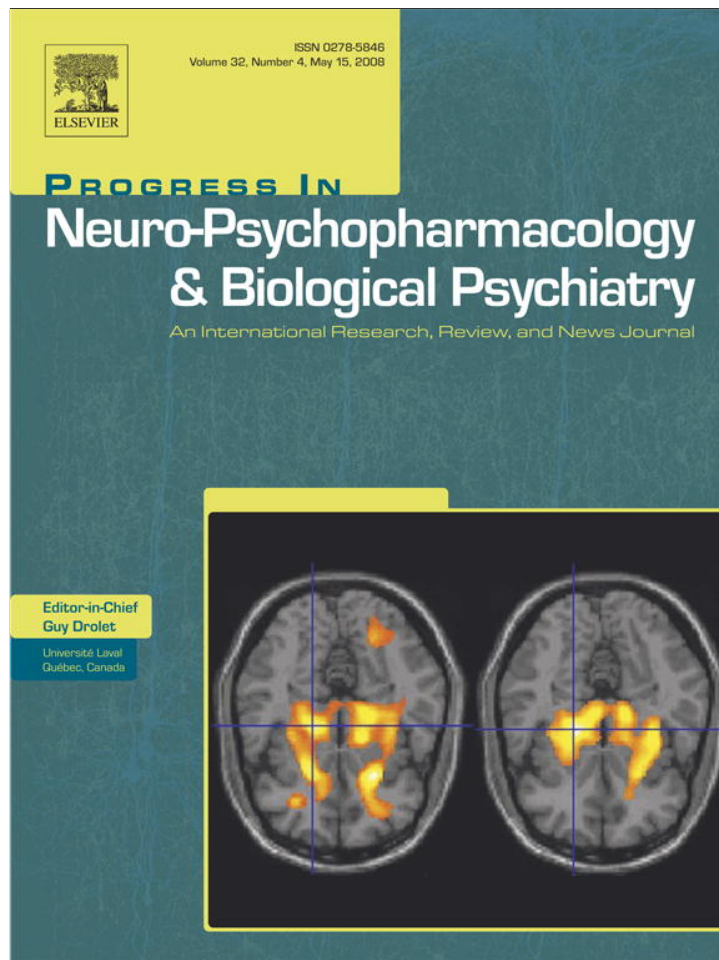


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Age-related cognitive decline in patients with mood disorders

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Abstract

Background: The relationship between depression and dementia is complex and appreciation of its true nature is evolving. Depression is an early symptom of dementia. Recent research suggests that mood disorders, in general, may be risk factors for the development of dementia.

Method: This was a cross-sectional study of the effect of aging on cognition in patients with mood disorders compared to normal controls. Patients and controls were tested with a comprehensive neurocognitive test battery, CNS Vital Signs. The question at issue was the rate of aging-related cognitive decline the same or different in mood disorder patients compared to normal controls.

Subjects: 455 patients with mood disorders, 336 with major depression and 119 with bipolar affective disorder, age 18–86, and 1003 normal controls, age 35–90. Normal controls were age 18 or older in the CNS Vital Signs normative database. The normal subjects were healthy, on no centrally-active medication, and free of psychiatric and neurological disorders.

Results: Cognitive performance in the two groups run in parallel from age 18 to 45; they begin to diverge during the next decade; after age 65, mood disorder patients, as a group, decline more sharply than normal controls. The differential rate of decline was seen in the domains of memory, attention, processing speed and executive function.

Conclusions: There seems to be an acceleration in age-related cognitive decline in patients with depression in particular, and mood disorders in general, compared to age-matched normal controls. It is likely, then, that as people age, the ones who develop depression, or who fail to recover from early episodes of depression, include a substantial number of patients at risk for developing dementia. This is consistent with the fact that late-life depression may be an early manifestation of dementia. The data are also consistent with the idea that mood disorders are a risk factor, albeit a weak one, for the development of dementia. From a slightly different perspective, one might imagine that some pathophysiological event is shared by the mood disorders and dementing conditions.

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Keywords: Depression; Mood disorders; Aging; Dementia; Age-related cognitive decline

The relationship between depression and dementia is complex and appreciation of its true nature is evolving. A generation ago, the concept of “pseudodementia” seemed sufficient to explain it. The rationale for the term, pseudodementia, was simple and straightforward:

because cognitive impairment is a symptom of depression, and depression is a symptom of early dementia, distinguishing one from the other is not always possible. Therefore, the only reliable differentiator is treatment response. If an elderly patient presents with cognitive impairment and depression, and treating the latter leads to resolution of the former, then the patient had “pseudodementia” (Kasahara et al., 2006). The term is used less often now, as new knowledge has accrued concerning the nature of depression and its relationship to medical illness in general and dementia in particular. It is not simply an “either-or” question.

The study of “late-onset” or “late-life” depression (LLD) has shed light on the relationship between depression and dementia. LLD is a term reserved for patients who experience their first depressive episode, in some studies after age 50 (Gallassi et al.,

Abbreviations: LLD, late-life depression; AD, Alzheimer’s disease; ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; VBM, verbal memory; VIM, visual memory; FTT, finger tapping test; SDC, symbol digit coding; ST, Stroop test; SAT, shifting attention test; CPT, continuous performance test; VS, vital signs; LC, locus coeruleus; NA, norepinephrine; CVD, cerebrovascular dementia; PET, positron emission tomography.

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2006), in others, 65 (Burgut et al., 2006). LLD has certain characteristics that are relevant to the development of dementia: cognitive impairment is a more prominent symptom of LLD than of early depression, especially deficits in memory (Gallassi et al., 2006), processing speed and executive function (Sheline et al., 2006). These also happen to be the earliest cognitive signs of dementia. LLD is frequently associated with symptoms reflecting hypofrontality (blunted affect, apathy, defective initiative, etc.) and with psychosis, which are also early signs of dementia. LLD shares with dementia an association with cardiovascular risk factors, inflammatory markers and the ApoE4 genotype (Gallarda, 1999). LLD also has a strong association with medical morbidity, especially cardiovascular pathology (Copeland et al., 1992, Chen et al., 2005).

Patients with LLD are at risk for dementia (Baldwin et al., 2006). In a study of 44 patients with “pseudodementia” who were followed for 4–18 years (average, 8 years), 39 (89%) developed probable Alzheimer’s disease (AD) (Kral and Emery, 1989). In a study of 27 elderly patients with depression accompanied by cognitive impairment, 43% developed dementia within 3 years (Alexopoulos et al., 1993). Patients with mild cognitive impairment (MCI) and depressive symptoms are twice as likely to develop AD compared to MCI patients who do not have depressive symptoms (Modrego and Ferrandez, 2004). There is a strong correlation between the onset of AD and a first episode of depression occurring during the preceding year (Robert et al., 2003).

In older patients who develop depression, cognitive impairment is likely to persist even after depression is successfully treated (Bhalla et al., 2006). In fact, a “substantial proportion” of older depressed individuals who are cognitively intact when depressed are likely to be impaired one year later, even though their depression has remitted (Bhalla et al., 2006). Not every patient who develops LLD will develop dementia; not every case of pseudodementia will develop AD. However, the co-occurrence of LLD with cognitive impairment is likely to be an early sign of dementia. (Burgut et al., 2006; Robert et al., 2003).

There is a second dimension to the relationship between depression and dementia. Depression is more than just an early symptom of dementia. In fact, mood disorders – at any age – are a risk factor, albeit a weak one, for the development of AD (Ownby et al., 2006). Even depression occurring when the patient was young (more than 25 years prior to ascertainment) is associated with the eventual development of AD (Robert et al., 2003). The hazard ratio for patients with bipolar affective disorder to ultimately develop dementia is 1.92, and for patients with unipolar depression, 2.13. The risk of developing dementia increases with the number of prior depressive episodes in both depressive and bipolar patients (Kessing et al., 2004).

There is an overlap between the cognitive deficits that are specific to depression and the cognitive deficits that characterize early dementia. In MCI and early dementia, cognitive deficits exist in memory, the executive functions, processing speed and complex attention (Brand et al., 1992; Burt et al., 2000; MacQueen et al., 2002a; Gualtieri and Johnson, 2005; Tabert et al., 2006; Brown et al., 1994; Jeste et al., 1996; Landro et al., 2001; Schatzberg and Kraemer, 2000). By the same token, cognitive deficits that are specific to depression reside in the

domains of executive function, processing speed and effortful attention (Gualtieri et al., 2006).

Memory impairment frequently occurs in association with mood disorders (Belanoff et al., 2001; Rinck and Becker, 2003) and depressed patients are aware of memory impairment in their day-to-day lives (MacQueen et al., 2002b). The relationship between depression and some specific component of the memory system, however, is ambiguous. Although studies have demonstrated problems with encoding as well as retrieval, recall as well as recognition (Brand et al., 1992; Burt et al., 1995), the common element is probably difficulty with tasks requiring sustained effort rather than with memory *per se* (Bartfai et al., 1991). Interestingly, when depressed patients are memory impaired, the problem is independent of the patient’s current mood state, but is related to the past course of the patient’s illness — for example, the number of prior depressive episodes. Thus, memory impairment is at least to a degree trait-related, in contrast to attentional dysfunction, which appears to be state-dependent (MacQueen et al., 2002b).

The intimacy of the relationship between mood disorders and dementia led us to examine the lifetime course of cognitive functions in patients with mood disorders. It is well-established that depression and bipolar disorder are associated with cognitive impairment, even in young people, and even when they are successfully treated and euthymic (Gualtieri et al., 2006). It is also a fact that neurocognitive functions decline gradually with age, beginning at age 30–35 (Gualtieri and Johnson, 2006a). It is not known, though, whether patients with mood disorders decline at the same rate as normal people. The data we present suggests that they do not.

1. Materials and methods

This was a cross-sectional study of the effect of aging on cognition in patients with mood disorders compared to normal controls.

1.1. Subjects

There were 455 patients with mood disorders, 336 with major depression and 119 with bipolar affective disorder, age

Table 1
Subjects

	NML	Mood
<i>N</i>	1003	455
Males	353	146
Females	305	603
%White	87.5	87.7
%Black	9.1	6.2
Computer familiarity	2.6	2.6
Mean age	45	41.2
Education	15.7	14.6
Age 18–34	296	157
Age 35–44	203	105
Age 45–54	233	117
Age 55–64	121	51
Age 65+	150	25

18–86, and 1003 normal controls, age 35–90 (Table 1). All of the patients were seen at the Neuropsychiatry Clinics in Chapel Hill and Charlotte, North Carolina. The diagnoses were made by the treating clinician on the basis of DSM-IVtr criteria, and independently reviewed by the first author. When the patients are evaluated at the Clinics, they are administered a comprehensive computerized neurocognitive test battery. The patients in this sample include patients on and off medication.

Table 2
Cognitive performance by age group in mood disorder patients and normal controls (ANOVA)

		N	Mean	St dev	F	P<		
Age 18–34	Memory	NML 261	99.20	8.05	27.37	0.0000		
		MD 144	92.68	16.98				
	Psychomotor speed	NML 255	180.15	24.84	39.27			
		MD 141	159.59	40.41				
	Reaction time	NML 255	605.86	88.84	7.86			
		MD 140	642.60	171.65				
	Complex attention	NML 250	6.78	6.47	46.70			
		MD 139	17.19	22.51				
	Cognitive flexibility	NML 251	48.24	12.11	48.66			
		MD 139	36.25	21.83				
	Age 35–44	Memory	NML 176	98.81	7.62		27.14	0.0000
			MD 92	92.25	12.99			
Psychomotor speed		NML 174	176.79	24.47	33.56			
		MD 91	156.26	32.26				
Reaction time		NML 175	630.27	92.12	7.82			
		MD 93	674.07	164.42				
Complex attention		NML 169	7.13	7.54	23.08			
		MD 93	21.06	36.37				
Cognitive flexibility		NML 171	45.98	14.09	24.32			
		MD 93	34.74	22.88				
Age 45=54		Memory	NML 206	97.29	7.63	28.02	0.0000	
			MD 109	90.49	15.19			
	Psychomotor speed	NML 190	166.09	21.07	20.80			
		MD 106	149.24	42.47				
	Reaction time	NML 190	643.51	90.67	9.57			
		MD 107	696.15	201.25				
	Complex attention	NML 186	7.26	6.21	23.66			
		MD 106	17.51	27.57				
	Cognitive flexibility	NML 187	43.14	13.09	25.13			
		MD 106	32.46	23.41				
	Age 55–64	Memory	NML 102	96.79	8.01	22.14		0.0000
			MD 50	89.30	11.32			
Psychomotor speed		NML 89	154.25	24.49	17.84			
		MD 49	129.41	44.69				
Reaction time		NML 89	707.05	131.61	4.11			
		MD 49	771.43	241.87				
Complex attention		NML 85	9.66	9.33	7.22			
		MD 49	16.18	18.75				
Cognitive flexibility		NML 85	38.09	16.97	7.54			
		MD 49	27.94	25.80				
Age 65+		Memory	NML 127	91.29	7.60	25.85	0.0000	
			MD 24	80.38	16.91			
	Psychomotor speed	NML 78	126.68	25.16	12.52			
		MD 22	102.23	38.79				
	Reaction time	NML 81	765.36	142.80	5.73			
		MD 22	868.23	275.85				
	Complex attention	NML 98	12.22	12.10	24.20			
		MD 22	27.77	18.25				
	Cognitive flexibility	NML 78	23.79	22.64	12.34			
		MD 22	3.95	26.01				

Table 3
Curve estimation, patients and controls

		R ²	F	P<
Memory	LIN	0.938	15 806	0.000
	QUAD	0.987	36 388	0.000
Psychomotor speed	LIN	0.879	7 245	0.000
	QUAD	0.962	11 407	0.000
Reaction time	LIN	0.935	13 162	0.000
	QUAD	0.951	8 577	0.000
Complex attention	LIN	0.282	333	0.000
	QUAD	0.283	168	0.000
Cognitive flexibility	LIN	0.687	2 062	0.000
	QUAD	0.797	1 662	0.000

The patients were selected from the CNS Vital Signs database if they met the following criteria:

1. Age 18 years or older.
2. Diagnosis, major depression or bipolar disorder.
3. No concurrent cognitive disorder; i.e., ADHD, learning disability, brain injury, mild cognitive impairment, dementia.
4. Stable health, aside from their mood disorder.

Normal controls were all subjects age 18 or older in the CNS Vital Signs normative database. The normal subjects were in good health; older patients were prone to the typical diseases associated with aging, and some were taking medications. But their medical conditions were stable, and medication use was limited. None were taking centrally-active medications, and all were free of present or past psychiatric/neurological disorders.

Subjects were divided into five age groups. The first age group, 18–34, is the epoch during which the neurocognitive functions measured by the CNS Vital Signs test battery are at their optimal level, in normal people. Thereafter, there is a gradual decline (Gualtieri and Johnson, 2006b).

1.2. The CNSVS battery

The CNS Vital Signs battery contains seven tests that are widely used by neuropsychologists, and known to be reliable and valid (32). The tests embrace an appropriate span of cognitive domains, and are known to be sensitive to most of the causes of mild cognitive dysfunction.

Verbal memory (VBM) and visual memory (VIM) are adaptations of the Rey Auditory Verbal Learning Test and the Rey Visual Design Learning Test (Taylor, 1959; Rey, 1964). VBM and VIM are recognition tests, however, not tests of recall. Correct responses from VBM and VIM are summed to generate a composite memory or memory domain score.

Table 4
MANOVA, diagnosis by age, race, gender and reaction time as covariates

	F	P<
Memory	1.74	0.0008
Psychomotor speed	1.71	0.0011
Reaction time	1.93	0.0001
Complex attention	1.24	0.1174
Cognitive flexibility	1.70	0.0014

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 test (Smith and Jones, 1982), 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) (Stroop, 1935) 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 (Le et al., 1998; Nagahama et al., 1998). 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. “Efficiency” on the SAT is calculated by dividing the response time by percentage correct.

The continuous performance test is a measure of vigilance or sustained attention (Rosvold and Delgado, 1956). 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, of whom 1003 were 18 years old or older. The test battery is widely used in research and clinical practice. Reliability, concurrent and discriminant validity are comparable to the conventional neuropsychological tests upon which the battery is based (Gualtieri and Johnson, 2006b).

2. Results

The data in Table 2 present the data for five age groups: 18 to 34, 35 to 44, 45 to 54, 55 to 64 and 65 and older. In both normal subjects and in the patients with mood disorders, cognitive performance declined with age. In every age group, and in every cognitive domain, patients with mood disorders performed less well than normal controls (Table 2).

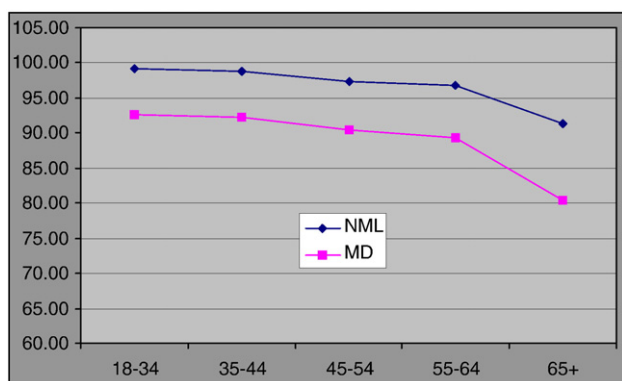


Fig. 1. Age-related decline in memory in mood disorder patients and normal controls.

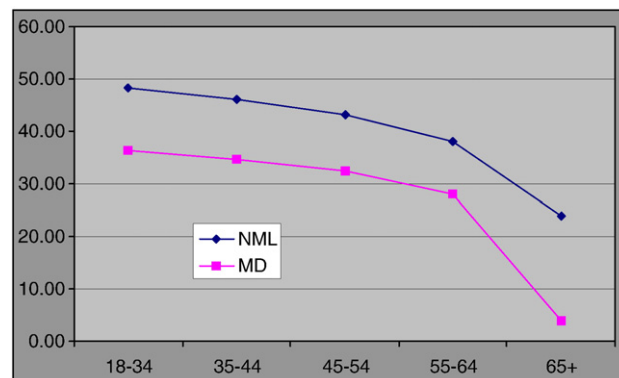


Fig. 2. Age-related decline in cognitive flexibility in mood disorder patients and normal controls.

Regression analysis indicated that the line that best represented age-related cognitive decline was quadratic rather than linear, with an acceleration of decline occurring after age 65 (Table 3). The exception was the domain of complex attention, to which neither a linear nor a quadratic curve represented a suitable fit.

Age-related decline in neurocognitive performance is more pronounced, however, in patients with mood disorders. A multiple analysis of variance was performed with diagnosis and age as fixed factors, and race and gender as covariates (Table 4). In order to assure that the relative decrements in cognitive performance were not simply the result of motor slowing, simple reaction time was also introduced as a covariate. Age-related cognitive decline was different in patients with mood disorders, compared to normal controls in every variable, save complex attention. When patients with unipolar depression ($N=231$) were compared to bipolar patients ($N=67$), analysis of variance revealed no differences.

In every domain, save that of complex attention, patients with mood disorders declined to a greater degree than normal controls. The data are displayed graphically in Fig. 1 for memory and in Fig. 2 for cognitive flexibility.

In order to illustrate this finding in summary terms, a standard score was generated for the four domains of memory, psychomotor speed, reaction time and cognitive flexibility by relating the average score of each age group to the average score generated by normals at age 18–35, when performance is

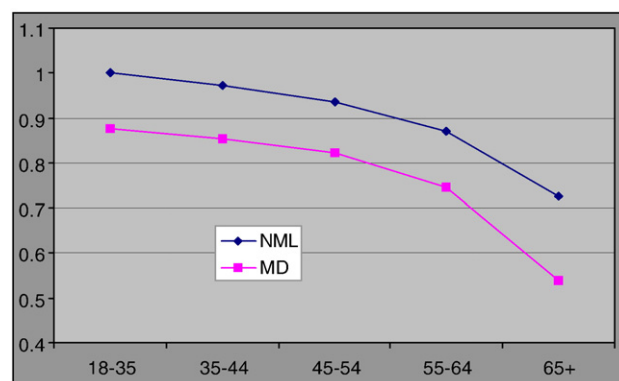


Fig. 3. Age-related change in neurocognition from age 18, normal controls and patients with mood disorders.

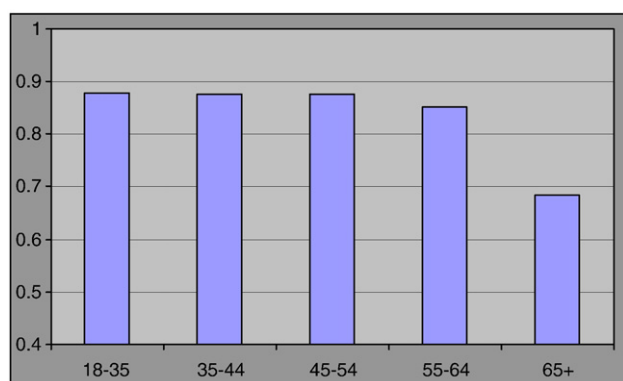


Fig. 4. Neurocognition in mood disorder patients as a percentage of normal controls.

optimal. A neurocognition index was calculated for each age group by averaging the standard scores of all domains. The change in neurocognition in normal controls and mood disorder patients is represented in Fig. 3. The two lines run in parallel from age 18 to 54, begin to diverge between age 55 and 64, and then diverge sharply past age 65.

Another way to illustrate the results of this investigation is to present the summary neurocognition scores of patients with mood disorders as a percent of normal control scores for each age group (Fig. 4). In age groups 18–35, 35–44 and 45–54, mood disorder patients' neurocognitive index scores are 87.9%, 87.7% and 87.6% of control scores. During age 55–64, they are 85.3% of control scores. Beyond age 65, they are 68.4% of control scores.

3. Discussion

The two premises upon which this investigation is based are well-founded. The first is that neurocognitive performance in tests of memory, attention, reaction time, psychomotor speed and executive function declines with age. This is a universal phenomenon, a fact of life, and it happens to patients who have neuropsychiatric disorders just as it happens to people who do not. The course of age-related cognitive decline is illustrated by normative statistics from the CNS Vital Signs database (Gualtieri and Johnson, 2006b). From this database, 1003 normal people, age 18–90, served as controls for this study.

The second premise is that patients with mood disorders perform less well on neurocognitive tests than normal controls do. This, too, is supported by a vast literature to which we have made a recent contribution (Gualtieri et al., 2006). Cognitive impairment occurs in untreated patients with mood disorders, but it tends to persist even after patients are successfully treated (Gualtieri et al., 2006).

The CNS Vital Signs database generated data from 455 patients, age 18–86, with major depression or bipolar disorder. Just as in normal people, patients with mood disorders have peak performance on neurocognitive tests between age 18 and 34. Thereafter begins an inexorable decline, slow and gradual at first, and then faster, and steeper.

The question at issue was the rate of change occurring in mood disorder patients compared to normal controls. In fact, what seems to happen is that the two groups run in parallel from age 18 to 45; that they begin to diverge during the next decade; and that after

age 65, mood disorder patients, as a group, decline more sharply than normal controls. What does this mean, with respect to the association between mood disorders and dementia?

First, it is necessary to acknowledge the limitations of our approach. Obviously, patients were not followed longitudinally from age 18 to 86; we are in the process of so doing, and we shall present the results of that investigation in 68 years. This was, rather, a cross-sectional study, and the problem is that depressed patients who presented to the clinic at different ages may have different conditions. Clearly, older patients are more likely to have had more discrete depressive episodes than younger patients; data on the number of previous episodes or on depression onset were not available to us, and, in a retrospective study, would be of limited reliability. In the same vein, data on depression severity, past or present, were not sufficiently reliable to be included in the analysis. The conclusions we draw, therefore, are necessarily limited.

On the other hand, it is appropriate to iterate that the investigation exercised controls that are not always found in published studies. For example, mood disorder patients with mild cognitive impairment or dementia were excluded from this study, as were patients who had any other kind of cognitive disorder (ADHD, learning disability, stroke, brain injury). Both groups, the mood disorder patients and the normal controls, were in good health. The analysis controlled for simple reaction time, thus assuring that the observed differences were cognitive in nature, and not a function of aging-related motor slowing. The cognitive battery used, CNS Vital Signs, has been demonstrated reliable and valid, comparable to conventional neuropsychological tests, and covers the broad range of neurocognitive functions pertinent to studies of dementia and other neuropsychiatric disorders (Gualtieri and Johnson, 2006b).

Bearing in mind the pluses and minuses of the methods employed, we believe that the following conclusions are warranted: there seems to be acceleration in age-related cognitive decline in patients with depression in particular, and mood disorders in general, compared to age-matched normal controls. It is likely, then, that as people age, the ones who develop depression, or who fail to recover from early episodes of depression, include a substantial number of patients who may be on their way to developing dementia. This is consistent with the fact that late-life depression is a risk factor for the development of dementia.

The data are also consistent with the idea that mood disorders, by their very nature, aggravate the process of aging-related cognitive decline. This is consistent with the fact that mood disorders are a risk factor, albeit a weak one, for the development of dementia. Or, from a slightly different perspective, there is some pathophysiological event that is shared by the mood disorders and dementing conditions.

The cognitive impairment of patients with mood disorders grows more severe as patients age, relative to normal controls. We are not aware of other research that has addressed this issue directly, although it is implicit in previous reports that indicate that the number of prior depressive episodes in mood disorder patients is directly correlated with dementia risk (Kessing et al., 2004). If the results of this investigation are supported by further research, then the implications will also deserve further exploration. On a theoretical level, what are the pathophysiological characteristics

of mood disorders that contribute to the association? On a clinical level, the cognitive status of older patients with depression should be monitored and addressed appropriately.

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