

**THE FREQUENCY OF COGNITIVE IMPAIRMENT IN PATIENTS WITH
ANXIETY, DEPRESSION AND BIPOLAR DISORDER:
AN UNACCOUNTED SOURCE OF VARIANCE IN CLINICAL TRIALS**

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ABSTRACT

BACKGROUND: Patients with anxiety, depression and bipolar disorder are known to be impaired relative to normal 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 five domains: memory, psychomotor speed, reaction time, attention and cognitive flexibility.

SUBJECTS: Clinic patients with generalized anxiety (N = 63), major depression (285) and bipolar disorder (96) compared to 907 normal controls. Subjects' age range was 18-65. Patients had no comorbid psychiatric disorders and no medical, neurological or developmental conditions that might affect cognition (e.g., ADHD, brain injury, MCI, chronic pain).

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

CONCLUSIONS: Substantial numbers of patients with anxiety, depression and bipolar disorder are cognitively impaired. A score that is 2 SD's below the mean is usually clinically important, and two 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.

When psychiatric patients are compared to normal controls, there is abundant evidence that they perform less well in 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 normal controls.⁵ Patients with bipolar disorder have cognitive impairments that are similar to those of unipolar depressives, in kind and degree⁶, 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 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 PTSD and OCD.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. It is hardly ever used as an exclusion criterion in clinical trials. It is ironic, perhaps, but understandable, if one considers these points:

Historically: In the past, 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.

Phenomenologically: 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.

Practically: 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; 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 guiding treatment and promoting 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 normal 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 who perform in the average or above average range. In one 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 are patients with depression, anxiety and bipolar disorder. The issue is not whether group differences

exist between patients and normal controls, because we know that they do. The question we shall address is the frequency of clinically meaningful neurocognitive impairment.

METHODS AND MATERIALS

SUBJECTS

The subjects of this investigation were 444 patients, age 18-65, with three psychiatric disorders: generalized anxiety (N = 63), major depression, unipolar, non-psychotic (285), and bipolar disorder (I or II) (96). They were all outpatients at the NC 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 de-identified data to be used for purposes of research and evaluation; they can take advantage of our website 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-IVtr 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.

From the CNS Vital Signs normative database of more than 1500 normal people, 907 controls were selected, age 18-65. ("Normals" were people who were in good health, medication-free, and free of any present or past cognitive, neurological or psychiatric disorder. They were recruited in community settings in North Carolina, Florida, Connecticut, Colorado and California.⁵)

NEUROCOGNITIVE EVALUATION

The CNS Vital Signs Assessment Battery contains seven tests that are widely used by neuropsychologists. Verbal memory (VBM) and visual memory (VIM) are adaptations of the Rey Auditory Verbal Learning Test and the Rey Visual Design Learning Test.^{21, 22} Correct responses from VBM and VIM are summed to generate a composite memory or memory domain score.

The finger tapping test (FTT) is one of the core tests of the Halstead-Reitan Battery, but similar tests were used by nineteenth century psychologists like Wundt, Galton and Cattell. Symbol digit coding (SDC) is based on the symbol digit modalities test²³, itself a variant of the Wechsler digit symbol substitution test. The total of right and left taps from the FTT and total correct responses on the SDC generates a composite score for "psychomotor speed."

The Stroop Test (ST)²⁴ in CNSVS has three parts that generate simple and complex reaction times. Averaging the two 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 one instruction set to another quickly and accurately. Color-shape tests like the SAT have been used in cognitive imaging studies.^{25, 26} 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.²⁷ A domain score for "complex attention" is generated by adding the number of errors committed in the CPT, the SAT and the Stroop.

The CNSVS battery has been normed in 1504 normal volunteers age 5-96. Peak performance on the tests is achieved during the third decade of life, and declines gradually thereafter. Test-retest reliability (TRT) ranges from 0.65 (Attention) to 0.87 (Psychomotor Speed). The TRT of the CNS VS 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 VS battery is comparable to similar, conventional neuropsychological tests.⁵ Discriminant validity has been established in studies of patients with mild cognitive impairment (MCI) and early dementia⁵; post-concussion syndrome (PCS) and severe traumatic brain injury²⁸; ADHD²⁹; depression³⁰; schizophrenia and bipolar disorder³⁰; and malingering.⁵

The CNS Vital Signs battery is widely used by psychiatrists, neurologists and neuropsychologists around the world.⁴⁷ It has been used in registration studies in more than 1,000 clinical sites around the world, in patients with schizophrenia, bipolar disorder, ADHD, depression and restless legs syndrome, mild cognitive impairment and epilepsy (www.cnsvs.com).

METHOD

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 age 18-65. 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 neurological conditions like epilepsy, MS and migraine were also excluded.

The second step was to select patients with diagnoses of major depression, generalized anxiety or bipolar disorder, I or II. This 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 PTSD, OCD, panic etc were also excluded. This final step yielded a relatively "pure" sample of patients with major depression (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 normal controls was evaluated in terms of their scores on the five domains of the CNSVS test battery: memory, psychomotor speed, reaction time, complex attention and cognitive flexibility. Cognitive impairment was measured by applying two cutoff scores: subjects who scored between 85 and 70 were between one and two standard deviations below the age-adjusted mean; subjects who scored below 70 were 2 SD's 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 SD's below the mean represents impairment. We did not consider a patient to be cognitively impaired, in this investigation, unless at least two domain scores were lower than 70 (see discussion).

RESULTS

The patient sample and the normal controls were predominantly white and well-educated, and reflective of the communities from which they were drawn. Females were under-represented in the depression and anxiety groups, compared to bipolar and normals (chi sq 57.7, df 3, $P < 0.01$) and non-whites were under-represented in the depression and bipolar groups (chi sq 39.8, df 3, $P < .01$). The groups did not differ in age ($F=1.94$) but the normals and bipolar patients tended to be better educated ($F=5.94$, $P < .0005$) and more familiar with computers ($F=3.01$, $P < 0.029$).

Table 1. Demographic characteristics of the sample

	MDD	GAD	BPAD	NML
N	285	63	96	907
Male	181	38	32	362
Female	103	25	64	529
White	250	54	89	773
Black	19	5	2	80
Hispanic	11	1	1	22
Asian	4	0	4	15
Native Am	1	2	0	6
Other	0	0	0	2
Age	40.49	39.13	38.57	41.39
CompNum	1.43	1.36	1.31	1.27
Education	14	14.88	15.47	15.63

NOTE, Table 1: GAD, generalized anxiety disorder. MDD, major depressive disorder. BPAD, bipolar affective disorder. NML, normal controls. Education in years. Computer familiarity was self-reported by subjects as "frequent" (1), "some" (2) or "never" (3).

The scores generated on the test battery are presented in Table 2, as raw scores and then as standardized scores. The Neurocognition Index (NCI) is the average of the five domain standard scores. Analysis of variance indicated significant group differences. Bonferroni correction indicated that the differences lay primarily between the patient groups and normals, but not among the three patient groups. (GAD patients differed from bipolar in cognitive flexibility, but that was the only significant intra-patient difference.)

The differences between treated and untreated patients in the three patient groups were not statistically significant (independent samples t test, $P < 0.01$). Nevertheless, in subsequent analyses, whether the patient was treated or not was treated 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 normal subjects and patients. Controlling for age, race, gender, years of education and computer familiarity in the MANOVA did not alter the statistical relationships.

Table 2. Raw Domain Scores by Diagnostic Category

	N	MDD		GAD		BPAD		NML		ANOVA		Cohen's d
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P<	
MEM	284	94.4	12.1	95.6	10.1	93.6	13.8	98.2	7.8	15.88	0.0000	13.2
PMS	283	154.8	34.4	158.5	31.6	154.9	36.4	173.1	22.9	42.01	0.0000	22.2
RT	284	689.3	143.2	660.6	178.0	679.6	163.5	638.2	100.9	14.74	0.0000	12.7
ATT	282	14.3	20.6	13.9	25.3	17.5	21.9	6.9	5.3	37.44	0.0000	20.7
CF	283	35.3	21.3	38.9	19.1	32.4	27.3	45.8	12.2	43.25	0.0000	22.4
NCI	285	88.5	24.2	91.6	19.3	84.4	28.3	100.1	10.3	56.50	0.0000	25.0
MEMss	284	91.7	23.9	94.0	19.7	90.2	26.6	100.0	15.1	20.13	0.0000	15.0
PMSss	283	89.3	22.5	91.3	20.5	88.5	23.5	100.4	15.0	37.57	0.0000	20.8
RTss	284	91.4	23.4	95.3	31.2	92.5	25.6	100.1	15.1	17.79	0.0000	14.2
ATTss	282	80.2	66.7	85.3	46.8	73.3	56.8	100.1	14.9	30.24	0.0000	18.6
CFss	283	88.7	27.1	92.2	26.1	84.7	33.0	100.2	15.1	34.83	0.0000	20.1

Among normal Ss, 14-17% scored below 85 in one domain or another and 1-4% scored below 70 (2-4). This is as expected. The standard scores upon which the analysis is based is calculated in terms of normative performance; 15% of the normal population score one SD below the mean, and 3% below two SD's, by definition.

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

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

Among treated bipolar patients, 27-37% scored below 85 and 4-29% scored below 70. In untreated patients 35-61% scored below 85 and 17-48% 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 x 5 domains), only one was statistically significant ($P < 0.01$). 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 $P < 0.01$. The comparative distributions of scores between normal controls and patients, however, were highly significant (Table 3).

Table 3. Distribution of Scores, Patients compared to Normal Controls

	MEM	PMS	RT	ATT	CF
Chi-Square	22.05	39.86	48.20	75.60	58.54
P<	0.0000	0.0000	0.0000	0.0000	0.0000

Table 4 indicates the frequency with which patients and normal controls scored below 70 in any domain. Eighty-nine per cent of normals had no scores less than 70, but only 61% of depressed patients, 60% of anxiety patients, and 57% of bipolar patients. Only 4% of normals had two or more scores in the impaired range, but 19% of anxiety patients did, 21% of depressed patients and 30% of bipolars.

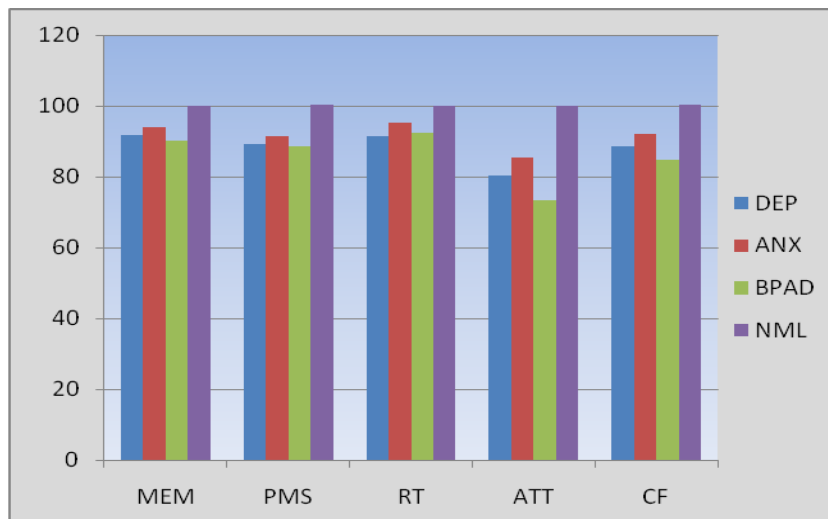
Table 4. Frequency of Domain Scores Below 70

Domains < 70	DEP	DEP%	ANX	ANX%	BPAD	BPAD%	NML	NML%
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

DISCUSSION

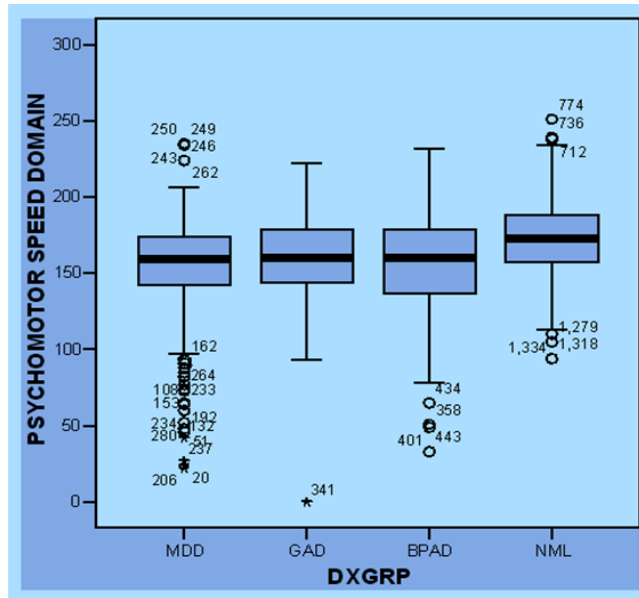
A standard approach to the evaluation of cognitive status in clinical groups is to compare mean values. We have done the same, as indicated in Table 2 and Figure 1. The figure illustrates that normal controls perform better on neurocognitive tests than patients do, but it also suggests that the differences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

Figure 1. Mean Differences in Cognition, 4 Patient Groups and Normals



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 normals 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 normals is substantial.

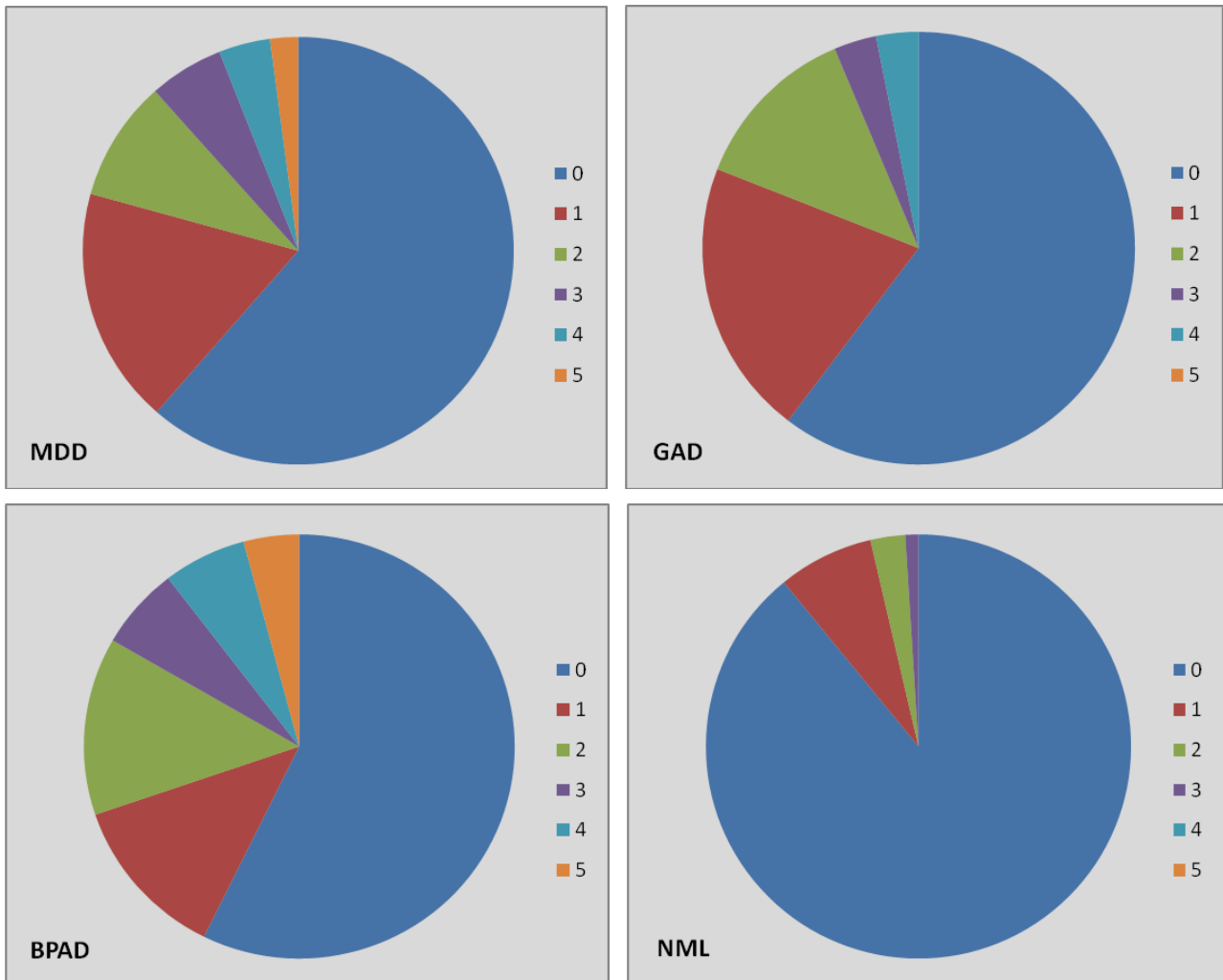
Figure 2. Mean Differences in Psychomotor Speed, 4 Patient Groups and Normals



NOTES: Figure 2, Psychomotor Speed Domain scores, patients with MDD, GAD, BPAD and normal controls.

Taking a different perspective on the problem of cognitive differences, however, conveys an altogether different message. In Figures 7-11, we employ pie charts to demonstrate graphically the data from Table 4: the frequency of cognitive impairment, in terms of the numbers of patients or normal controls who score 2 standard deviations below the mean in 0, 1, 3, 4, or 5 domains.

Figures 3-6. Frequency of Domain Scores Lower than 70 in Patients and Normal Controls.



NOTES. Figure 3, MDD patients. No domain scores below 70, blue; one domain score below 70, red. Two domain scores below 70, green. Three domain scores below 70, purple. Four domain scores below 70, light blue. Five domain scores below 70, orange. Figure 4, GAD patients. Figure 5, BPAD patients. Figure 6, normal controls.

To determine that a group of depressed patients, for example, score lower than normal 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 standard deviations. 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 depression, generalized anxiety and bipolar disorder are found, in this study, to be weak in at least one major neurocognitive domain. The numbers speak for themselves: 18-61% of patients with depression, anxiety or bipolar disorder score more than 1 SD below the mean on at least one cognitive domain, and as many as 48% score more than 2 SD's below the mean. The percentage of patients who are cognitively impaired is substantial: 19 to 30% score 2 SD's below the mean on two or more cognitive domains; this, in contrast to only 4% of normal 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 <70 in two or more cognitive domains.²⁹ In another published study of 57 patients with very early dementia, 56% scored <70 in two 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 kids 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 this 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?*³¹

Cole was being ironic, but the issue he addressed is not specious. Our data amplifies 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, where 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 tests³²; for example, visual-spatial skills and driving or certain kinds of employment.^{33, 34} Neurocognitive ability is related to quality of life in community-dwelling elderly³⁵ and patients with mental illness.³⁶ A recent meta-analysis of 68 papers relating cognitive testing to a functional outcome arrived at two 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."³⁷

The data we have presented lend themselves to enlightened speculation, but they are not permissive of wider claims. The sample, for example, was generated in two 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, like 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, medication compliance, etc? 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 at his or her performance. But 15% of the population falls within that range. A low score (70-85) on one 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 (AD) and "Mild Cognitive Impairment" (MCI). MCI is an intermediate or a transitional state between normal aging and dementia.³⁸ A simple definition is that MCI patients have more cognitive impairment than one would expect from normal aging, but their normal daily activities are undisturbed. MCI is recognized as a risk factor for AD³⁹ 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.⁴⁰ Nevertheless, the most common criterion used in MCI 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 one domain.⁴¹ 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 AD in particular.^{37, 40, 42, 43} In this light, our criterion for cognitive impairment – 2 SD's below the mean in two or more cognitive domains – is quite conservative.

A psychiatrist reviewing data of the sort presented in Figures 1-6 would be forgiven for stifling a yawn. The same data, presented in Figures 7-10, should raise 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 likely to be, the advice we give to patients, 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 percent.⁴⁴ Developers of antidepressants have tried a number of strategies to reduce placebo responses in order to demonstrate drug efficacy, but have generally been frustrated.⁴⁵

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.⁴⁵

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.⁴⁶ 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.

Reference List

- (1) Farrin L, Hull L, Unwin C, Wykes T, David A. Effects of depressed mood on objective and subjective measures of attention. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2003;15:98-104.
- (2) Landro N, Stiles T, Sletvold H. Neuropsychological function in nonpsychotic unipolar major depression. *Neuropsychiatry, Neuropsychology and Behavioral Neurology* 2001;14(4):233-40.

- (3) Porter RJ, Gallagher P, Thompson JM, Young AH. Neurocognitive impairment in drug-free patients with major depressive disorder. *Br J Psychiatry* 2003;182:214-20.
- (4) Barch DM, Sheline YI, Csernansky JG, Snyder AZ. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. *Biological Psychiatry* 2003;53(5):376-84.
- (5) Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol* 2006 October;21(7):623-43.
- (6) Scott J, Stanton B, Garland A, Ferrier IN. Cognitive vulnerability in patients with bipolar disorder. *Psychological Medicine* 2000;30(2):467-72.
- (7) Wilder-Willis KE, Sax KW, Rosenberg HL, Fleck DE, Shear PK, Strakowski SM. Persistent attentional dysfunction in remitted bipolar disorder. *Bipolar Disorders* 2001;3(2):58-62.
- (8) Rubinsztein JS, Michael A, Paykel E, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. *Psychological Medicine* 2000;30(5):1025-36.
- (9) Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. *Psychiatry Research* 2001 May 10;102(1):9-20.
- (10) El-Badri SM, Ashton CH, Moore PB, Marsh VR, Ferrier IN. Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. *Bipolar Disorders* 2001;3(2):79-87.
- (11) Clark L, Iversen SD, Goodwin GM. Sustained attention deficit in bipolar disorder. *British Journal of Psychiatry* 2002 April;180:313-9.
- (12) Ruiz-Caballero JA, Bermudez J. Anxiety and attention: is there an attentional bias for positive emotional stimuli? *J Gen Psychol* 1997 April;124(2):194-210.
- (13) Peretti CS. [Anxiety and cognition disorders]. *Encephale* 1998 May;24(3):256-9.
- (14) Brand N, Jolles J. Information processing in depression and anxiety. *Psychol Med* 1987 February;17(1):145-53.
- (15) Tallis F. The neuropsychology of obsessive-compulsive disorder: a review and consideration of clinical implications. *Br J Clin Psychol* 1997 February;36 (Pt 1):3-20.
- (16) Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological deficits in obsessive-compulsive disorder: a comparison with unipolar depression, panic disorder, and normal controls. *Arch Gen Psychiatry* 1998 May;55(5):415-23.
- (17) Andres-Perpina S, Lazaro-Garcia L, Canalda-Salhi G, Boget-Llucia T. [Neuropsychological aspects of obsessive compulsive disorder]. *Rev Neurol* 2002 November 16;35(10):959-63.
- (18) Papageorgiou C, Rabavilas A, Liappas I, Stefanis C. Do obsessive-compulsive patients and abstinent heroin addicts share a common psychophysiological mechanism? *Neuropsychobiology* 2003;47(1):1-11.
- (19) Royall D, Lauterbach E, Kaufer D, Malloy P, Coburn K, Black KJ. The cognitive correlates of functional status. *J Neuropsychiatry Clin Neurosci* 2007;193:249-65.
- (20) Gualtieri CT, Johnson LG, Benedict KB. Neurocognition in depression: patients on and off medication versus healthy comparison subjects. *J Neuropsychiatry Clin Neurosci* 2006;18(2):217-25.

- (21) Taylor EM. *The appraisal of children with cerebral deficits*. Cambridge, MA: Harvard University Press; 1959.
- (22) Rey A. *L'examen clinique en psychologie*. Paris: Presses Universitaires de France; 1964.
- (23) Smith DW, Jones KL. *Recognizable Patterns of Human Malformation*. 3 ed. Philadelphia: Saunders; 1982.
- (24) Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643-62.
- (25) Le TH, Pardo JV, Hu X. 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. *Journal of Neurophysiology* 1998 March;79(3):1535-48.
- (26) Nagahama Y, Sadato N, Yamauchi H et al. Neural activity during attention shifts between object features. *Neuroreport* 1998 August 3;9(11):2633-8.
- (27) Rosvold HE, Delgado JM. The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. *Journal of Comparative & Physiological Psychology* 1956;49(4):365-72.
- (28) Gualtieri CT, Johnson L. A computerized Screening Battery to Distinguish MCI from Early Dementia. 2005.
- (29) Gualtieri CT, Johnson LG. Efficient allocation of attentional resources in patients with ADHD: maturational changes from age 10 to 29. *J Atten Disord* 2006 February;9(3):534-42.
- (30) Gualtieri CT, Johnson LG. Antidepressant side effects in children and adolescents. *J Child Adolesc Psychopharmacol* 2006 February;16(1-2):147-57.
- (31) Cole JO. Symposium on long-acting phenothiazines in psychiatry. Introduction. *Diseases of the Nervous System* 1970;31:Suppl:5.
- (32) Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. *Neuropsychol Rev* 2003 December;13(4):181-97.
- (33) Wen JH, Boone K, Kim K. Ecological validity of neuropsychological assessment and perceived employability. *J Clin Exp Neuropsychol* 2006 November;28(8):1423-34.
- (34) Whelihan WM, DiCarlo MA, Paul RH. The relationship of neuropsychological functioning to driving competence in older persons with early cognitive decline. *Arch Clin Neuropsychol* 2005 March;20(2):217-28.
- (35) Plehn K, Marcopulos BA, McLain CA. The relationship between neuropsychological test performance, social functioning, and instrumental activities of daily living in a sample of rural older adults. *Clin Neuropsychol* 2004 February;18(1):101-13.
- (36) Fujii DE, Wylie AM, Nathan JH. Neurocognition and long-term prediction of quality of life in outpatients with severe and persistent mental illness. *Schizophr Res* 2004 July 1;69(1):67-73.
- (37) Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. *International Psychogeriatrics* 2004 June;16(2):129-40.
- (38) Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L. Introduction: Mild cognitive impairment: beyond controversies, towards a consensus. *Journal of Internal Medicine* 2004 September;256(3):181-2.

- (39) Grundman M, Petersen RC, Ferris SH et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Archives in Neurology* 2004 January;61(1):59-66.
- (40) Collie A, Maruff P. An analysis of systems of classifying mild cognitive impairment in older people. *Australian and New Zealand Journal of Psychiatry* 2002;36(1):133-40.
- (41) Petersen RC. *Mild Cognitive Impairment: Aging to Alzheimer's Disease*. 2003.
- (42) Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented.[comment]. *NEURO* 2000;55(12):1847-53.
- (43) Arnaiz E, Almkvist O, Ivnik RJ et al. Mild cognitive impairment: a cross-national comparison. *Journal of Neurology, Neurosurgery & Psychiatry* 2004 September;75(9):1275-80.
- (44) Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002 April 10;287(14):1840-7.
- (45) Lakoff A. The mousetrap: managing the placebo effect in antidepressant trials. *Mol Interv* 2002 April;2(2):72-6.
- (46) Kampf-Sherf O, Zlotogorski Z, Gilboa A et al. Neuropsychological functioning in major depression and responsiveness to selective serotonin reuptake inhibitors antidepressants. *J Affect Disord* 2004 November 1;82(3):453-9.
- (47) Iversen, GL, Brooks, BL, Weiss, MD. Identifying frank neurocognitive impairment in children with ADHD, Ms submitted, 2007.