The Frequency of Cognitive Impairment in Patients With Anxiety, Depression, and Bipolar Disorder: An Unaccounted Source of Variance in Clinical Trials

C. Thomas Gualtieri, M.D., and Dexter W. Morgan, B.A.

Background: Patients with anxiety, depression, and bipolar disorder are known to be impaired relative to healthy controls on neurocognitive tests, but the degree of impairment may be obscured if the data are analyzed in terms of group means.

Method: Patients and controls were administered a comprehensive neurocognitive assessment that measured performance in 5 domains: memory, psychomotor speed, reaction time, attention, and cognitive flexibility. Clinic patients diagnosed per DSM-IV-TR criteria with generalized anxiety disorder (N = 63), major depressive disorder (N = 285), and bipolar I or II disorder (N = 96) were compared with 907 controls. Subjects' age range was 18 to 65 years. Patients had no comorbid psychiatric disorders and no medical, neurologic, or developmental conditions that might affect cognition (e.g., attention-deficit/hyperactivity disorder, brain injury, mild cognitive impairment, chronic pain). Data on patients and controls (collected from March 2003 through February 2007) were taken from a clinical database that also contained neurocognitive test scores.

Results: There were small differences between patients and controls, between different patient groups, and between treated and untreated patients when neurocognitive results in terms of group means were compared. Comparisons of results in terms of the frequency with which patients and controls fell below certain cutoff scores amplified the importance of these differences. Only 4% of controls fell below a standard score of 70 (2 standard deviations below the mean) on 2 or more cognitive domains, but 19% of anxiety patients, 21% of depressed patients, and 30% of bipolar patients fell below the standard score.

Conclusions: Substantial numbers of patients with anxiety, depression, and bipolar disorder are cognitively impaired. A score that is 2 standard deviations below the mean is usually clinically important, and 2 domain scores in that range is cause for serious concern. The importance of this finding is discussed, with respect to clinical trials, in terms of establishing a homogeneous trial population and minimizing the placebo response rate.

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Dr. Gualtieri is one of the developers of the CNS Vital Signs neurocognitive assessment battery. Dr. Gualtieri has conducted clinical trials on behalf of Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech, Cephalon, Eli Lilly, GlaxoSmithKline, Medeva, Organon, Pfizer, Shire, Wyeth-Ayerst, and UCB; has been a speaker for and/or consultant to Eli Lilly, GlaxoSmithKline, Pfizer, Shire, and Wyeth; and is a partner in CNS Vital Signs, LLC. Mr. Morgan is associated with CNS Vital Signs, LLC.

Corresponding author and reprints: C. Thomas Gualtieri, M.D., NC Neuropsychiatry, 400 Franklin Square, 1829 East Franklin St., Chapel Hill, NC 27514 (e-mail: tg@ncneuropsych.com).

When psychiatric patients are compared with healthy controls, there is abundant evidence that they perform less well on neurocognitive tests. Patients with depression are subject to multiple neuropsychological deficits, most notably attention and the executive functions.[1–5] Patients whose depression is successfully treated with modern antidepressants perform better on cognitive tests than untreated patients, but not as well as controls.[5] Patients with bipolar disorder have cognitive impairments that are similar to those of unipolar depressives, in kind and degree,[6] and which may persist, despite clinical euthymia.[7] This is true even of the best clinical responders, "patients in excellent clinical remission and who reported good social adaptation."[8(p1027)] Their degree of cognitive impairment correlates with the number of previous affective episodes[6,9] and may worsen as the disease progresses.[10,11]

Patients with anxiety resemble patients with mood disorders in tests of attention, memory, information processing, and executive control.[12,13] Their deficits may or may not be clinically manifest. Anxious patients may be impaired in their performance on neurocognitive tests (especially if they have test anxiety), but, as a rule, deficits are less prominent than they are in depressed patients.[14] The notable exceptions, of course, are posttraumatic stress disorder and obsessive-compulsive disorder.[15–18]

The association between mood/anxiety disorders and impairment on neurocognitive tests, if not in real-world situations, is strong and consistent. However, formal cognitive evaluation plays a small part in the evaluation of psychiatric patients or the treatments that are brought to

bear on their behalf and is hardly ever used as an exclusion criterion in clinical trials. It is ironic, perhaps, but understandable, if one considers the following.

Historically, psychiatric disorders were conceptualized as "functional" or "emotional" in nature and distinct from "cognitive" disorders like dyslexia and mental retardation or "organic" disorders like dementia. This terminology is woefully obsolete, but it is largely preserved in the orientation of psychiatrists in practice. It has never been possible to establish a reliable association between specific cognitive domains and specific psychiatric diagnoses. In other words, it is not possible to use a neurocognitive test to establish the diagnosis of a particular psychiatric condition or to distinguish, for example, between depression and anxiety or bipolar disorder.

The focus of psychiatric treatment is on overt symptom control. If one can treat anxiety effectively, the patient's accompanying functional difficulties should improve as well. What is the point of addressing secondary manifestations of the disorder as long as the primary problem is dealt with satisfactorily? The failure of neurocognitive tests to predict functional status remains a vexing problem.[19]

Nevertheless, neurocognitive testing has the potential for guiding and perhaps improving clinical practice and for establishing the dimensions of a patient's condition, its severity, and the degree of disability associated with it. Accurate assessment has the potential to guide treatment and promote rehabilitation. On a more basic level, cognitive testing allows researchers to explore the cognitive correlates of the patient's behavioral and emotional symptoms and to understand how complex functional systems participate in the evolution of psychiatric disorders. It is, after all, simply an assumption to assert that the feeling of anxiety, for example, is the primary problem, while cognitive bias in information processing is secondary. It may be the other way around.

It is possible that an alternative approach to studying cognition in psychiatric patients might be more fruitful. Establishing that patients in group A perform worse than controls on a neurocognitive test is one way to approach the problem, but it is not the only way, or even the best way. Differences in group means may or may not be meaningful; cognitive impairments that occur in a few patients can be obscured by the larger numbers of patients who perform in the average or above-average range. In 1 study of depressed patients, for example, we established that neurocognitive performance measured in terms of a global neurocognition index was 3% lower than matched controls in treated patients and 7% lower in untreated patients.[20] The clinical importance of a 3% decrement, or even 7%, however, remained to be demonstrated.

In this investigation, we shall deal with the problem of cognitive differences in a different way. Our subjects were patients with depression, anxiety, and bipolar disorder. The issue is not whether group differences exist between patients and controls, because we know that they do. The question we shall address is the frequency of clinically meaningful neurocognitive impairment.

METHOD

Subjects

The subjects of this investigation were 444 patients, aged 18 to 65 years, with 3 psychiatric disorders (DSM-IV-TR criteria): generalized anxiety disorder (GAD) (N = 63); major depressive disorder, unipolar, nonpsychotic (N = 285); and bipolar disorder (I or II) (N = 96). They were all outpatients at the North Carolina Neuropsychiatry Clinics in Chapel Hill and Charlotte, private clinics specializing in neuropsychiatric evaluation and medication treatment. Every new patient at the Neuropsychiatry Clinics is administered a computerized neurocognitive test battery. Once patients achieve a satisfactory clinical response to treatment, and medications are stable for at least 4 weeks, they are tested again. Patients give written informed consent to allow their deidentified data to be used for purposes of research and evaluation; they can take advantage of our Web site to withdraw consent at any time.

This was a convenience sample of patients attending a clinic. Some patients were currently taking medications for their condition disorder; others were untreated. Patients' psychiatric diagnoses were conferred by a psychiatrist using DSM-IV-TR criteria. The diagnoses were confirmed by a second psychiatrist. All of the patients had taken the CNS Vital Signs computerized screening battery: untreated patients as part of their initial evaluation at the clinic and treated patients after they had achieved a therapeutic response and were on a stable medication dose for at least 4 weeks. Data were collected from March 2003 through February 2007.

From the CNS Vital Signs normative database of more than 1500 healthy people, 907 controls were selected, aged 18 to 65 years. ("Controls" were people who were in good health, medication free, and free of any present or past cognitive, neurologic, or psychiatric disorder. They were recruited in community settings in North Carolina, Florida, Connecticut, Colorado, and California.[5])

Neurocognitive Evaluation

The CNS Vital Signs neurocognitive assessment battery contains 7 tests that are widely used by neuropsychologists. Verbal memory and visual memory are adaptations of the Rey Auditory Verbal Learning Test and the Rey Visual Design Learning Test.[21,22] Correct responses from verbal memory and visual memory are summed to generate a composite memory or memory domain score.

The Finger Tapping Test is one of the core tests of the Halstead-Reitan Battery,[23] but similar tests were used by 19th century psychologists like Wundt, Galton, and Cattell. Symbol Digit Coding is based on the Symbol Digit Modalities Test,[24] itself a variant of the Wechsler Digit-Symbol Substitution test.[25] The total of right and left taps from the Finger Tapping Test and total correct responses on the Symbol Digit Coding generate a composite score for psychomotor speed.

The Stroop Test[26] in the CNS Vital Signs battery has 3 parts that generate simple and complex reaction times. Averaging the 2 complex reaction time scores from the Stroop Test generates a domain score for reaction time. It might be more precise to refer to this domain as "information processing speed."

The Shifting Attention Test (SAT) measures the subject's ability to shift from 1 instruction set to another quickly and accurately. Color-shape tests like the SAT have been used in cognitive-imaging studies.[27,28] A domain score for cognitive flexibility is generated by taking the number of correct responses on the SAT and subtracting the number of errors on the SAT and the Stroop Test.

The Continuous Performance Test is a measure of vigilance or sustained attention.[29] A domain score for complex attention is generated by adding the number of errors committed on the Continuous Performance Test, the SAT, and the Stroop Test.

The CNS Vital Signs battery has been standardized in 1504 healthy volunteers aged 5 to 96 years. Peak performance on the tests is achieved during the third decade of life and declines gradually thereafter. Test-retest reliability ranges from 0.65 (attention) to 0.87 (psychomotor speed). The test-retest reliability of the CNS Vital Signs battery is comparable to those reported for similar traditional tests and to similar tests in other computerized test batteries.[5] The concurrent validity of the CNS Vital Signs battery is comparable to similar conventional neuropsychological tests.[5] Discriminant validity has been established in studies of patients with mild cognitive impairment and early dementia,[5] postconcussion syndrome and severe traumatic brain injury,[30] attention-deficit/hyperactivity disorder (ADHD),[31] depression,[32] schizophrenia and bipolar disorder,[32] and malingering.[5]

The CNS Vital Signs battery is widely used by psychiatrists, neurologists, and neuropsychologists around the world (G. L. Iversen, Ph.D.; B. L. Brooks, Ph.D.; M. D. Weiss, M.D., manuscript submitted). It has been used in registration studies in more than 1000 clinical sites around the world in patients with schizophrenia, bipolar disorder, ADHD, depression, restless legs syndrome, mild cognitive impairment, and epilepsy (www.cnsvs.com).

Procedures

The Neuropsychiatry Clinics maintain a database of clinical data and neurocognitive test scores. The database contained more than 7000 records at the time of this analysis. There were 3569 patients aged 18 to 65 years. The first step was to exclude patients with overt cognitive disorders (ADHD, learning disability, brain injury, mild cognitive impairment, early dementia). Patients with chronic pain, sleep disorders, and neurologic conditions such as epilepsy, multiple sclerosis, and migraine were also excluded.

The second step was to select patients with diagnoses of major depressive disorder, generalized anxiety disorder, or bipolar disorder I or II. This procedure yielded 691 patients with depression, 340 with anxiety, and 199 with bipolar disorder. The third step was to exclude comorbid psychiatric disorders, so patients with mixed anxiety and depression were excluded; patients with posttraumatic stress disorder, obsessive-compulsive disorder, or panic disorder were also excluded. This final step yielded a relatively "pure" sample of patients with major depressive disorder (but not anxiety) and generalized anxiety (but not depression). The bipolar group excluded other diagnoses but combined types I and II. None of the bipolar patients were manic.

The performance of patients and controls was evaluated in terms of their scores on the 5 domains of the CNS Vital Signs test battery: memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility. Cognitive impairment was measured by applying 2 cutoff scores: subjects who scored between 85 and 70 were between 1 and 2 standard deviations (SDs) below the age-adjusted mean; subjects who scored below 70 were 2 SDs or more below the mean.

Performance was also evaluated in terms of the number of domains in which subjects scored below 70. We used a conservative method to establish whether a patient might be considered "cognitively impaired." Theoretically, a domain score that is more than 2 SDs below the mean represents impairment. We did not consider a patient to be cognitively impaired in this investigation unless at least 2 domain scores were lower than 70 (see Discussion).

RESULTS

The patient sample and the controls were predominantly white, well educated, and reflective of the communities from which they were drawn (Table 1). Women were underrepresented in the depression and anxiety groups compared with bipolar patients and controls ($\chi^2 = 57.7$, $df = 3$, $p < .01$) and nonwhites were underrepresented in the depression and bipolar groups ($\chi^2 = 39.8$, $df = 3$, $p < .01$). The groups did not differ in age ($F = 1.94$), but the controls and bipolar patients tended to be better educated ($F = 5.94$, $p < .0005$) and more familiar with computers ($F = 3.01$, $p < .029$).

The scores generated on the test battery are presented in Table 2 as raw scores and standardized scores. The

Table 1. Demographic Characteristics of Patients and Controls

Characteristic	Major Depressive Disorder	Generalized Anxiety Disorder	Bipolar I or II Disorder	Controls
N	285	63	96	907
Sex, N				
Male	181	38	32	362
Female	103	25	64	529
Race, N				
White	250	54	89	773
Black	19	5	2	80
Hispanic	11	1	1	22
Asian	4	0	4	15
Native American	1	2	0	6
Other	0	0	0	2
Age, mean, y	40.49	39.13	38.57	41.39
Computer familiarity[a]	1.43	1.36	1.31	1.27
Education, mean, y	14	14.88	15.47	15.63

[a]Computer familiarity was self-reported by subjects as frequent (1), some (2), or never (3).

Table 2. Raw Domain Scores by Diagnostic Category of Patients and Controls

	Major Depressive Disorder		Generalized Anxiety Disorder		Bipolar I or II Disorder		Controls		Analysis of Variance		
Domain	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p <	Cohen's d
Raw score											
Memory	94.4	12.1	95.6	10.1	93.6	13.8	98.2	7.8	15.88	.0000	13.2
Psychomotor speed	154.8	34.4	158.5	31.6	154.9	36.4	173.1	22.9	42.01	.0000	22.2
Reaction time	689.3	143.2	660.6	178.0	679.6	163.5	638.2	100.9	14.74	.0000	12.7
Complex attention	14.3	20.6	13.9	25.3	17.5	21.9	6.9	5.3	37.44	.0000	20.7
Cognitive flexibility	35.3	21.3	38.9	19.1	32.4	27.3	45.8	12.2	43.25	.0000	22.4
Neurocognition Index	88.5	24.2	91.6	19.3	84.4	28.3	100.1	10.3	56.50	.0000	25.0
Standardized score											
Memory	91.7	23.9	94.0	19.7	90.2	26.6	100.0	15.1	20.13	.0000	15.0
Psychomotor speed	89.3	22.5	91.3	20.5	88.5	23.5	100.4	15.0	37.57	.0000	20.8
Reaction time	91.4	23.4	95.3	31.2	92.5	25.6	100.1	15.1	17.79	.0000	14.2
Complex attention	80.2	66.7	85.3	46.8	73.3	56.8	100.1	14.9	30.24	.0000	18.6
Cognitive flexibility	88.7	27.1	92.2	26.1	84.7	33.0	100.2	15.1	34.83	.0000	20.1

Neurocognition Index is the average of the 5 domain standard scores. Analysis of variance indicated significant group differences. Bonferroni correction indicated that the differences lay primarily between the patient groups and controls, but not among the 3 patient groups. (GAD patients differed from bipolar patients in cognitive flexibility, but that was the only significant intrapatient difference.)

The differences between treated and untreated patients in the 3 patient groups were not statistically significant (independent samples t test, $p < .01$). Nevertheless, in subsequent analyses, whether the patient was treated or not was used as a covariate. Multiple analysis of variance indicated significant differences among the 4 groups. Post hoc analysis with Bonferroni correction indicated the source of the difference was not among the patient groups but between control subjects and patients. Controlling for age, race, gender, years of education, and computer familiarity in the multivariate analysis of variance did not alter the statistical relationships.

Among control subjects, 14% to 17% scored below 85 in 1 domain or another and 1% to 4% scored below 70 (2–4), as was expected. The standard scores upon which the analysis is based are calculated in terms of normative performance; 15% of the control population scores 1 SD below the mean and 3% below 2 SDs, by definition.

Table 3. Distribution of Scores: Patients Compared With Controls

Statistic	Memory	Psychomotor Speed	Reaction Time	Complex Attention	Cognitive Flexibility
χ^2	22.05	39.86	48.20	75.60	58.54
p <	.0000	.0000	.0000	.0000	.0000

Among treated patients with depression, 27% to 32% scored below 85 and 0% to 18% scored below 70. In untreated patients, 28% to 37% scored below 85, and 16% to 39% scored below 70.

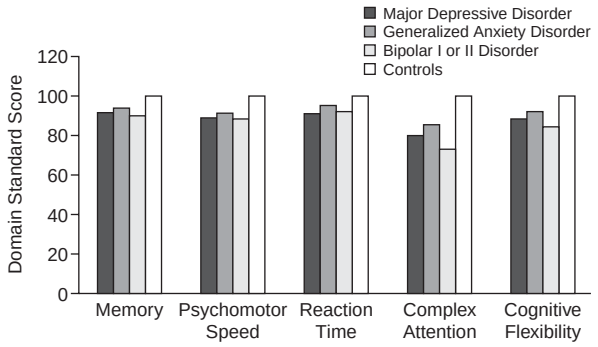
Among treated anxiety patients, 18% to 25% scored below 85, and 4% to 22% scored below 70. In untreated anxiety patients, 33% to 50% scored below 85, and 8% to 42% scored below 70.

Among treated bipolar patients, 27% to 37% scored below 85, and 4% to 29% scored below 70. In untreated

Table 4. Frequency of Domain Scores < 70 Among Patients and Controls

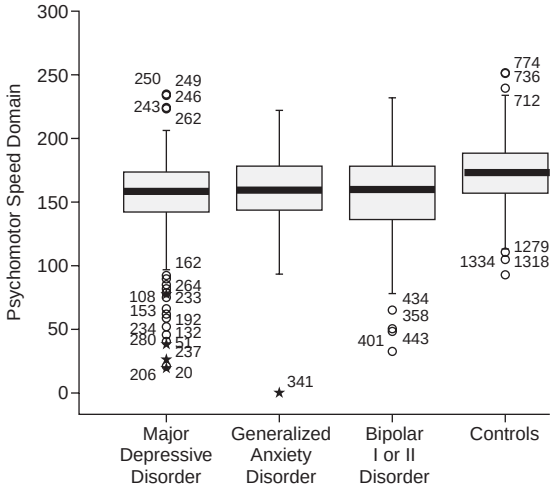
Domains < 70	Depression, N	Depression, %	Anxiety, N	Anxiety, %	Bipolar I or II Disorder, N	Bipolar I or II Disorder, %	Controls, N	Controls, %
0	175	61.4	38	60.3	55	57.3	808	89.1
1	51	17.9	13	20.6	12	12.5	66	7.3
2	26	9.1	8	12.7	13	13.5	24	2.6
3	16	5.6	2	3.2	6	6.3	9	1.0
4	11	3.9	2	3.2	6	6.3	0	0.0
5	6	2.1	0	0.0	4	4.2	0	0.0
2–5	59	20.7	12	19.0	29	30.2	33	3.6

Figure 1. Mean Differences in Cognition Among 3 Patient Groups and Controls[a]



[a]The scores for each cognitive domain are standardized, with a mean of 100 and a standard deviation of 15. On this metric, the mean scores of controls are 100.

Figure 2. Mean Differences in Psychomotor Speed Among 3 Patient Groups and Controls[a]



[a]Stars are outliers more than 2 SDs from the mean; circles are outliers between 1 and 2 SDs from the mean.

patients, 35% to 61% scored below 85, and 17% to 48% scored below 70.

The comparative distributions of scores (normal, 70–84 and below 70) were measured by the Kruskal-Wallis test. The differences among patient groups, and within each patient group between treated and untreated patients, were not important. The groups of untreated patients seemed to include more impaired patients than the groups of treated patients, but of 15 comparisons (3 patient groups × 5 domains), only 1 was statistically significant ($p < .01$). The bipolar group seemed to contain more impaired subjects than the depression and anxiety groups, but none of the comparisons were significant at the level of $p < .01$. The comparative distributions of scores between controls and patients, however, were highly significant (Table 3).

Table 4 indicates the frequency with which patients and controls scored below 70 in any domain. Among controls, 89% had no scores less than 70 compared with 61% of depressed patients, 60% of anxiety patients, and 57% of bipolar patients. Only 4% of controls had 2 or more scores in the impaired range compared with 19% of anxiety patients, 21% of depressed patients, and 30% of bipolar patients.

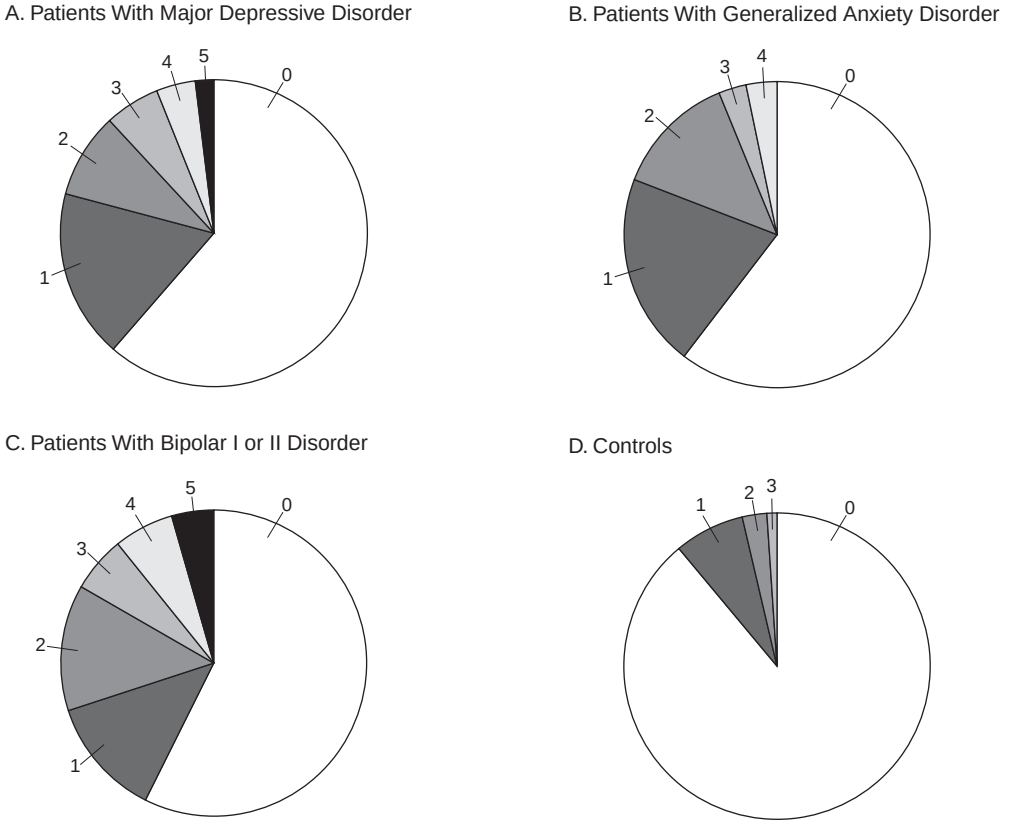
DISCUSSION

A standard approach to the evaluation of cognitive status in clinical groups is to compare mean values. We have done the same, as indicated in Table 2 and Figure 1. The figure illustrates that controls perform better on neurocognitive tests than do patients, but it also suggests that the differences are small.

Another conventional way to present the data from Table 2 is the boxplot. The data for psychomotor speed is presented in Figure 2; it conveys a great deal more information than Figure 1. In terms of mean differences, it indicates that controls score better than patients and have more outliers on the unfavorable side of the mean. But it also conveys the impression that the differences are small and that overlap between patients and controls is substantial.

Taking a different perspective on the problem of cognitive differences, however, conveys an altogether different message. In Figures 3A–D, we employ pie charts to demonstrate graphically the data from Table 4: the frequency of cognitive impairment in terms of the numbers of pa-

Figure 3. Frequency of Domain Scores < 70 Among 3 Patient Groups and Controls[a]



[a]0 = no domain scores < 70, 1 = 1 domain score < 70, 2 = 2 domain scores < 70, 3 = 3 domain scores < 70, 4 = 4 domain scores < 70, and 5 = 5 domain scores < 70.

tients or controls who score 2 SDs below the mean in 0, 1, 2, 3, 4, or 5 domains.

To determine that a group of depressed patients, for example, score lower than controls on a test of executive function and that the difference is statistically significant is interesting, but is it meaningful? Depressed patients, like every group of neuropsychiatric patients, are a diverse group. Even if we consider patients without comorbid conditions, as we did in this investigation, they are diverse in terms of the severity and chronicity of their condition, treatment response, and functional disability. Our data indicate that they are diverse as well in terms of the degree to which they are cognitively impaired. The degree to which they are impaired, however, is imperfectly captured by traditional presentation of means and SDs. That method is necessary, of course, but it is not sufficient. A mean value dilutes the importance of patients with cognitive impairment by combining their data with the much larger group who are not impaired at all or who perform at a superior level. Presenting the data in terms of frequency, on the other hand, amplifies the relative importance of the cognitively impaired group.

Substantial numbers of patients with major depressive disorder, generalized anxiety disorder, and bipolar I or II disorder were found in this study to be weak in at least 1 major neurocognitive domain. The numbers speak for themselves: 18% to 61% of patients with depression, anxiety, or bipolar disorder score more than 1 SD below the mean on at least 1 cognitive domain and as many as 48% score more than 2 SDs below the mean. The percentage of patients who are cognitively impaired is substantial: 19% to 30% score 2 SDs below the mean on 2 or more cognitive domains, in contrast to only 4% of controls. These numbers are even more striking because they are noted in a largely middle-class, well-educated sample of patients attending a private clinic.

To lend perspective to these data, in a study we published of 95 untreated children and adolescents with ADHD, 25% of the patients scored less than 70 in 2 or more cognitive domains.[31] In another published study of 57 patients with very early dementia, 56% scored less than 70 in 2 or more cognitive domains.[5] So, the frequency of cognitive impairment in the present sample of depressed, anxious, and bipolar patients was about the

same as untreated youth with ADHD but less than patients with early dementia. This kind of comparison may seem like comparing apples to oranges, but it does speak to an important issue in the study of cognitive performance in psychiatric patients. In 1970, during the early days of psychopharmacology, Jonathan Cole wrote the following about neurocognitive drug effects:

> What type of behavioral toxicity would one, for example, expect from a drug that reduces critical flicker fusion frequency and after-image sensitivity without affecting reaction time, tapping speed, or the recall of digits forward?[33(p31)]

Cole was being ironic, but the issue he addressed is not specious. Our data amplify the importance of cognitive impairment among patients with mood and anxiety disorders; but what end is served by so doing? Neurocognitive tests are sensitive and precise, especially when administered by computer, in which case timing is more incessant than in conventionally administered tests, and subject response is recorded in milliseconds. But what is their meaning to the patient's day-to-day life in the real world? This is the problem of "ecological validity."

Overall, research suggests that neuropsychological tests have a moderate level of ecological validity when predicting everyday cognitive functioning. The strongest relationships tend to be noted when the outcome measure corresponds to the cognitive domain assessed by the neuropsychological tests,[34] for example, visual-spatial skills and driving or certain kinds of employment.[35,36] Neurocognitive ability is related to quality of life in community-dwelling elderly[37] and patients with mental illness.[38] A recent meta-analysis of 68 articles relating cognitive testing to a functional outcome arrived at 2 salient conclusions: the variance in functional status that can be attributed to cognition is surprisingly modest, but general cognitive screening measures are "surprisingly strong correlates of functional status."[19(p249)]

The data we have presented lend themselves to enlightened speculation but are not permissive of wider claims. The sample, for example, was generated in 2 private neuropsychiatric clinics catering largely to a well-educated, middle-class population. This fact makes the discovery of high rates of cognitive impairment even more impressive, but it limits the degree to which the findings can be generalized. Correlation with important variables, like disease severity, number of prior episodes, and treatment response was not done but is the focus of ongoing research. Data are not available at this point concerning important covariates such as family history of cognitive disorders or dementia. Nor is there data concerning the functional correlates of neurocognitive impairment in the lives of these patients. Were patients aware of their impairment? Does it affect their work performance, driving skills, or medication compliance? Are cognitively impaired patients different from non-impaired patients in dimensions beyond the scope of the test battery?

A more fundamental question is this: at what point can one say that a patient is cognitively impaired on the basis of a neurocognitive test battery? A well-educated person who scores less than 85 is usually disappointed with his or her performance. But 15% of the population falls within that range. A low score (70–85) on 1 or more cognitive tests may or may not be meaningful; whether it is or not is a decision guided by further testing and appropriate clinical correlates. A single score below 70, however, is fairly and squarely in the impaired range and demands specific attention.

This question has been dealt with, if imperfectly, in studies of Alzheimer's disease and mild cognitive impairment. Mild cognitive impairment is an intermediate or transitional state between normal aging and dementia.[39,40] A simple definition is that patients with mild cognitive impairment have more cognitive impairment than one would expect from normal aging, but their normal daily activities are undisturbed. Mild cognitive impairment is recognized as a risk factor for Alzheimer's disease,[41] and the diagnosis is made by administering neuropsychological tests. There is no consensus, however, about how precisely the condition should be defined, and minor differences in the defining criteria have resulted in big differences in prevalence and outcome.[42] Nevertheless, the most common criterion used in mild cognitive impairment studies is a score 1.5 SD below the mean on a test of memory or executive function or 1.0 SD below the mean on tests of more than 1 domain.[43] The validity of this criterion may be questioned,[19] but it has guided studies that have consistently identified patients with an accelerated rate of progression to dementia in general and in Alzheimer's disease in particular.[39,42,44,45] In this light, our criterion for cognitive impairment—2 SDs below the mean in 2 or more cognitive domains—is quite conservative.

A psychiatrist reviewing data of the sort presented in Figures 1 and 2 would be forgiven for stifling a yawn. The same data presented in Figures 3A–D should raise some concern. By conservative estimate, 19% of anxiety patients, 21% of depression patients, and 30% of bipolar patients are cognitively impaired. How effective is our treatment, the advice we give to patients, or our efforts in cognitive therapy if we are blind to such an important element of the patient's mental state? If these findings are replicated, they may also have an impact on psychiatric research.

For example, in clinical trials, the high placebo response rate in studies of patients with mood and anxiety disorders is an especially vexing problem. The placebo effect is unpredictable and seemingly unmanageable and costs drug companies hundreds of millions of dollars in failed trials and delayed or shelved compounds. The response rate to placebo in depression trials, for example,

ranges from 12 to 50%.[46] Developers of antidepressants have tried a number of strategies to reduce placebo responses in order to demonstrate drug efficacy but have generally been frustrated.[47]

One problem with clinical trials is that it remains unclear whether patients classified as depressed or anxious or bipolar all share the same disease. The key tool for assembling populations for clinical trials and measuring their response is the standardized rating scale. However, drug developers are not convinced that all those patients who are classified by standardized rating scales actually share the same illness. In fact, they are quite skeptical about the capacity of the standard rating scales to produce a consistent patient population for testing. From painful experience, they have learned that patients admitted under these criteria vary tremendously in their response to drugs and placebos.[47]

Not a great deal is known about the cognitive diversity of patients with mood and anxiety disorders, but preliminary investigations have suggested that it may have some bearing on drug response.[48] Our data suggest that cognition is a strong contributor to the diversity of clinical populations with depression, anxiety, and bipolar disorder. With respect to the conduct of clinical trials, it is probably a major source of uncontrolled variance.

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