996. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. American Journal of Psychiatry 153, 1411–1417.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Archives of General Psychiatry 55, 694–700.

Judd, L.L., Schettler, P.J., Akiskal, H.S., 2002. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatric Clinics of North America 25, 685–698.

Keller, M.B., Hanks, D.L., 1994. The natural history and heterogeneity of depressive disorders: implications for rational antidepressant therapy. Journal of Clinical Psychiatry 55, 25–31 (Suppl A).

Kluger, A., Goldberg, E., 1990. IQ patterns in affective disorder, lateralized and diffuse brain damage. Journal of Clinical and Experimental Neuropsychology 12 (2), 182–194.

Landro, N.I., Stiles, T.C., Sletvold, H., 2001. Neuropsychological function in nonpsychotic unipolar major depression. Neuropsychiatry, Neuropsychology, and Behavioral Neurology 14, 233–240.

Lee, A.S., Murray, R.M., 1988. The long-term outcome of Maudsley depressives. British Journal of Psychiatry 153, 741–751.

Manly, J.J., Patterson, T.L., Heaton, R.K., Semple, S.J., White, D.A., Velin, R.A., Atkinson, J.H., McCutchan, J.A., Chandler, J.L., Grant, I., 1997. The relationship between neuropsychological functioning and coping activity among HIV-positive men. AIDS and Behavior 1, 81–91.

Merriam, E.P., Thase, M.E., Haas, G.L., Keshavan, M.S., Sweeney, J.A., 1999. Prefrontal cortical dysfunction in depression determined by Wisconsin Card Sorting Test performance. American Journal of Psychiatry 156, 780–782.

Neu, P., Kiesslinger, U., Schlattmann, P., Reischies, F.M., 2001. Time-related cognitive deficiency in four different types of depression. Psychiatry Research 103, 237–247.

Paradiso, S., Lamberty, G.J., Garvey, M.J., Robinson, R.G., 1997. Cognitive impairment in the euthymic phase of chronic unipolar depression. Journal of Nervous and Mental Disease 185, 748–754.

Popescu, C., Ionescu, R., Jipescu, I., Popa, S., 1991. Psychomotor functioning in unipolar and bipolar affective disorders. Romanian Journal of Neurology and Psychiatry 29, 17–33.

Porter, R.J., Gallagher, P., Thompson, J.M., Young, A.H., 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. British Journal of Psychiatry 182, 214–220.

Purcell, R., Maruff, P., Kyrios, M., Pantelis, C., 1997. Neuropsychological function in young patients with unipolar major depression. Psychological Medicine 27, 1277–1285.

Purcell, R., Maruff, P., Kyrios, M., Pantelis, C., 1998. Neuropsychological deficits in obsessive–compulsive disorder: a comparison with unipolar depression, panic disorder, and normal controls. Archives of General Psychiatry 55, 415–423.

Richards, P.M., Ruff, R.M., 1989. Motivational effects on neuropsychological functioning: comparison of depressed vs. nondepressed individuals. Journal of Consulting and Clinical Psychology 57, 396–402.

Rogers, M.A., Bradshaw, J.L., Pantelis, C., Phillips, J.G., 1998. Frontostriatal deficits in unipolar major depression. Brain Research Bulletin 47, 297–310.

Ruff, R.M., Light, R.H., Evans, R.W., 1987. The Ruff Figural Fluency Test: a normative study with adults. Developmental Neuropsychology 3, 37–51.

Sapolsky, R.M., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of General Psychiatry 57, 925–935.

Schatzberg, A.F., Posener, J.A., DeBattista, C., Kalehzan, B.M., Rothschild, A.J., Shear, P.K., 2000. Neuropsychological deficits in psychotic vs. nonpsychotic major depression and no mental illness. American Journal of Psychiatry 157, 1095–1100.

Sheline, Y.I., 2000. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biological Psychiatry 48, 791–800.

Sheline, Y.I., Wang, P.W., Gado, M.H., Csernansky, J.G., Vannier, M.W., 1996. Hippocampal atrophy in recurrent major depression. Proceedings of the National Academy of Sciences of the United States of America 93, 3908–3913.

Sheline, Y.I., Sanghavi, M., Mintun, M.A., Gado, M.H., 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. Journal of Neuroscience 19, 5034–5043.

Steffens, D.C., Wagner, H.R., Levy, R.M., Horn, K.A., Krishnan, K.R., 2001. Performance feedback deficit in geriatric depression. Biological Psychiatry 50, 358–363.

Swann, A.C., Katz, M.M., Bowden, C.L., Berman, N.G., Stokes, P.E., 1999. Psychomotor performance and monoamine function in bipolar and unipolar affective disorders. Biological Psychiatry 45, 979–988.

Sweeney, J.A., Kmiec, J.A., Kupfer, D.J., 2000. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biological Psychiatry 48, 674–684.

Tavares, J.V., Drevets, W.C., Sahakian, B.J., 2003. Cognition in mania and depression. Psychological Medicine 33, 959–967.

Tham, A., Engelbrektson, K., Mathé, A.A., Johnson, L., Olsson, E., Åberg-Wistedt, A., 1997. Impaired neuropsychological performance in euthymic patients with recurring mood disorders. Journal of Clinical Psychiatry 58, 26–29.

Trichard, C., Martinot, J.L., Alagille, M., Masure, M.C., Hardy, P., Ginestet, D., Feline, A., 1995. Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. Psychological Medicine 25, 79–85.

Veiel, H.O., 1997. A preliminary profile of neuropsychological deficits associated with major depression. Journal of Clinical and Experimental Neuropsychology 19, 587–603.

Velligan, D.I., Mahurin, R.K., Diamond, P.L., Hazleton, B.C., Eckert, S.L., Miller, A.L., 1997. The functional significance of symptomatology and cognitive function in schizophrenia. Schizophrenia Research 25, 21–31.

Vythilingam, M., Vermetten, E., Anderson, G.M., Luckenbaugh, D., Anderson, E.R., Snow, J., Staib, L.H., Charney, D.S., Bremner, J.D., 2004. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biological Psychiatry 56, 101–112.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale—Revised. The Psychological Corporation—Harcourt Brace Jovanovich Inc, San Antonio, TX.

Wechsler, D., 1987. Wechsler Memory Scale—Revised. Psychological Corporation, New York.

Weiland-Fiedler, P., Erickson, K., Waldeck, T., Luckenbaugh, D.A., Pike, D., Bonne, O., Charney, D.S., Neumeister, A., 2004. Evidence for continuing neuropsychological impairments in depression. Journal of Affective Disorders 82, 253–258.

Wilder-Willis, K.E., Shear, P.K., Steffen, J.J., Borkin, J., 2002. The relationship between cognitive dysfunction and coping abilities in schizophrenia. Schizophrenia Research 55, 259–267.

Williams, R.A., Hagerty, B.M., Cimprich, B., Therrien, B., Bay, E., Oe, H., 2000. Changes in directed attention and short-term memory in depression. Journal of Psychiatric Research 34, 227–238.