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Identifying Cognitive Impairment in Adults with Mood Disorders Using Computerized Testing

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Abstract

Objective: To develop and evaluate psychometric criteria for identifying cognitive impairment in adults with mood disorders. **Participants & Methods:** Participants were adults between the ages of 20 and 54, including 659 healthy control subjects, 84 unmedicated outpatients diagnosed with depression, 59 outpatients diagnosed with depression who were on medications at the time of the evaluation, and 43 outpatients with bipolar disorder. All completed the CNS Vital Signs computerized battery. This battery of seven tests yields five domain scores (Memory, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility). **Results:** Base rates of low domain scores were calculated, using different cut-offs, for the healthy control subjects and the patients with mood disorders. Having two scores at or below the 5th percentile occurred in 31.2% of the patients and only 8.2% of the control subjects [$\chi^2(1)=66.67$, $p<.0001$; Odds Ratio=5.1, 95% CI=3.4–7.7]. This low false positive rate was maintained across age groups, sexes, and education levels. African Americans (N=49) had higher false positive rates (i.e., 14.3%) than Caucasians (N=570; 7.0%). A larger proportion of patients with bipolar disorder (41.9%) than patients with depression (27.1-28.6%) met criteria for cognitive impairment. **Conclusion:** A substantial minority of adults with mood disorders appear to have cognitive impairment. The psychometric criterion for cognitive impairment on this computerized test battery has a low false positive rate.

Introduction

It is well established that mood disorders are associated with cognitive impairment (Robinson et al., 2006; Zakzanis, Leach, & Kaplan, 1998). The nature and extent to which depression causes objective cognitive impairment, however, is not fully understood. Some studies suggest that cognitive impairment associated with depression is quite limited (Grant, Thase, & Sweeney, 2001; Rohling, Green, Allen, & Iverson, 2002), difficult to detect, and is more likely to occur in those who are more seriously ill (McDermott & Ebmeier, 2009). There is emerging evidence that neurocognitive functioning improves following treatment (e.g., Deuschle et al., 2004; Doraiswamy et al., 2003; Neu et

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al., 2005; O'Connor et al., 2005; Rocca et al., 2005; Vythilingam et al., 2004; Wroolie et al., 2006), and neuropsychological test results at baseline can partially predict response to treatment (Dunkin et al., 2000; Kampf-Sherf et al., 2004; Mohlman & Gorman, 2005). Cognitive impairment is pronounced in patients with bipolar disorder and it persists when the patients are euthymic (Robinson et al., 2006; Torres, Boudreau, & Yatham, 2007). Mood disorders with psychosis are associated with a large adverse effect on neurocognitive functioning (Bora, Yucel, & Pantelis, 2009).

The accurate identification and quantification of neurocognitive impairment is important for research relating to neurobiological underpinnings, treatment, and functional outcome in patients with mood disorders. It is essential, methodologically, that we have accurate methods for identifying those patients who are objectively cognitively impaired and separate them from patients who have the subjective experience of poor thinking skills but perform normally on cognitive testing. Based on group statistics, in individual studies or in meta-analyses, mood disorders are associated with a small-to-medium adverse effect on cognitive functioning (Robinson et al., 2006; Zakzanis et al., 1998). However, group statistics can obscure individual and subgroup differences. If present, these individual or subgroup differences in cognition might have important implications for research and clinical practice.

The purpose of this study was to examine cognitive functioning in mood disorders at the level of the individual. We hypothesized, based on our preliminary research, that (a) only a minority of patients with mood disorders have measurable cognitive impairment, (b) this minority is driving the small-to-medium effect sizes detected in group statistics, and (c) if you remove this minority from the group statistical analyses, the significant effect sizes will virtually disappear. If true, the effect sizes reported in the literature seriously under-estimate the adverse effects of mood disorders on cognition. They are diluted by the majority of patients who have no measurable cognitive impairment. Moreover, cognitive impairment associated with mood disorders is limited to a minority of patients with the majority being broadly cognitively normal. Using a large healthy normative sample and archival clinical groups, we will (a) develop and evaluate psychometric criteria for identifying cognitive impairment in adults with mood disorders, and (b) evaluate the three above-mentioned hypotheses.

Methods

Participants

A healthy normative sample and three clinical groups were used for this study. Ethical approval for the use of this large, de-identified, archival database was granted by the University of British Columbia. Older adults were excluded. Participants were adults between the ages of 20 and 54, including 659 healthy control subjects, 84 unmedicated outpatients diagnosed with depression, 59 outpatients diagnosed with depression who were on medications at the time of the evaluation, and 43 outpatients with bipolar disorder. Clinicians at the North Carolina Neuropsychiatry Clinics gave a primary diagnosis of depression or bipolar disorder to all patients according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (American Psychiatric Association, 2000).

This is a sample of convenience; no formal diagnostic interviewing or symptom rating scales were collected. The clinical characteristics of the patient samples (e.g., age of onset, number of prior episodes, and severity/phase of illness) were not recorded in the database. The authors of this study utilized an archival database; we had no role in data collection or the clinical evaluations of the subjects. The unmedicated outpatients with depression (Iverson, Brooks, & Young, in press) and the patients with bipolar disorder (Iverson, Brooks, Young, Johnson, & Gualtieri, 2009) were selected from previously published studies. This study is primarily methodological in nature. It was not our intent to

characterize or differentiate the nature or pattern of cognitive deficits in depression or bipolar disorder. Heterogeneous samples of outpatients with mood disorders were sufficient to examine the hypotheses.

The demographic characteristics of the four samples are described in Table 1. The majority of each sample was women, and the vast majority were Caucasian. Each participant self-reported their total number of years of education. Our experience, when conducting follow-up interviews with research subjects, is that some over-estimate their years of education by counting part-time studies or short-term certificate programs as full years. Thus, the level of education of the four samples might be a slight over-estimate. It is likely, however, that the average education of these samples is clearly greater than high school, with most having some form of technical, college, or university education.

Table 1. Demographic characteristics of the samples.

	Healthy Normative Sample	Depression Unmedicated	Depression Medicated	Bipolar Disorder
Sample Size	659	84	59	43
Mean Age (SD)	38.1 (10.2)	37.7 (9.9)	40.1 (8.9)	36.6 (9.9)
Age Range	20-54	20-54	20-54	21-54
Mean Education (SD)	15.8 (2.2)	15.1 (2.2)	14.8 (2.5)	15.1 (2.3)
Education Range	7-20	8-20	8-18	8-19
Male/Female (%)	36/64	26.2/73.8	27.1/72.9	32.6/67.4
Caucasian/African American/Hispanic (%)	86.5/7.4/2.4	94.9/5.1/0	88.1/10.7/1.2	95.3/2.3/2.3
Computer Use Sample Size	378	80	39	43
Computer Use: None/Some/Frequent (%)	2.1/19.3/78.6	1.3/16.3/82.5	12.8/25.6/61.5	4.7/27.9/67.4

Note: SD = Standard deviation. Years of education is based on self-report.

Measures

CNS Vital Signs (Appendix A) is comprised of seven common neuropsychological measures, including verbal and visual memory, finger tapping, symbol digit coding, a Stroop test, a shifting attention test, and a continuous performance test (see Appendix A). The battery generates 15 primary scores, which are used to calculate 5 domain (index) scores (Memory, Psychomotor Speed, Reaction Time, Cognitive Flexibility, and Complex Attention). The measures have adequate test-retest reliability, adequate concurrent validity with traditional paper and pencil measures and other computerized tests, and the domain (index) scores have been shown to discriminate between various clinical groups (Gualtieri & Johnson, 2005, 2006a; Gualtieri, Johnson, & Benedict, 2006).

Results & Discussion

Calculations for the base rates of low scores involve simultaneously examining the five domain scores, rather than performance on each domain in isolation. The base rates of low domain scores were calculated by using four cutoff scores that might be routinely used in clinical practice, including: (a) more than 1 standard deviation (SD) below the mean (i.e., < 85), (b) below the 10th percentile (i.e., < 81), (c) at or below the 5th percentile (i.e., ≤ 76), and (d) more than 2 SDs below the mean (i.e., < 70).

The base rates of low domain scores for healthy adults, stratified by age, sex, race, education, and computer use, are presented in Appendix A. It is common for healthy adults to obtain one low score. For example, 41% obtained one or more scores below 1SD (<16th percentile) and 22.8% obtained one or more scores ≤ the 5th percentile. Thus, clinicians and researchers need to be cautious when interpreting a single low CNS VS composite score.

The base rates of low domain scores for adults with mood disorders are presented in Appendix B. Patients with mood disorders are more likely to obtain low scores than healthy controls subjects.

Having two scores at or below the 5th percentile occurred in 31.2% of the patients with mood disorders and only 8.2% of the control subjects [$\chi^2(1)=66.67$, $p<.0001$; Odds Ratio=5.1, 95% CI=3.4–7.7]. A larger proportion of patients with bipolar disorder (41.9%) than patients with depression (27.1-28.6%) had two or more scores in this range.

Having two domain scores at or below the 5th percentile seems to be a reasonable psychometric criterion for identifying cognitive impairment, given its low false positive rate. This low false positive rate was maintained across age groups, sexes, and education levels (see Appendix B). African Americans (N=49) had higher false positive rates (i.e., 14.3%) than Caucasians (N=570; 7.0%). The information presented in Appendix B is ready for use by clinicians and researchers. It allows a more sophisticated and evidence-based approach to the interpretation of cognitive test performance.

A minority of each clinical group was identified using this criterion (i.e., 2 or more scores ≤5th percentile) as having cognitive impairment. The test results for each of these subgroups, compared to healthy controls and patients who did not meet criterion, are presented in Figures 1-3. What is apparent from these figures is that most patients with mood disorders appear to have broadly normal cognitive functioning (white bars). However, a minority appears to have very significant cognitive impairment (grey bars). This minority, in each clinical group, is responsible for the medium effect sizes when considering *all patients* in each group. However, alone, these subgroups have a very large effect size for cognitive impairment.

Figure 1. Memory composite scores by groups
(Grey bars are the subgroup of patients identified as cognitively impaired; error lines represent 1SD)

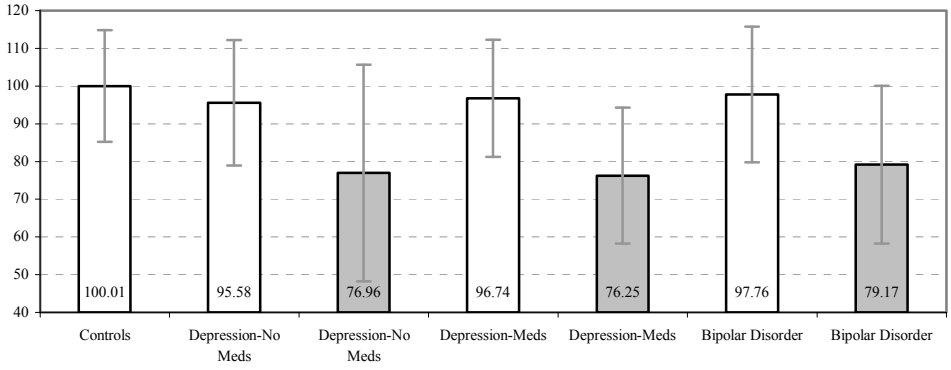


Figure 2. Reaction time composite scores by groups
(Grey bars are the subgroup of patients identified as cognitively impaired; error lines represent 1SD)

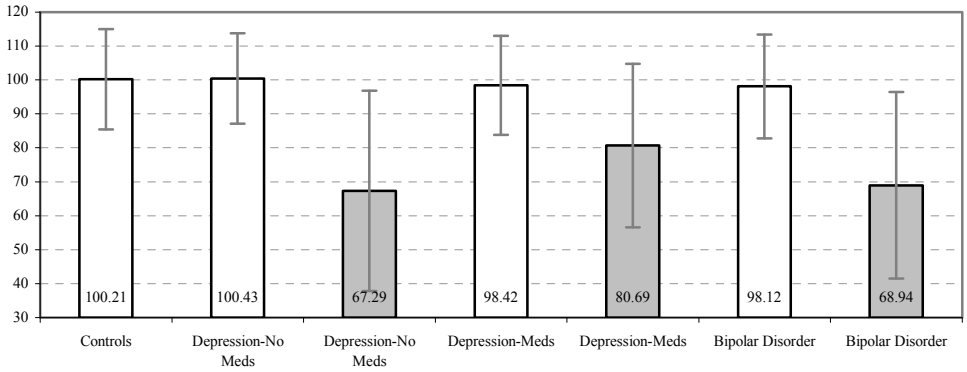
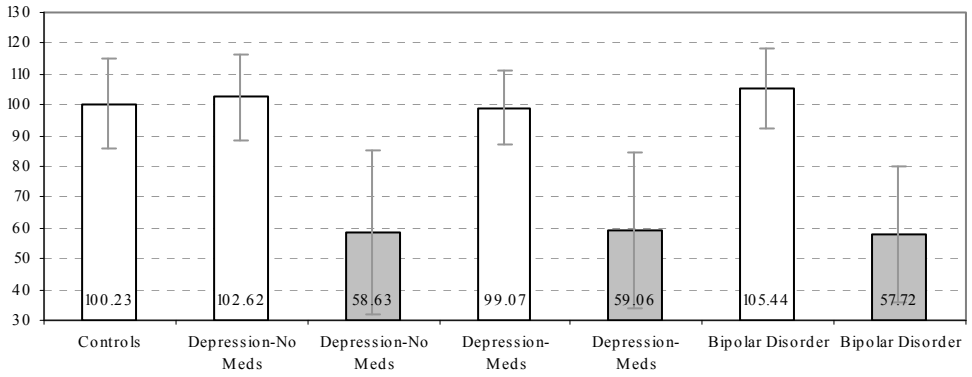


Figure 3. Cognitive flexibility composite scores by groups
(Grey bars are the subgroup of patients identified as cognitively impaired; error lines represent 1SD)



The purpose of this study was to examine cognitive functioning in mood disorders at the level of the individual. As hypothesized (a) only a minority of patients with mood disorders have measurable cognitive impairment, (b) this minority appears to be driving the effect sizes detected in group statistics, and (c) if you remove this minority from the group statistical analyses, the significant effect sizes will virtually disappear. Obviously, if you identify a subgroup of patients who perform poorly on cognitive testing, using a cutoff score at or below the 5th percentile on two or more domains, you expect that subgroup, when examined in isolation, to have very low average scores across CNS Vital signs (i.e., the grey bars in Figures 1-3). The magnitude of the low scores might be surprising to some readers, however. What is more interesting is that when the subgroup of patients with obvious cognitive impairment is removed, the remaining majority of each of the three clinical groups has scores that approximate the distributions of healthy adults. In other words, the majority of patients with mood disorders appear to have broadly normal cognitive functioning, and a minority appear to have frankly impaired cognitive functioning. The distribution of cognitive functioning in mood disorders appears to be bimodal.

Therefore, the effect sizes reported in the literature under-estimate the adverse effects of mood disorders on cognition because they are diluted by the majority of patients who have no measurable cognitive impairment. This study suggests that cognitive impairment associated with mood disorders is limited to a minority of patients with the majority being broadly cognitively normal.

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Appendix A. Descriptions of the CNS Vital Signs measures.

Measure	Description
Verbal Memory	This test measures recognition memory for words. Fifteen words are presented, one by one, on the screen every two seconds. For immediate recognition, the participant has to identify those figures nested among fifteen new figures. Then, after six more tests, there is a delayed recognition trial.
Visual Memory	This test measures recognition memory for figures. Fifteen geometric figures are presented, one by one, on the screen. For immediate recognition, the participant has to identify those figures nested among fifteen new figures. Then, after five more tests, there is a delayed recognition trial.
Finger Tapping	Participants are asked to press the Space Bar with their right index finger as many times as they can in 10 seconds. They do this once for practice, and then there are three test trials. The test is repeated with the left hand.
Symbol Digit Coding	The test consists of serial presentations of screens, each of which contains a bank of eight symbols above and eight empty boxes below. The participant types in the number that corresponds to the symbol that is highlighted. Only the digits from 2 through 9 are used; this is to avoid the confusion between "1" and "I" on the keyboard. Moreover, the participant is only allowed to use the numbers 2-9 at the top of a traditional keyboard (i.e., the computer program does not allow a person to use a numerical pad). This prevents the potential for a distinct advantage for those who are skilled at using the numerical pad or for those that are right- versus left-handed.
Stroop Test	The test has three parts. In the first part, the words RED, YELLOW, BLUE, and GREEN (printed in black) appear at random on the screen, and the participant presses the space bar as soon as he or she sees the word. In the second part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in color. The participant is asked to press the space bar when the color of the word matches what the word says. In the third part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in color. The participant is asked to press the space bar when the color of the word does not match what the word says.
Shifting Attention Test	A measure of ability to shift from one instruction set to another quickly and accurately. Participants are instructed to match geometric objects either by shape or by color. Three figures appear on the screen, one on top and two on the bottom. The top figure is either a square or a circle. The bottom figures are a square and a circle. The figures are either red or blue (mixed randomly). The participant is asked to match one of the bottom figures to the top figure. The rules change at random (i.e., match the figures by shape, for another, by color).
Continuous Performance	A measure of vigilance or sustained attention or attention over time. The participant is asked to respond to the target stimulus "B" but not to any other letter. In five minutes, the test presents 200 letters. Forty of the stimuli are targets (the letter "B"), 160 are non-targets (other letters). The stimuli are presented at random, although the target stimulus is "blocked" so it appears eight times during each minute of the test.

The five CNS-VS domain scores (i.e., Index scores), initially established through a factor analysis of the raw data (Gualtieri & Johnson, 2006b), are derived by summing multiple primary raw scores. Domain scores are presented as index scores, with a mean of 100 and standard deviation of 15. Correct responses from the verbal and visual memory tests are summed to generate a composite *Memory Domain* score. The total of right and left taps from the Finger Tapping Test and the total correct responses on the Symbol-Digit Coding Test generate a composite score for *Psychomotor Speed*. Averaging the two complex reaction time scores from the Stroop Test generates a domain score for *Reaction Time*. However, it would be more precise to conceptualize this domain score as information processing speed in a test of executive function, or reaction time within a test of executive functioning. The number of correct responses on the Shifting Attention Test, minus the number of errors on the Shifting Attention Test and the Stroop Test, is used to create a domain score for *Cognitive Flexibility*. A domain score for *Complex Attention* is generated by adding the number of errors committed in the Continuous Performance Test, the Shifting Attention Test, and the Stroop Test. The overall summary score, called the *Neurocognition Index*, is the average of the five domain scores.

Appendix B. Base rates of low domain scores on the CNS Vital Signs in healthy adults.

		Age Groups				Sex		Race		Education Groups			Computer Use	
Number of Domain Scores Below Cutoffs	**Total Sample N=659**	**20-29 N=155**	**30-39 N=177**	**40-49 N=238**	**50-54 N=89**	**M N=236**	**F N=420**	**Cauc N=570**	**A-A N=49**	**12 N=27**	**13-15 N=94**	**16+ N=226**	**Some N=73**	**Frequent N=297**
<16th Percentile														
Zero Domain Scores Below Cutoff	59.0	62.6	55.4	59.2	59.6	61.4	57.4	60.5	49.0	55.6	51.1	60.6	50.7	61.3
1 or More Domains Below Cutoff	41.0	37.4	44.6	40.8	40.4	38.6	42.6	39.5	51.0	44.4	48.9	39.4	49.3	38.7
2 or More Domains Below Cutoff	18.2	20.0	17.5	19.7	12.4	12.3	21.7	17.0	22.4	14.8	21.3	19.0	26.0	17.2
3 or More Domains Below Cutoff	7.7	8.4	7.9	7.6	6.7	5.1	9.3	7.2	8.2	3.7	11.7	6.6	11.0	7.4
4 or More Domains Below Cutoff	2.1	2.6	2.3	1.3	3.4	0.8	2.9	1.8	4.1	---	3.2	2.2	5.5	1.7
5 Domains Below Cutoff	0.6	0.6	1.1	0.4	---	0.4	0.7	0.5	2.0	---	3.2	0.4	4.1	0.3
<10th Percentile														
Zero Domain Scores Below Cutoff	68.0	73.5	61.6	68.5	69.7	69.5	66.9	69.6	59.2	66.7	60.6	67.3	57.5	69.7
1 or More Domains Below Cutoff	32.0	26.5	38.4	31.5	30.3	30.5	33.1	30.4	40.8	33.3	39.4	32.7	42.5	30.3
2 or More Domains Below Cutoff	12.0	13.5	11.9	11.8	10.1	9.3	13.6	10.5	20.4	11.1	14.9	13.3	17.8	11.8
3 or More Domains Below Cutoff	4.1	4.5	2.8	3.8	6.7	2.1	5.2	4.0	4.1	3.7	4.3	4.0	6.8	3.4
4 or More Domains Below Cutoff	0.9	0.6	1.1	0.8	1.1	0.4	1.2	0.7	2.0	---	1.1	1.3	4.1	0.3
≤ 5th Percentile														
Zero Domain Scores Below Cutoff	77.2	80.0	74.0	77.3	78.7	79.2	76.0	78.9	63.3	77.8	73.4	76.1	69.9	78.8
1 or More Domains Below Cutoff	22.8	20.0	26.0	22.7	21.3	20.8	24.0	21.1	36.7	22.2	26.6	23.9	30.1	21.2
2 or More Domains Below Cutoff	8.2	9.7	7.3	7.6	9.0	6.8	9.0	7.0	14.3	7.4	8.5	9.7	12.3	7.7
3 or More Domains Below Cutoff	1.8	1.9	1.1	1.3	4.5	0.8	2.4	1.6	2.0	---	2.1	2.7	4.1	1.7
4 or More Domains Below Cutoff	0.3	---	---	0.4	1.1	---	0.5	0.2	---	---	---	0.4	---	0.3
≤ 2nd Percentile														
Zero Domain Scores Below Cutoff	89.5	92.9	89.8	88.2	86.5	90.3	89.0	90.5	83.7	88.9	89.4	85.8	83.6	88.9
1 or More Domains Below Cutoff	10.5	7.1	10.2	11.8	13.5	9.7	11.0	9.5	16.3	11.1	10.6	14.2	16.4	11.1
2 or More Domains Below Cutoff	2.7	1.9	1.7	3.4	4.5	3.0	2.6	2.1	2.0	---	2.1	4.0	6.8	2.4
3 or More Domains Below Cutoff	0.3	0.6	---	---	1.1	0.4	0.2	0.2	---	---	1.1	0.4	1.4	0.3

Note: Based on the following five domain scores: Memory, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility. M = Male, F = Female; Cauc = Caucasian and A-A = African American. Computer use is self-report as 'some' or 'frequent.' Demographic variables were missing for some subjects.

First Definition of Cognitive Impairment: 4 scores below 1SD, OR 3 scores below 10th percentile, OR 2 scores below 5th percentile: False positives in total sample: 8.6%. Using this Boolean algorithm, 32.8% of the adult clinical sample is impaired.

Second Definition of Cognitive Impairment: 2 scores below 5th percentile: False positives in total sample: 8.2% (see Appendix B, total sample column). Using this criterion, 31.2% of the adult clinical sample is impaired (Appendix C, total clinical sample column).

Appendix C. Base rates of low domain scores on the CNS Vital Signs in adults with mood disorders.

Number of Domain Scores Below Cutoffs	Total Clinical Sample N=186	Unmedicated Depression N=84	Heterogeneous Depression N=59	Bipolar Disorder N=43
<16th Percentile				
Zero Domain Scores Below Cutoff	36.6	38.1	39.0	30.2
1 or More Domains Below Cutoff	63.4	61.9	61.0	69.8
2 or More Domains Below Cutoff	44.1	44.0	35.6	55.8
3 or More Domains Below Cutoff	26.9	27.4	22.0	32.6
4 or More Domains Below Cutoff	17.7	17.9	13.6	23.3
5 Domains Below Cutoff	9.1	9.5	8.5	9.3
<10th Percentile				
Zero Domain Scores Below Cutoff	43.0	42.9	47.5	37.2
1 or More Domains Below Cutoff	57.0	57.1	52.5	62.8
2 or More Domains Below Cutoff	38.2	36.9	33.9	46.5
3 or More Domains Below Cutoff	23.7	23.8	16.9	32.6
4 or More Domains Below Cutoff	15.6	14.3	13.6	20.9
5 Domains Below Cutoff	7.5	8.3	5.1	9.3
≤ 5th Percentile				
Zero Domain Scores Below Cutoff	48.9	51.2	50.8	41.9
1 or More Domains Below Cutoff	51.1	48.8	49.2	58.1
2 or More Domains Below Cutoff	31.2	28.6	27.1	41.9
3 or More Domains Below Cutoff	19.4	17.9	15.3	27.9
4 or More Domains Below Cutoff	12.9	11.9	10.2	18.6
5 Domains Below Cutoff	6.5	7.1	3.4	9.3
≤ 2nd Percentile				
Zero Domain Scores Below Cutoff	60.8	64.3	61.0	53.5
1 or More Domains Below Cutoff	39.2	35.7	39.0	46.5
2 or More Domains Below Cutoff	24.2	22.6	20.3	32.6
3 or More Domains Below Cutoff	15.1	15.6	11.9	18.6
4 or More Domains Below Cutoff	8.6	8.3	6.8	11.6
5 Domains Below Cutoff	4.8	4.8	3.4	7.0

Note: Based on the following five domain scores: Memory, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility.