DEPRESSION IN CORTICAL AND SUBCORTICAL DEMENTIA SYNDROMES

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ABSTRACT

The concept of subcortical dementia predicts higher rates of depressive symptomatology in dementia syndromes with predominant subcortical pathology. This hypothesis was evaluated by comparing the frequency and severity of depressive symptomatology in three diagnostic conditions: Alzheimer's disease (AD) (n=30), subcortical vascular disease (SVD) (n=30), and Parkinson's disease (PD) (n=30). While AD and PD are prototypical exemplars of cortical and subcortical dementia syndromes respectively, SVD provides a test of the generality of the hypothesis as a subcortical neurodegenerative condition whose pathology is not confined to a single subcortical nucleus. A secondary aim of the study was to compare assessment methods for

the ascertainment of depressive symptomatology. Assessment methods included the Hamilton Rating Scale for depression derived from interview with the patient's primary caregiver (HRS_{CG}) and from interview with the patient (HRS_{EX}), and the self-report Geriatric Depression Scale.

The severity of current depressive symptomatology across the three neurodegenerative disorders followed a consistent pattern across each method of assessment. Specifically, scores on self-report (GDS), examiner ratings (HRS_{EX}), and caregiver ratings (HRS_{CG}) of depression were most severe in patients with Parkinson's disease (PD), intermediate in subcortical vascular disease (SVD), and least severe in Alzheimer's disease (AD). There were reliable differences between PD and AD patients for all measures; PD-SVD and AD-SVD comparisons were only significant for the HRS_{EX}. The presence of clinically significant depression based on cut-off scores and fit to DSM-III-R criteria also followed the same pattern. However, method variance in the measurement of depression cannot be discounted because of the three methods of symptom assessment were highly correlated only in Parkinson's disease.

DEDICATION

To

Ruth Hutchinson Dassler (1903-1979)

An indomitable spirit that will always be part of me

and

Shawn Benjamin Gilley (1989-)

My hope for the future

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Finally, to the patients and their respective caregivers, I can only hope that something I accomplish in my career will help reduce the pain and suffering of these terrible diseases.

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INTRODUCTION

Dementia refers to the behavioral consequences of neuropathological conditions, regardless of etiology, long-term prognosis, and demographic factors. While there exists no universally accepted definition of dementia, there is general agreement that dementia represents an acquired persistent impairment of intellectual function of sufficient severity to disrupt social and occupational competence (e.g., American Psychiatric Association, 1980; Cummings & Benson, 1983). Clinical criteria specify impaired intellectual function as (a) performance on a global mental status examination in the impaired range, and (b) deficits in two or more specific areas of cognition (memory, language, visuo-spatial skills, abstract reasoning, etc.) (McKhann et al., 1984). Many patients with dementia also display a wide range of mood and behavioral disturbances which contribute to the overall disruption of social and occupational functioning.

Dementia is not itself a disease entity but merely one symptom of a wide range of disorders. Alzheimer's disease (AD) is the most common source of dementia, accounting for 50-60% of the cases, followed by multiple

infarction (MID) in 20% (Katzman, 1986). The balance of cases result from diverse etiology such as toxic exposure, metabolic disorders, substance abuse, neoplasms, trauma, and extrapyramidal disorders (see Cummings & Benson, 1983; Katzman, 1986). The prevalence of dementia in persons over 65 is approximately 10-15% (Evans et al., 1989), including up to 6% with severe dementia (Mortimer, Schuman, & French, 1981; Schoenberg, Anderson, & Haerer, 1985). While there has not been any systematic change in the age-specific prevalence rates of dementia, increased life expectancy for older segments of the population is expected to dramatically increase the overall incidence of dementia, creating what some authors have referred to as a "deluge" (Wells, 1981) or an "epidemic" (Plum, 1979) of new cases by the turn of the century.

Most neuropsychological research efforts have been directed at the documentation of cognitive deficits in different types of dementia. For example, information-processing paradigms have been used extensively to address the nature of memory deficits in AD, including the semantic-episodic (e.g., Shimamura, Salmon, Squire, & Butters, 1987), primary-secondary (Wilson, Bacon, Fox, & Kaszniak, 1983), and implicit-explicit (Schacter,

1987) dimensions. Emotional sequelae, on the other hand, have been less commonly studied and are poorly understood in their relationship to the underlying disease.

DEPRESSION AND DEMENTIA

Dementia is not a unitary construct but rather a broad symptom complex. There is considerable heterogeneity in the clinical presentation of different neurodegenerative conditions, presumably reflecting differences in the underlying chemical and/or structural pathology. At present, the only available theoretical framework concerning neuropsychological differences between subtypes of dementia is the "cortical-subcortical" distinction.

Albert, Feldman, and Willis (1974) introduced the term "subcortical dementia" to describe the cognitive and behavioral disturbances of patients with lesions in subcortical nuclei. These disturbances include slowness of mental activity, inattention, poor acquisition of new information or forgetfulness, defective ability to manipulate acquired knowledge, and changes in personality. The personality changes involve apathy (loss of interest in social, instrumental tasks, and

personal hygiene), emotional lability (episodic irritability, euphoria, or tearfulness), and depression. Patients with subcortical dementia also lack the characteristic features of "cortical" dementia: aphasia, amnesia, apraxia, and agnosia. In addition, subcortical dementias are relatively mild in comparison to their cortical counterparts (e.g., Alzheimer's disease, Pick's disease). The disabling features of the lesions in subcortical nuclei primarily arise from disruption of sensation and movement, echoing Fisher's (1968) comments on the effect of small subcortical infarcts: these conditions lick the psyche, but bite the soma. Table 1 provides a contrast between subcortical and cortical dementia.

Depression is the most widely recognized psychiatric disorder in conditions associated with subcortical dementia. Estimates of the prevalence of depressive symptomatology in Parkinson's disease (Mayeux, Stern, Rosen, & Levanthal, 1981) and Huntington's disease (McHugh & Folstein, 1975) suggest that approximately half of these patients satisfy the diagnostic criteria for depressive disorders. Depression has also been described in relatively rare extrapyramidal degenerative disorders such as Wilson's

Table 1. Differential characteristics of cortical and subcortical dementias.

Characteristic	Cortical Dementia	Subcortical Dementia
Language		
Expressive	Abnormal	Preserved (except for naming)
Articulation	Normal	Dysarthric, hypophonic
Receptive	Abnormal	Preserved
Memory		
Recent	Abnormal (learning or storage deficit)	Abnormal (retrieval deficit)
Remote	Abnormal	Preserved
Visuo-spatial	Abnormal	Generally preserved

Table 1. Differential characteristics of cortical and subcortical dementias - Continued.

Characteristic	Cortical Dementia	Subcortical Dementia
Cognition	Severe impairment in one or more specific areas (e.g., abstract reasoning, calculation)	Slow, disorganized thought but without specific deficits
Motor System		
Posture	Normal	Abnormal
Tone	Normal	Increased
Movements	Normal	Abnormal (tremor, chorea)
Gait	Normal	Abnormal

disease, progressive supranuclear palsy, Syndenham chorea, and the Hallervordern-Spatz syndrome. In reviewing research on the relationship between basal ganglia disorders and emotion, Mayeux (1983) concluded that nearly every patient with an extrapyramidal movement disorder also presents with some type of emotional disturbance, although not necessarily of sufficient severity to warrant a psychiatric diagnosis.

There is a growing body of evidence supporting the distinction between cortical and subcortical dementia in terms of performance on specific measures of cognitive function (see Brown & Marsden, 1988). However, there is little data on the relative specificity of depression to neurodegenerative disorders associated with subcortical dementia. Demonstration of this specificity would have important diagnostic implications as well as provide some insight into possible biological bases of depression.

Depression in subcortical dementia syndromes

The basis for depression in these disparate conditions has yet to be established. It is tempting to argue that depression is a byproduct of the structural and/or neurochemical alterations in these conditions

(Cummings, 1986). However, the heterogeneity of pathology leaves the "final common pathway" for depression open to debate. An equally compelling argument can be made for the role of individual reactions to chronic disease, particularly with respect to the impact on movement, in accounting for depression (Gotham, Brown, & Marsden, 1986).

Questions of etiology aside, the relationship between depression and Parkinson's disease (PD) is noteworthy for two reasons. PD has become the disease of choice in the study of subcortical dementia (e.g., Huber & Paulson, 1986). It is clearly the most common degenerative extrapyramidal disorder, affecting nearly one per thousand in the population (Hoehn & Yahr, 1967). Second, depression has been extensively studied in PD patients and these data illustrate the current methodology and phenomenology of depression in subcortical dementia syndromes.

PD is a complex motor disturbance (bradykinesia, resting tremor, rigidity, and disruptions of gait, posture, and equilibrium) which results from the loss of pigmented brainstem nuclei, particularly in the substantia nigra. In addition to mild cognitive changes, the most common behavioral manifestation is

depression. Depending upon the sampling technique, clinically significant depression is reported in 32-63% of patients with PD (see Mayeux, 1984). The severity of depression appears to be correlated with the severity of the movement disorder in untreated PD patients (Hoehn et al., 1976) but is unrelated to residual motor dysfunction following dopaminergic replacement therapies (e.g., Gotham, Brown, & Marsden, 1986; Horn, 1974; Marsh & Markham, 1973; Mayeux et al., 1981).

There have been few attempts to compare subcortical and cortical dementia syndromes on measures of depression. Mayeux, Stern, Rosen, and Benson (1983) report that significant depressive symptomatology was present in 35 of 57 PD patients (61%) and 8 of 20 HD patients (40%). In contrast, none of 46 AD patients exhibited significant depression although 9 of these patients had mild, transient depressive symptoms early in the course of the disorder. These estimates were based on self-report (Beck Depression Inventory) in PD and HD patients and neurologist ratings in AD patients. Huber, Shuttleworth, Paulson, Bellchambers, and Clapp (1986) failed to find differences on a depression scale (Zung Self-rating Depression Scale) between AD and PD

patients, with both groups scoring significantly greater than normal controls on this measure.

Depression in Alzheimer's disease

Alzheimer's disease (AD) is a degenerative neurological condition whose primary clinical feature is progressive dementia (Semple, Smith, & Swash, 1982). Impaired recent memory is usually the first recognized symptom with subsequent deterioration of language, spatial judgment, and praxis. While there is some heterogeneity in the clinical presentation as well as rate of progression, most AD patients exhibit severe global cognitive impairment within ten years of symptom onset. Extrapyramidal signs and primitive reflexes are also associated with the later stages of the disease.

There is little consensus about the frequency of depression in AD. Most reviews of the clinical presentation of AD patients either do not mention depression (Cummings & Benson, 1983) or suggest that it is uncommon (Roth, 1980; Semple, Smith, & Swash, 1982). Post (1975) indicates that brief periods of dysphoric mood are evident in AD but classifies these occurrences as a subclinical phenomenon. Nicol (1968) cites AD as a neurological condition that is noteworthy for a

particularly low incidence of depression throughout the course of the disease.

However, a growing body of evidence points to the presence of affective symptoms and major depressive episodes in a substantial number of patients with AD. There are numerous case reports of patients with suspected AD and concurrent depression (DeMuth & Rand, 1980; Devanand & Nelson, 1985; Feinberg & Goodman, 1984; McAllister & Price, 1982; Sharberg, 1978; Snow & Wells, 1981). Depression has also been reported as a common presenting complaint in patients with suspected AD. Most of the evidence comes from retrospective studies of patients with presenile onset AD. Table 2 summarizes the prevalence of depression in these patients prior to final diagnosis of dementia. The criteria for depression is not clearly specified in these studies and primarily relies on secondary information (e.g., medical records). Nonetheless, the data clearly suggest the recognition of affective symptoms in these patients, typically early in the course when medical attention is first sought.

Recent attempts to study depression in well-defined AD samples have produced variable estimates of prevalence, ranging from 0% (Knevesich et al., 1983) to

Table 2. Prevalence of depression as a presenting complaint in patients subsequently diagnosed as having dementia.

Study	Sample Size	No. with Depression	%
Goodman (1953)	23	5	21.7
Ziegler (1954)	40	6	15.0
Sim & Sussman (1962)	46	24	52.0
Rosenstock (1970)	11	4	36.4
Gustafson (1975)	57	17	30.0
Nott & Fleminger (1975)	15	6	40.0
Liston (1977)	50	24	48.0
Totals	242	86	35.5

85.9% (Merriam et al., 1988). Table 3 summarizes the results of six available studies encompassing 511 total patients. Excluding the two extreme estimates, 82 patients have been identified as depressed out of a total of 312 patients, yielding an overall prevalence of estimate of 26.3%. The criteria for depression in these studies are consistent with current psychiatric practice, including DSM-III criteria for affective disorders (Reding et al., 1985; Reifler et al., 1986), cut-off scores on the Hamilton Rating Scale (HRS) (Knevesich et al., 1983; Lazarus et al., 1987), and a diagnostic algorithm based on the Schedule of Affective Disorders and Schizophrenia (SADS) (Merriam et al., 1988). The patients in each study were diagnosed as AD based on extensive medical, radiological, and neuropsychological work-ups. (Furthermore, the diagnosis of AD was made independently in each investigation and any referral bias seems unlikely as patients in most studies were from consecutive patient series (Merriam et al., 1988; Reding et al., 1985; Reifler et al., 1986) or all AD patients from an inpatient ward (Kral, 1983).)

The highest estimate of depression in AD (86%) was obtained by Merriam et al. (1988) and is more than

Table 3. Prevalence of depression in AD.

Study	Dementia[1] Severity	Sample Size	Percent Depression	Source[2]	Criteria[3]
Kral (1983)	S	40	15%	Pt	NS
Knevesich et al. (1983)	Mi	24	0%	Pt	HRS
Reding et al. (1985)	Mi-Mo	99	19%	Pt	DSM
Reifler et al. (1986)	Mi-S	131	31%	Pt	DSM
Lazarus et al. (1987)	Mi-Mo	42	40%	Pt	HRS
Merriam et al. (1988)	Mi-S	175	86%	SO	SADS
Totals		511	45%		

[1]Mi=Mild; Mo=Moderate; S=Severe

[2]Pt=Patient Interview/Observation; SO=Significant Other Interview

[3]NS=Not Specified; DSM=DSM-III Major Affective Disorder or Dysthymic Disorder; HRS=Hamilton Rating Scale (Cutoff Score >11); SADS=Schedule of Affective Disorders and Schizophrenia (Change Version)

double other available estimates. Their method involved a semi-structured interview of a significant other, using queries from the SADS, while other studies have utilized interview and observation of the patient directly. The disparity between estimates based on the SADS and the HRS are puzzling. Endicott, Cohen, Nee, Fleiss, and Sarantakos (1981) report high correlations between the HRS total score and the SADS depressed mood subscale (.84) as well as the SADS endogenous symptoms subscale (.80) in a sample of 48 depressed inpatients. Hence, there is some evidence of significant shared variance between the two scales with normal administration (structured interview with the patient).

Affective symptoms were also broadly defined in the Merriam et al. (1988) study. For instance, dysphoria was defined as an affirmative response to any question regarding depressed mood, sadness, fearfulness, excessive worrying, or helplessness. Loss of interest in usual activities required the acknowledgment of diminished level of activity or pleasure derived from activities by the patient. Ninety-seven percent of the sample exhibited significant mood disturbance based on evidence of either dysphoria or loss of interest. There was also evidence of impersistence of mood disturbance.

Of patients who satisfied criteria for depressive episode in this study, 89.8% were able to be cheered or distracted during dysphoric periods according to the significant other.

Unreliability of clinical ratings may also contribute to method variance in these studies. For example, interrater reliability on the HRS was reported to be only .68 in Lazarus et al. (1987). Most published estimates of interrater reliability for the HRS exceed .85 (e.g., Hamilton, 1960; Waldron & Bates, 1965). It is unclear what impact interrater differences might have had on overall prevalence estimates. However, the estimates reported by Lazarus et al. (1987) for AD patients (40%) and normal controls (12%) are much higher than estimates in Knevesich et al. (1983) for both groups (0%) using the HRS.

In summary, depressive symptomatology is not uncommon in patients with suspected AD. Nonetheless, the assessment of depression in AD is complicated by overlapping symptomatology (Miller, 1980) and the potential unreliability of the patient as a source of information given significant cognitive impairment. Despite these limitations, most available studies

suggest that significant depressive symptomatology is evident in a quarter to a third of AD patients.

Depression in cerebrovascular disease

Vascular disease is the second most common source of dementia, with prevalence estimates ranging from 8% to 34% of dementia cases (Cummings & Benson, 1983). Vascular dementia is particularly common in acute-care facilities, accounting for over 72% of dementia cases in one survey of 2,000 consecutive admissions (Erkinjuntti, Wikstrom & Palo, 1986). The clinical presentation of these patients is quite variable, reflecting differences in the extent, distribution, and pathogenesis of the vascular pathology.

Dementia is rarely the result of a single vascular event but is currently viewed as the cumulative effect of vascular damage throughout the cerebrum (e.g., Hachinski, 1983). Progression of dementia proceeds in a step-wise fashion, each step downward reflecting the presence of a new area of infarction (Roth, 1980). Tomlinson, Blessed, and Roth (1970) have shown that gross mental status changes are related to the volume of infarcted tissue with 50 ml as the threshold for effect in their sample. Specific cognitive and neurological

deficits resulting from embolic or thrombotic occlusion in the cerebral vasculature are related to the cortical and subcortical territories irrigated by the affected vessel (Hachinski, 1983; Tomlinson, 1977). As a consequence, MID is often viewed as a heterogeneous condition in terms of its presentation, usually including a mixture of "cortical" and "subcortical" features.

A straightforward and clinically meaningful distinction can be drawn between cortical and subcortical infarction. Cortical regions are primarily affected by infarcts in medium to large cerebral arteries or by watershed infarcts in the border zones between major vessels. In contrast, subcortical infarction typically involves small penetrating vessels and results in lacunes. Lacunes are residual cavitary lesions, rarely more than 1-2 cm in diameter, most often the result of occlusion by lipohyalinosis and disorganization of the vessel wall (Fisher, 1982).

Lacunar infarction as the sole source of vascular pathology appears to be relatively common, found in 19-30% of cases with either radiological or post-mortem evidence of infarction (Fisher, 1967; Mohr, Caplan, & Melski, 1978). Lacunes are predominantly found in the

basal ganglia, pons, thalamus, centrum ovale, and to a lesser extent in the cerebellum and internal capsule (Fisher, 1982). Hypertension appears to be the single greatest risk factor for lacunar infarction although lacunes have been reported in normotensive patients, particularly those with diabetes (Cole & Yates, 1968) and those over age 60 (Fang, 1972). The clinical presentation of patients with lacunar infarction was first described by Marie (1901) as "l'etat lacunaire" or lacunar state. This syndrome consisted of progressive neurological decline, marked by brief episodes of pure motor hemiparesis, and eventual development of small-step gait, imbalance, dysarthria, dysphagia, bradykinesia, incontinence, pseudobulbar signs, and dementia.

Subcortical arteriosclerotic encephalopathy, or Binswanger's disease, is another vascular disorder affecting subcortical regions. Multiple lacunes are often seen in SAE, but diffuse softening (demyelination and axonal degeneration) of the subcortical white matter is the cardinal pathological feature (Olszewski, 1965). Clinically, these patients are typically hypertensive and exhibit a progressive dementia often accompanied by

focal motor signs, incontinence, gait disturbance, and a pseudobulbar syndrome (Caplan & Schoene, 1978).

The clinical literature clearly points to an association between depression and cerebral ischemic disease. In particular, depression has been described as a common sequelae of cerebrovascular accidents (Adams & Victor, 1985; Brain, 1945; Slater & Roth, 1969). Based on clinical observations, Roth (1955) included depression as one of the cardinal clinical features of patients with "arteriosclerotic psychosis" or dementia secondary to multiple infarction. Roth suggested that the depression was typically mild ("a depressive coloration of the personality") but subsequently has reported major depressive episodes in approximately 20% of patients with multi-infarct dementia (Roth, 1978).

Most studies of affective disorders in cerebrovascular disease have examined depression in patients with a single vascular lesion, usually infarction in the territory of a medium to large cerebral artery. A high incidence of depression has been reported in the immediate post-stroke period (0-6 months) (Robinson et al., 1983). However, the presence of depressive features in the clinical presentation of infarct patients does not appear to be equally probable

for all areas of infarction. Depression has been most closely tied to the proximity of lesions to the frontal poles (Folstein, Maiberger, & McHugh, 1977; Lipsey, Robinson, & Pearson, 1983; Robinson, Starr, & Kubos, 1982; Robinson & Szetela, 1981). There is a slightly greater representation of left hemisphere lesions in the patients with depression in these series (e.g., Benson & Robinson, 1983) but laterality differences have not been firmly established (Sinyor et al., 1986).

Hachinski, Lassen, and Marshall (1974) included depression as one of 13 clinical features thought to differentiate MID from AD. The specificity of depression to vascular dementia has received modest support. Most studies comparing MID and AD patients have reported higher rates of psychiatric diagnosis for depression in MID patients (Brucht et al., 1984; Cummings et al., 1987; Gustafson & Nilsson, 1985; Loeb & Gandolfson, 1979), although there have been several negative reports (Reding et al., 1985; Rosen et al., 1980). The prevalence of significant depression ranges from 6% (Reding et al., 1985) to 30% (Brucht et al., 1984) with most studies falling in the 20-30% range (Brucht et al., 1984; Cummings et al., 1987; Gustafson & Nilsson, 1985; Loeb & Gandolfson, 1979; Rosen et al.,

1980; Roth, 1978). In contrast, prevalence of depression in AD patients is less than 20% in all of these studies (but see Lazarus et al., 1987; Reifler et al., 1986; Merriam et al., 1988). In addition, Cummings et al. (1987) also report significantly higher scores for MID patients on the Hamilton Rating Scale than AD patients. The diagnosis of MID in these studies followed DSM-III criteria for MID and no attempt was made to classify MID patients on the basis of cortical, subcortical, or mixed vascular involvement.

Extension of the concept of subcortical dementia to vascular disorders suggests that patients with subcortical pathology should be at high risk for depression. Depression has been alluded to as part of a constellation of "personality changes" which include loss of incentive, apathy, and pseudobulbar affect. For example, prominent mood changes, including depression, were reported in 20 out of 30 patients in one series of patients with subcortical vascular dementia (Ishii et al., 1986). Depression was identified in 10 of 47 cases of Binswanger's disease culled from the literature in the review by Babikian and Roper (1987).

Taken together, the widely held assumption that depression is specific to vascular dementia relative to AD appears to have modest empirical support. Across all studies, the rate of depression favors vascular forms of dementia with some overlap in prevalence estimates. No study, however, has attempted to systematically compare rates of depression in AD and subcortical vascular dementia (SVD) samples as an extension of the theoretical concept of subcortical dementia.

Limitations of the subcortical-cortical distinction

The distinction between subcortical and cortical dementia has been the subject of numerous reviews (e.g., Albert, 1984; Cummings, 1984; Cummings & Benson, 1984; Whitehouse, 1986). It is safe to say that this framework has numerous theoretical and empirical shortcomings. Perhaps foremost of these limitations, the concept has been criticized as an unwarranted simplification in terms of anatomical relationships and behavioral function (Boller et al., 1980; Cohn & Neumann, 1978; Hakim & Mathieson, 1979; Mayeux, Rosen, & Stern, 1984). Some subcortical nuclei (e.g., substantia nigra) receive afferents from cortical structures (particularly the frontal lobes). Other subcortical

nuclei (e.g., thalamic) have both afferent and efferent connections to cortical structures. Alzheimer's disease, the prototypic "cortical" dementia, may result from the degeneration of cholinergic afferents within the subcortical nucleus basalis of Meynert (Whitehouse et al., 1981).

From a behavioral standpoint, most reviews point to the difficulty in translating the features of subcortical dementia into meaningful operationalization (e.g., Albert, 1984; Whitehouse, 1986). Furthermore, the features of subcortical dementia bear striking similarity to frontal lobe disorders (Mesulam, 1986; Nuata, 1971). Hence, there appears to be little basis on which to separate subcortical dementias from focal lesions of the frontal lobe or from cortical dementias predominantly affecting frontal lobe function (Neary, Snowden, Northern, & Goulding, 1988). Intraclass differences among cortical and subcortical dementia syndromes have been virtually ignored. For example, there is little similarity in presentation of the two primary variants of cortical dementia - Pick's disease and AD (Cummings & Benson, 1984; Neary, Snowden, Northern, & Goulding, 1988). Likewise, important differences are evident among the various subtypes of

subcortical dementia (Whitehouse, 1986). Finally, severity of dementia has often been confounded with heterogeneity of presentation in comparative cognitive studies between subcortical and cortical dementia. In particular, patients with subcortical dementia are usually less severely impaired on measures of dementia severity (e.g., Huber et al., 1986; Mayeux et al., 1983). Consequently, it may be difficult to distinguish mild AD from subcortical dementia. This problem has led to speculation that quantitative differences in psychological test performance may not differ because patients with subcortical and cortical disorders may fail for different reasons (Cummings & Benson, 1984). Hence, unobservable psychological processes are posited to account for the lack of observable differences in performance.

Nonetheless, the concept has demonstrated some heuristic value primarily because of the behavioral similarity of patients with lesions in different subcortical regions (Cummings, 1986). Likewise, differences have emerged in behavioral studies between cortical dementia (as defined by AD) and subcortical dementia (as defined by PD) (e.g., Huber et al., 1986). This yields one simple prediction regarding conditions

which produce progressive degenerative dementia. The probability of depression in these various conditions will be related to the extent that subcortical features predominate the presentation. Depression would, therefore, be expected to be elevated in both extra-pyramidal degenerative disorders (e.g., PD) as well as SVD, but comparatively rare in cortical degenerative disorders (i.e., AD). Meaningful evaluation of this hypothesis is predicated upon resolving problems in the measurement of depression in these disorders.

The problem of measurement

The most common approach to the measurement of depression has been the construction of symptom interviews which attempt to capture the salient dimensions of the clinical domain of depression. In fact, symptoms which differentiate clinically depressed psychiatric patients from normal controls have been the basis for test construction for numerous self-report (e.g., Beck Depression Inventory, Zung Self-rating Scale) and psychiatric rating scales (e.g., Hamilton Rating Scale, Brief Psychiatric Rating Scale). The respectable psychometric properties of these measures attests to the success of this approach (Carroll,

Fielding, & Blashki, 1973; Lyerly, 1978; Schnurr, Hoaken, & Jarrett, 1976). However, the psychometric adequacy of measures of depression for patients with neurological disease affecting the central nervous system is uncertain and rarely studied. Several potential sources of measurement error warrant special consideration in this population.

Scales of depression are composite measures in which individual items relate to different symptoms of depression. Depression is typically quantified on the basis of the number and intensity of appropriate signs and symptoms, summed to provide a convenient index of severity. Consequently, the validity of the total score on a measure of depression is clearly limited by the extent to which individual items are unique to depression. This condition cannot be satisfied in many neurological disorders because of overlapping symptomatology between these conditions and depression. For instance, the stooped posture, masked facies, and paucity and slowness of spontaneous movement associated with Parkinson's disease are similar in appearance to psychomotor retardation. Appetite loss and sleep disturbance are also side effects of anti-parkinsonian agents. Abrupt tearfulness and other poorly modulated

affective changes are described in a wide range of conditions producing frontal release or "pseudo-bulbar" signs (Poeck, 1969; Lieberman & Benson, 1977). Emotional lability, apathy, and lethargy are among the earliest signs of increased intracranial pressure (Rossman, 1969).

In patients with AD and vascular forms of dementia, the diagnostic specificity of symptoms related to mental clarity (e.g., confusion, inability to concentrate, memory complaints), level of spontaneous activity (i.e., agitation, restlessness, retardation, lethargy, rapid fatigue), and sleep disturbance is questionable. Deterioration of cognitive function is the basis for the diagnosis of dementia and thus has no apparent value in the diagnosis of depression. The prevalence of agitation and retardation have not been well documented. In one series of patients with biopsy-proven Alzheimer's disease, agitation was noted in 45% of the patients (Mohs et al., 1983). The architecture of sleep (particularly the density of stages 3 and 4) is also thought to be dramatically altered in degenerative neurological disorders (Miles & Dement, 1980).

The empirical contribution of dementia to scores on measures of depression is unclear. Elevations on the

HRS, SDS, and BDI have been observed in patients with senile dementia relative to normal controls (e.g., Heidell & Kidd, 1974; Huber et al., 1986; Miller, 1980). However, no attempt has been made to demonstrate specificity of these three measures in differentiating depressed and nondepressed patients with dementia.

A second potential source of measurement error in patients with dementia concerns reliance on self-report. Self-report measures and psychiatric rating scales rely heavily on the patient to describe the range, intensity, and duration of affective symptoms. Under most circumstances, this approach is a reasonable one. However, dementia may be expected to affect the accuracy of these ratings, particularly at more severe levels of cognitive disturbance. It is unreasonable to assume that reliable and meaningful estimates of affective symptomatology can be obtained from patients who cannot accurately report the date, their current location, or recent personal events.

Management of these two potential sources of error is not straightforward. The overlap between neurological disorders and depression affects the specificity of the behavioral manifestations of affective disturbance. Psychometric approaches to this

problem favor the assignment of differential weights to test items based upon their relationship to the underlying dimension of interest within a specific target population. Weights are assigned in proportion to the amount of variance accounted for by individual items with respect to the phenomenon of interest. For instance, items pertaining to intrapsychic manifestations of depression (sense of failure, dissatisfaction, sense of punishment, morbid ideation, indecision, loss of social interest) have been found to maximally discriminate depressed and nondepressed medical patients using item-response models (Clark et al., 1982; Gibbons et al., 1984). A simplified approach to this problem would be to eliminate (i.e., assign a weight of 0) those items which are not specific to the target syndrome, which also favors the exclusive emphasis on intrapsychic symptoms of depression in patients with central nervous system disorders and dementia. Unfortunately, intrapsychic symptoms require self-report, which runs afoul of the second source of measurement error in patients with dementia: namely, the reduction in reliability and validity of self-report measures in the face of cognitive dysfunction.

Further, another cost of this approach is likely to be a reduction in the sensitivity of measurement.

Emphasis on observable, behavioral manifestations of depression may provide a partial solution, although specificity may be compromised. Several advantages are apparent. First, it is possible to bypass self-report. Someone who is familiar with the behavior patterns of the patient should be able to accurately estimate the frequency of the target behaviors. Reliance on such a collateral source of information would permit evaluation at all levels of dementia. Second, this method does not require gratuitous assumptions or costly empirical study of the specificity of individual symptoms to the syndrome of depression. The discriminability parameters of item-response models require large samples for reliable estimation (Lord & Novick, 1968), which is unfeasible as a precondition for investigations of dementia. Third, it does not necessitate any reduction in the sensitivity of measurement. Finally, from a logical standpoint, perfect specificity is rarely obtained by any diagnostic tool. For example, a number of pathological conditions can produce lucencies on CT scans of the brain although

confirmation of a specific condition may require a tissue sample.

OVERVIEW

The aims of the present study were two-fold. First, the hypothesized relationship between depression and subcortical dementia syndromes was evaluated by comparing the frequency and severity of depressive symptomatology in three groups: AD, SVD, and PD. While AD and PD are prototypical exemplars of cortical and subcortical dementia syndromes respectively, SVD provides a test of the generality of the hypothesis as a subcortical neurodegenerative condition whose pathology is not confined to a single subcortical nucleus. A secondary aim of the study was to compare assessment methods for the ascertainment of depressive symptomatology. Assessment methods included the Hamilton Rating Scale for depression (HRS) (Hamilton, 1960, 1967) derived from interview with the patient's primary caregiver, the HRS in standard format (patient interview and examiner ratings), and the self-report Geriatric Depression Scale (Yesavage, et al, 1983). The emphasis on behavioral features of depression in the HRS facilitates the use of a observer-report format,

thereby potentially circumventing some of the salient measurement problems outlined in the previous section. Preliminary data on the concurrent validity and interrater reliability of the observer-report HRS are presented in Appendices A and B. The level of agreement among these assessment methods provides an index of potential utility and may help reconcile some discrepancies in previous reports of the frequency of clinically significant depression in dementia syndromes.

METHOD

Subjects

Thirty AD patients and 30 SVD patients were selected from outpatient referrals to the Rush Alzheimer's Disease Center (RADC) at Rush-Presbyterian-St. Luke's Medical Center (RPSLMC) between June 1, 1989 and December 31, 1989. The RADC is the state-designated regional Alzheimer's disease center for northern Illinois whose catchment area encompasses approximately 12 million, including the city of Chicago and its suburbs. Referrals are made directly to the clinic (self and physician referrals). As of December 31, 1989, the RADC had a total patient registry of 1144 patients.

Thirty PD patients were selected from the outpatient population of the Movement Disorders Center at RPSLMC between June 1, 1989 and September 31, 1989. Approximately 500 PD patients are followed through this service.

Selection for study was made after a complete diagnostic work-up. The RADC work-up consists of complete physical and neurological examination, neuropsychological evaluation, and routine blood studies

for initial and follow-up evaluations. Magnetic resonance (MR) scan is usually obtained at the initial visit unless a recent scan is available from another institution. It was not possible to evaluate reliability of diagnosis between RADC physicians, however all cases were reviewed for uniform application of diagnostic criteria by a single neurologist (David A. Bennett, MD).

The diagnostic evaluation in the Movement Disorders Center consists of a complete neurological evaluation with detailed examination of movement parameters. Other procedures (e.g., neuropsychological testing, MR scan) are obtained on a case by case basis. Final diagnosis in the Movement Disorders Center is based on consensus review of each case by staff neurologists. New patients are subjected to a standardized videotaped examination which are reviewed by the group.

It was necessary for all participants to have a responsible adult in the home who could routinely observe the patient and participate in data collection procedures. Specific selection criteria for each diagnostic condition are listed below.

Alzheimer's Disease. The selection criteria for AD patients follows the NINCDS/ADRDA workgroup consensus criteria for probable AD (McKhann et al., 1984). Inclusion criteria include evidence of dementia on clinical examination (neurologist rating), evidence of dementia on psychometric examination, deficits in at least two areas of cognition, and progressive cognitive decline with onset between the ages of 40 and 90. Psychometric evidence of dementia was defined as performance within the "impaired" range on either the Mini-Mental State (MMS) Examination (Folstein, Folstein, & McHugh, 1975) or the Dementia Rating Scale (DRS; Mattis, 1976). Standard cutoff scores for these measures were used: 23 or less on the MMS and 129 or less on the DRS. Ratings of areas of deficit were made by the neuropsychologist after review of a detailed neuropsychological examination, including global measures of mental status (MMS, DRS) and specific measures of attention, memory, language, and praxis.

Exclusion criteria for AD patients are as follows:

(a) no evidence of clouded consciousness;

(b) no concurrent systemic or neurologic disorder;

(c) no history of significant substance abuse, head trauma with loss of consciousness greater

than one hour, or previous intracranial surgery;

(d) not currently on psychoactive medications;

(e) no history or presentation suggestive of cerebrovascular disease: no radiological evidence of focal pathology; Hachinski Ischemia Scale (Hachinski et al, 1974) < 4; no more than one of the following five features from the Hachinski Ischemia Scale: abrupt onset of cognitive impairment, step-wise progression, focal neurological signs, focal neurological symptoms, and history of stroke/transient ischemic attack.

The final sample represents 7.75% of 387 patients seen in the RADC over the 6 months of data collection. Of 357 patients excluded from participation, 80 AD patients met all criteria but did not have a matching SVD case. Reasons for exclusion in the remainder included 118 patients with the clinical diagnosis of AD which did not meet inclusion and exclusion diagnostic criteria, 124 patients with clinical diagnoses other than AD, and 35 patients not living with the identified primary caregiver.

Table 4 summarizes demographic and clinical variables for AD patients included in this study, AD patients satisfying entry criteria but not included, and the general population of AD patients in the RADC. Patients included were similar in all aspects except slightly lower age ($\underline{F}(2,731) = 4.1$, $\underline{p} < .05$) and less cognitive impairment ($\underline{F}(2,731) = 10.9$, $\underline{p} < .05$) on the MMS. Of note, means on the principle dependent measures (GDS, HRS_{EX}, HRS_{CG}) were similar between included and excluded patients.

Subcortical Vascular Dementia. The selection criteria for SVD were based on evidence of dementia, history and presentation compatible with cerebrovascular disease, and radiological evidence of subcortical infarction. This category includes patients with suspected lacunar infarction and/or Binswanger's disease. These two conditions have similar clinical presentations with hypertension as the primary risk factor for each condition. In addition, radiological evidence of lacunes is evident on MR scan in each condition. The only distinguishing characteristic appears to be more extensive involvement of subcortical white matter in Binswanger's disease seen on postmortem examination,

Table 4. Comparisons of AD patients: study participants, patients excluded from study, and total RADC population.

	Included	Excluded	RADC
N	30	80	624
Age	71.8± 7.4	74.0± 8.6	73.8± 9.1
Age at onset	70.5± 7.8	69.9± 8.0	68.7± 9.7
Sex (proportion male)	.43	.29	.34
Race (proportion white)	.90	.85	.86
Socioeconomic Status[1]	39.2±15.6	38.2±15.9	41.9±15.3
Education	11.9± 2.9	12.0± 3.4	11.7± 3.8
Premorbid IQ estimate[2]	112.2±13.2	112.5±14.1	111.1±13.9
MMS	19.3± 5.4	15.6± 5.5	11.9± 6.2
GDS[3]	6.9± 5.5	7.2± 4.9	--
HRS_{EX}[4]	3.8± 3.9	4.3± 3.7	--
HRS_{CG}[5]	5.6± 5.6	6.5± 6.6	--

[1]Hollingshead and Redlich (1956) two-factor estimate

[2]Regression formula of Wilson et al. (1978)

[3]GDS = Geriatric Depression Scale

[4]HRS_{EX} = Hamilton Rating Scale - examiner ratings

[5]HRS_{CG} = Hamilton Rating Scale - caregiver ratings

suggesting that the two conditions probably lie along a continuum. There is no a priori basis for clinically separating the two conditions, and Roman (1984, 1985, 1987) has strongly advocated grouping the two conditions as a single disease entity. We have chosen to refer to these patients with a neutral classification of SVD rather than adopt the potentially confusing distinction of "Senile Dementia of the Binswanger's Type" suggested by Roman (1987).

Inclusion criteria for SVD were as follows:

(a) the criteria for progressive dementia outlined above for AD patients;

(b) history of presentation suggestive of cerebrovascular disease based on at least two of the following five features from the Hachinski Ischemia Scale: abrupt onset of cognitive impairment, step-wise progression, focal neurological signs, focal neurological symptoms, history of stroke/transient ischemic attack;

(c) presence of one of the following cardiovascular risk factors: hypertension by history or examination, diabetes mellitus by history or examination, or evidence of cardiac

disease (previous myocardial infarction, previous cardiac surgery, congestive heart failure, or angina pectoris);

(d) evidence on MR scan of either (1) three or more discrete bilateral foci or hyperintensity on T2 weighted images in the characteristic lacunar territories or (2) periventricular high signal throughout the entire centrum ovale on T2 weighted images.

Exclusion criteria for SVD were similar to those for AD except for those related to cerebrovascular disease. These criteria include:

(a) no evidence of clouded consciousness;

(b) no concurrent systemic or neurologic illness other than those involving the cardiovascular system;

(c) no history of significant substance abuse, head trauma with loss of consciousness greater than one hour, or previous intracranial surgery;

(d) not currently on psychoactive medications;

(e) no radiological evidence of focal pathology other than that listed above.

The final sample represents 7.75% of 387 patients seen in the RADC over the 6 months of data collection. The remaining 357 patients included 30 AD patients in this study, 16 cases of vascular dementia which did not satisfy entry criteria, and 311 patients with clinical diagnoses other than SVD.

No SVD patients satisfying entry criteria were omitted from the study. Table 5 compares the SVD sample in this study with the general population of SVD patients in the RADC on demographic and clinical characteristics. These groups were similar on all dimensions.

Parkinson's Disease. All patients had a clinical diagnosis of idiopathic PD with at least two cardinal signs (rigidity, resting tremor, bradykinesia, postural reflex abnormality) and at least two years duration. In addition, all were responsive to dopaminergic replacement therapy and stable on current dose regimen for at least three months. This excludes patients with secondary parkinsonism due to insults to the extrapyramidal motor system (e.g., arteriosclerosis, infarction, anoxia, calcification, drugs) and those

Table 5. Comparison of SVD patients: study participants and total RADC SVD population.

	Included	RADC
N	30	93
Age	71.9 ± 7.5	74.7 ± 8.1
Age at onset	68.9 ± 8.0	70.2 ± 7.6
Sex (proportion male)	.43	.53
Race (proportion white)	.90	.88
Socioeconomic status[1]	42.3 ± 15.7	39.6 ± 16.2
Education	12.0 ± 2.6	12.8 ± 2.3
Premorbid IQ estimate[2]	112.9 ± 12.9	115.6 ± 15.1
MMS	19.7 ± 5.5	18.1 ± 3.8
GDS[3]	10.2 ± 6.1	--
HRS_{EX}[4]	7.4 ± 5.2	--
HRS_{CG}[5]	9.1 ± 6.8	--

[1]Hollingshead and Redlich (1956) two-factor estimate

[2]Regression formula of Wilson et al. (1978)

[3]GDS = Geriatric Depression Scale

[4]HRS_{EX} = Hamilton Rating Scale - examiner ratings

[5]HRS_{CG} = Hamilton Rating Scale - caregiver ratings

requiring alteration of medication regimen due to side effects or diminished efficacy.

Exclusion criteria were as follows:

(a) no evidence of clouded consciousness;

(b) no significant impairment of mental status (MMS <24)

(c) no other concurrent systemic or neurologic illness;

(d) no history of significant substance abuse, head trauma with loss of consciousness greater than one hour, or previous intracranial surgery;

(e) not currently on psychoactive medications;

(e) no radiological evidence of focal pathology.

A total of 51 PD patients were available for study. Three patients did not satisfy entry criteria and the remainder could not be paired with AD and SVD patients. Demographic and clinical features of PD participants and PD patients excluded from the study are presented in Table 6. Both groups were similar in all characteristics except level of cognitive impairment.

Table 6. Comparison of PD patients: study participants and patients excluded from study.

	Included	Excluded
N	30	21
Age	70.9 ± 8.0	67.4 ± 8.2
Age at onset[1]	59.7 ± 11.3	56.7 ± 10.8
Sex (proportion male)	.43	.63
Race (proportion white)	1.00	1.00
Socioeconomic status[2]	37.9 ± 13.9	39.2 ± 14.8
Education	12.1 ± 2.5	12.8 ± 2.9
Premorbid IQ estimate[3]	114.2 ± 14.2	115.9 ± 13.8
MMS	28.9 ± 1.3	25.9 ± 2.7
GDS[4]	14.7 ± 5.4	15.6 ± 6.0
HRS_{EX}[5]	11.3 ± 6.6	12.3 ± 5.8
HRS_{CG}[5]	12.6 ± 7.1	13.9 ± 7.9

[1]For comparison purposes, a mean age of onset of 57.9 has been reported for 200 PD patients from this clinic population (Koller et al., 1986)

[2]Hollingshead and Redlich (1956) two-factor estimate

[3]Regression formula of Wilson et al. (1978)

[4]GDS = Geriatric Depression Scale

[5]HRS_{EX} = Hamilton Rating Scale - examiner ratings

[6]HRS_{CG} = Hamilton Rating Scale - caregiver ratings

Subject Characteristics. Table 7 summarizes patient and informant characteristics for the 3 diagnostic conditions. All groups were similar in age, gender, race, education, socioeconomic status, estimated premorbid intellectual ability, and relationship of informant to the patient. In addition, AD and SVD patients were similar in age at onset, level of cognitive impairment on the MMS, and severity of extrapyramidal signs on the NYU scale. However, PD patients had earlier disease onset ($F(2,87)=19.1$, $p<.0001$), less cognitive impairment on the MMS ($F(2,87)=32.9$, $p<.0001$), and more severe extrapyramidal signs on the NYU scale ($F(2,87)=54.0$, $p<.0001$).

MEASURES

Mini-Mental State (MMS)

This 30-item measure is a standardized screening examination covering orientation, attention, memory, and language (Folstein, Folstein, & McHugh, 1975). Scores range from 0 to 30 based on the number of correct items. The standard cut-off for "normal" performance is 24 and the mean for cognitively intact elderly is 26 (Folstein et al., 1986). The normative data reported by Folstein

Table 7. Demographic and clinical characteristics for AD (N = 30), SVD (N = 30), and PD (N = 30).

	AD	SVD	PD
Age	71.7± 7.4	71.9± 7.5	70.9± 8.0
Age at onset	70.5± 7.8	68.9± 8.0	59.7±11.3
Sex (proportion male)	.43	.43	.43
Race (proportion white)	.90	.90	1.00
Socioeconomic Status[1]	39.2±15.6	42.3±15.7	37.9±13.9
Education	11.9± 2.9	12.0± 2.6	12.1± 2.5
Premorbid IQ estimate[2]	112.9±12.9	112.2±13.2	114.2±14.2
MMS	19.3± 5.4	19.7± 5.5	28.9± 1.3
NYU[3]	1.2± 1.8	1.5± 3.2	7.0± 4.1
Informant			
Spouse	21	23	24
Child	7	7	6
Other relative	2	0	0

[1]Hollingshead and Redlich (1956) two-factor estimate

[2]Regression formula of Wilson et al. (1978)

[3]NYU = New York University Parkinson's Disease Scale

et al. (1986) indicate the specificity (correct classification as normal/abnormal) for a score of 24 to be .95 for all elderly subjects, although lower (.70) for those with less than nine years of education. Test-retest reliability for a one-month retest interval has been reported to be .85 for normal controls and .90 for patients with dementia (Anthony, Le Resche, Niaz, Von Korff, & Folstein, 1982). Significant correlations with other measures of dementia severity (Chui, Teng, Henderson, & Moy, 1985; Reisberg, Ferris, deLeon, & Crook, 1982) and duration of symptoms in AD patients (Teng, Chui, Schneider, & Metzger, 1987) support the scale's validity.

Hamilton Rating Scale - Examiner Ratings

The Hamilton Rating Scale (HRS) (Hamilton, 1960, 1967) is a 17-item observer rating scale which covers the affective, psychomotor, and somatic symptoms of depression. Ratings are completed by professional examiners after clinical interview and observation of the patient. The presence and severity of individual symptoms in the previous week are rated in accordance with specific behavioral anchors. The HRS completed by the examiner will be denoted as the HRS_{EX}.

The selection of the HRS for this study was based on item content and psychometric properties. The emphasis on the behavioral manifestations rather than intrapsychic features of depression in the HRS (Carroll, Fielding, & Blashki, 1974) facilitates the use of the patient's caregiver as the primary data source. The few items which focus on intrapsychic features (e.g., guilt) are rated in accordance with the content and frequency of statements made by the patient and hence open to observation. Further, the lack of items pertaining to cognitive dysfunction (e.g., concentration and memory problems) eliminates an obvious confound in studying patients with dementia syndromes.

The psychometric properties of the HRS have been studied and appear adequate (see Table 8). The HRS covers most symptoms in the psychiatric syndrome of depression (American Psychiatric Association, 1980), has relatively homogeneous item content (internal consistency estimates $\geq$ .82), and has adequate interrater reliability in most applications (.85-.90). However, interrater reliability may be somewhat lower in AD and related disorders (e.g., Lazarus et al., 1987). The validity of the HRS is supported by generally high correlations with other scales of depression (e.g., Zung

Table 8. Summary of psychometric properties of the HRS.

Feature	Reported Range	References
Inter-rater Reliability	.85-.90	Hamilton (1960) Waldron & Bates (1965)
Internal Consistency	.82-.90	Yesavage et al. (1983)
Validity Coefficients (with other measures)*		
a. BDI	.75-.82	Brink et al. (1982) Briggs et al. (1980)
b. SRS	.79-.87	Carroll et al. (1973) Zung (1972)
c. GDS	.82-.83	Brink et al. (1982) Yesavage et al. (1983)
Sensitivity/Specificity at HRS = 11	.86/.80	Yesavage et al. (1983)
Effect Size** in Treatment Studies	1.26	Edwards et al. (1984)

*BDI=Beck Depression Inventory; SRS=Zung Self-Rating Scale; GDS=Geriatric Depression Scale.

**Effect size = [pre-treatment mean - post-treatment mean] / (s.d.)$(n)^{-2}$

Self-Rating Scale for depression, Beck Depression Inventory, Geriatric Depression Scale) and response to treatment (see Edwards et al., 1984).

Hamilton Rating Scale - Caregiver Ratings

The HRS is typically completed during interviews with the patient supplemented by clinical impressions. However, impaired cognition threatens the validity of patient self-report as the basis for ratings of the presence and frequency of HRS symptomatology in dementia syndromes. As an alternative, it should be possible to obtain reliable and accurate estimates of HRS symptoms from the patient's primary caregiver. The HRS is appropriate for this approach given the reliance on the behavioral manifestations of depression. In fact, Hamilton (1960, 1967) recommended the use of supplementary information from other observers (e.g., family members, ward staff) in completing the HRS.

Preliminary data on the validity and interrater reliability of the HRS based on the interviews with the patient's primary caregiver (HRS_{CG}) has been collected. In 34 PD patients, the correlation between the HRS_{CG} and HRS_{EX} was .89; the correlation between the HRS_{CG} and the Beck Depression Inventory was .87 (see Appendix A).

Interrater reliability was evaluated in 41 patients (see Appendix B) by comparing HRS_{CG} ratings for two interviewers with the same caregiver. The correlation between the two HRS_{CG} estimates was .92. Agreement between raters on the presence of individual symptoms exceeded chance for all items (Yule's coefficient $\underline{Y}$ = .56 - 1.00). There was no significant difference between raters on HRS_{CG} total scores or individual items.

In addition to total score, two classification schemes based on HRS_{CG} scores was examined. First, previous studies of depression have used a standard cutoff score ($\geq$ 11) to classify patients as depressed (e.g., Knevesich et al., 1983; Lazarus et al., 1987). In addition, some approximation to standard diagnostic criteria appears desirable. DSM-III-R criteria (see Table 9) for a major depressive episode require evidence of pervasive mood disturbance plus at least four vegetative or intrapsychic symptoms. Mood disturbance (Criterion A) was defined exclusively by the presence of dysphoric on the modified HRS. Loss of interest or pleasure in usual activities is difficult to ascertain in dementia apart from reduction in overall level of activity. Criterion B will be satisfied by the

TABLE 9. DSM-III-R Diagnostic Criteria for Major Depressive Episode.

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from a persistently sad facial expression.)

B. At least four of the following symptoms have been present nearly every day for a period of at least two weeks (in children under six, at least three of the first four):

TABLE 9. DSM-III-R Diagnostic Criteria for Major Depressive Episode - Continued.

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(1) poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six, consider failure to make expected weight gains);

(2) insomnia or hypersomnia;

(3) psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity);

(4) loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy);

(5) loss of energy; fatigue;

TABLE 9. DSM-III-R Diagnostic Criteria for Major Depressive Episode - Continued.

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(6) feelings of worthlessness; self-reproach, or excessive or inappropriate guilt (either may be delusional);

(7) complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with marked loosening of associations or incoherence;

(8) recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt.

C. Neither of the following dominate the clinical picture when an affective syndrome is absent (i.e., symptoms in criteria A and B above):

(1) preoccupation with a mood-incongruent delusion or hallucination;

(2) bizarre behavior.

TABLE 9. DSM-III-R Diagnostic Criteria for Major Depressive Episode - Continued.

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder.

E. Not due to any Organic Mental Disorder or Uncomplicated Bereavement.

presence of four or more of the seven symptoms addressed by HRS items. It should be noted that this approach provides only a loose approximation of DSM-III-R criteria, however.

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a self-report measure specifically designed as a screening instrument for depression in geriatric patients (Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer, 1983). The GDS consists of 30 items primarily covering changes in self-perceived mood; there are no items pertaining to somatic complaints. The response format is simple (yes/no) with 20 items coded positively and 10 items coded negatively. Items were selected on the basis of face validity and high item-total correlation. Psychometric properties of the GDS are adequate (see Table 10). In addition, several recent studies have validated its use in geriatric medical populations (Konig, Meador, & Cohen, 1988; Norris, Gallagher, Wilson, & Winograd, 1987). However, there is contradictory data on the use of the GDS in patients with dementia. In patients with mild dementia, significantly higher GDS scores have been reported in

Table 10. Summary of psychometric properties of the GDS.

Feature	Reported Range	References
Internal Consistency	.94	Yesavage et al. (1983)
Test-Retest Stability (1 week interval)	.85	Yesavage et al. (1983)
Validity Coefficients (with other measures)*		
a. SRS	.84	Carroll et al. (1973) Zung (1972)
b. HRS	.83	Brink et al. (1982) Yesavage et al. (1983)
Sensitivity/Specificity at HRS = 11	.84/.95	Yesavage et al. (1983)

*SRS = Zung Self-Rating Scale

patients with coexistent depression (Parmalee et al., 1989; Yesavage, Brink, Rose, & Adey, 1983). Nonetheless, increased false positive and false negative classification errors based on GDS cut-off scores in AD (Burke, Houston, Boust, & Roccaforte, 1989) and mixed dementia syndrome (Kafonek, Ettinger, Rocca, et al., 1989) patients suggest limited validity in these populations.

Other Variables

Demographic data was collected through standardized interview with PD patients and with the primary caregiver for AD and SVD patients. These variables included age, sex, race, years of formal education, and occupation. Premorbid intellectual function (Wechsler Adult Intelligence Scale - Full Scale IQ) was estimated from these variables using the regression formula of Wilson et al. (1978).

Duration of disease was ascertained through interview with the primary caregiver. This interval was defined as the time in months between the first appearance of symptoms of sufficient severity to interfere with social or occupational functioning to the time of the interview. When the interval could only

be pinpointed as a range, the midpoint of the range was chosen. Age at onset (AAO) was computed by subtracting duration of disease from the patient's current age. The sample was dichotomized into early AAO (< 65 years) and late AAO (≥ 65 years) according to traditional cut-off values (American Psychiatric Association, 1980).

Extrapyramidal signs (EPS) were rated with a modified version of the New York University (NYU) Parkinson's disease scale (Lieberman, Dziatolowski, Gopinathan, Kupersmith, Neophytides, & Korein, 1980). Total NYU score reflects the summation of severity of resting tremor, cogwheel rigidity, bradykinesia, postural instability, and festinating gait. The presence of EPS in AD and SVD was defined as at least one of the following signs on a standard neurological examination: resting tremor, cogwheel rigidity, or bradykinesia. Gait and postural abnormalities are relatively common in AD and SVD patients apart from other extrapyramidal signs (Pearce, 1974; Thompson & Marsden, 1987) and were not included as indicator signs.

PROCEDURE

All patients were drawn from routine clinic visits or screening visits for drug studies. A matching procedure was used to minimize differences in age and dementia severity. In a preliminary study, SVD patients were found to be older and less severely impaired than healthy AD patients, although there was considerable overlap in the distributions of age and dementia severity. Patients were selected to form a homogeneous triad with AD and PD patients matched to the SVD patient with respect to age. A maximum tolerance of two years was used in matching age. In addition, selection was further constrained by matching AD and SVD patients on dementia severity on the MMS. Tolerance in matching on MMS scores was two points. For all matching procedures, SVD patients served as the reference case because of the relative rarity of these patients.

The patient and the primary caregiver was evaluated separately. The MMS, GDS, and HRS_{EX} were obtained during a 30-45 minute evaluation. The primary caregiver was interviewed to complete the HRS_{CG} within five days of the clinic visit by a trained, independent research assistant, blind to the results of the patient examination and the hypotheses under consideration.

HYPOTHESES

Group Effects

(1) The null hypothesis for this study is that no differences in severity and prevalence of depression were expected between the AD, PD, and SVD groups.

(2) The alternative hypotheses follow predictions based on the subcortical/cortical dementia framework (Cummings, 1986). AD is the exemplar of cortical dementia whereas SVD and PD are exemplars of subcortical dementia.

    (a) The severity and prevalence of depression will be greater for SVD patients than AD patients.

    (b) The severity and prevalence of depression will be greater for PD patients than AD patients.

    (c) The severity and prevalence of depression will be similar for SVD and PD patients.

Measurement Covariance

Based on preliminary data (see Appendix A), the three measures of depression (GDS, HRS_{EX}, and HRS_{CG}) were expected to be highly correlated with concordant

classification (depressed/nondepressed) using cut-off scores in PD patients. A strong relationship between the GDS and HRS_{EX} was also expected in AD and SVD patients because these measures were drawn from same source (the patient). The correspondence between these measures and the HRS_{CG} is unknown, but anticipated to be lower in patients with significant dementia because of the presumed impact of cognitive impairment on patient-derived data.

Exploratory Analyses

Age at onset and extrapyramidal signs (EPS) are of particular interest among potential covariates of depression in each diagnostic condition. Age at onset has been related to differential patterns of symptomatology in AD (Mayeux et al., 1985) and PD (Zetusky, Jankovic, & Pirozzolo, 1985). The presence of EPS is thought to reflect disruption of a complex neuronal circuit involving the putamen (modulated by dopaminergic input from the substantia nigra), thalamus, and supplementary motor association areas of the frontal lobes (Albin, Young, & Penney, 1989). EPS are defining features of PD, but are also found in SVD (Thompson & Marsden, 1987) and AD (Pearce, 1974). Thus, the

severity of EPS (as measured by the NYU scale) not only marks disease severity in PD, but may also reflect the integrity of this final common pathway in AD and SVD.

Several recent observations point to an association between depression and selective involvement of several aminergic brainstem nuclei in AD patients, including the locus ceruleus (Zubenko & Moossy, 1988; Zweig, Ross, Hedreen, Steele, Cardillo, Whitehouse, Folstein, & Price, 1988), substantia nigra (Zubenko & Moossy, 1988), and dorsal raphe (Zweig et al., 1988). While direct test of this hypothesis is beyond the scope of this study, both age at onset and EPS have been implicated in differential involvement of these systems in AD (e.g., Chui et al., 1985). Further, presenile (< age 65) has been identified as a covariate (and potential marker) of depression in AD (Zubenko & Moossy, 1988; Zweig et al., 1988). In addition, the density of neurofibrillary tangles in the substantia nigra of depressed AD patients (Zubenko & Moossy, 1988) may also be associated with a higher frequency of extrapyramidal signs (e.g., cogwheel rigidity, bradykinesia) in these patients.

DATA ANALYSIS

Total Scores. Total scores on the GDS, HRS_{EX}, and HRS_{CG} were analyzed using analysis of variance (ANOVA). Given significant overall F statistics (alpha = .05), group differences were examined using the Bonferroni multiple comparison procedure with a family-wise alpha of .05. This method provides for efficient and accurate estimation for samples of equal size (Miller, 1977). This conservative approach was taken because three between-group comparisons per measure result in nine total comparisons and a maximum experiment-wise Type I error rate of .45. The Bonferroni correction applied for each measure of depression provides a maximum total experiment-wise error rate across three measures of .15. Given that these measures are not orthogonal, the actual error rate is somewhat lower.

Frequency Estimates. Frequency of depression based on cut-off scores for each measure and DSM-III-R approximation was evaluated with respect to diagnostic condition. For each frequency estimate, the relationship between depression and diagnostic condition was analyzed as a 3 x 2 contingency table with

a chi-square statistic (alpha = .05). The interpretation of this statistic is straightforward but limited in utility as a measure of strength of association apart from rejection of the null hypothesis. Rejection of the null hypothesis was followed by three pair-wise comparisons (2x2) to determine specific differences among the groups using chi-square statistics. Management of experiment-wise error rate for these comparisons paralleled the procedure outlined in the previous section. Specifically, the family-wise error rate across three between-group comparisons was held at .05 by adopting a stringent alpha (.05/3 = .0167) for each pairwise comparison.

Source Variance. Correlations among measures of depression provide an index of shared variance for each diagnostic condition. However, the effect of method variance attributable to the source of information is not likely to be uniform across all symptoms of depression. Consequently, agreement between examiner and caregiver informant ratings on the presence of symptoms covered by the HRS was also examined. The kappa statistic (Cohen, 1960) is often used as index of interrater agreement corrected for chance, but the

absolute value of kappa has been shown to vary with base rate of the condition of interest (Spitznagel & Helzer, 1985). This problem limits the utility of the kappa statistic for this study where the base rate of symptoms associated with depression vary widely across diagnostic conditions. Yule's coefficient of colligation, Y, has been shown to less sensitive to base rate differences (Spitznagel & Helzer, 1985) and was chosen as the index of agreement between examiner and caregiver ratings for each HRS symptom. Pseudo-Bayes correction for cell frequency of 0 was applied to avoid asymptotic distortion (Bishop, Feinberg, & Holland, 1975).

RESULTS

Severity and Frequency of Depression

Mean scores on the measures of depression varied consistently as function of diagnostic condition (see Figure 1). Levels of depressive symptomatology were highest in Parkinson's disease (PD), intermediate in subcortical vascular disease (SVD), and lowest in Alzheimer's disease (AD). Principle analyses of these data are summarized in Table 11. The overall effects of diagnostic condition were significant for each measure. The null hypothesis of equivalent group means can be rejected for each measure of depression.

Specific comparisons among means were made using the Bonferroni procedure, a conservative test which adjusts alpha for total number of between-group comparisons. For the self-report Geriatric Depression Scale (GDS), mean scores were significantly higher in PD relative to the SVD and AD groups. The SVD and AD comparison approached significance ($p<.10$). In contrast, all groups were significantly different on the Hamilton Rating Scale completed by the examiner (HRS_{EX}). Finally, only the difference between PD and AD groups was significant for the Hamilton Rating Scale based on

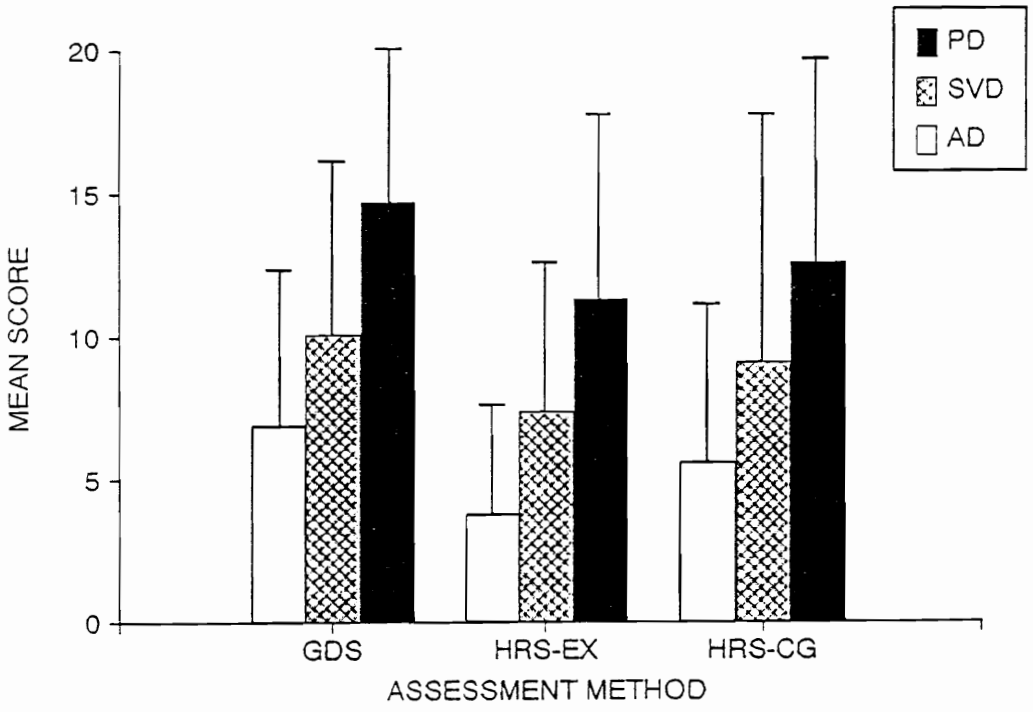

Figure 1. Mean scores on measures of depression by diagnostic conditions.

Table 11. Means and standard deviations of measures of depression by diagnostic condition and summary of analyses.

	Measure		
Condition	GDS	HRS_{EX}	HRS_{CG}
AD	6.9 ± 5.5	3.8 ± 3.9	5.6 ± 5.6
SVD	10.1 ± 6.1	7.4 ± 5.3	9.1 ± 6.8
PD	14.7 ± 5.4	11.3 ± 6.2	12.6 ± 7.1
Univariate Tests			
$F_{(2,87)}$	13.9	15.3	8.6
p	.0001	.0001	.0004
Multiple Comparisons			
LSD[1]	AD<SVD<PD	AD<SVD<PD	AD<SVD<PD
BC[2]	AD, SVD<PD	AD<SVD<PD	AD<PD

[1]Least significant difference

[2]Bonferonni correction

interview with the primary caregiver (HRS_{CG}), although other comparisons approached significance ($p<.10$).

Therefore, of the three component alternative hypotheses, only the predicted difference between PD and AD groups was consistently demonstrated across the three outcome measures. The difference between SVD and AD conditions was in the predicted direction, but failed to reach statistical significance for the GDS and HRS_{CG} measures. The expected similarity in mean scores between PD and SVD was rejected for the GDS and HRS_{EX} and there was a trend for higher scores on the HRS_{CG} for PD patients.

Correlations among the three measures of depression within each diagnostic condition are presented in Table 12. In PD patients, all measures were highly related, suggesting a common measurement core. However, in patient groups with dementia, the concordance between measures was lower. All measures were significantly intercorrelated in AD, but shared variance (r^2: .113 - .487) was limited. In SVD patients, HRS_{CG} scores were unrelated to the GDS and HRS_{EX}.

The impact of dementia severity on the intercorrelations between the three measures of depression was examined using a median split of the AD

Table 12. Intercorrelations between measures of depression for (a) AD, (b) SVD, and (c) PD patients.

a. AD (N = 30)

	GDS	HRS_{EX}	HRS_{CG}
GDS	--		
HRS_{EX}	.70*		--
HRS_{CG}	.34*	.48*	--

b. SVD (N = 30)

	GDS	HRS_{EX}	HRS_{CG}
GDS	--		
HRS_{EX}	.66*	--	
HRS_{CG}	-.09	.01	--

c. PD (N = 30)

	GDS	HRS_{EX}	HRS_{CG}
GDS	--		
HRS_{EX}	.77*	--	
HRS_{CG}	.80*	.92*	--

*$\underline{P}$ < .05, one-tailed

and SVD samples based on MMS scores. Table 13 present intercorrelations for each diagnostic condition for "mild" (MMS = 19-26) and "moderate" (MMS = 8-18) dementia severity. The pattern and magnitude of correlations was comparable between dementia severity levels in each diagnostic condition. Thus, there was no evidence of a graded effect of dementia severity on the dissociation between scores on the different measures.

Frequency estimates of clinically significant levels of depression based on standard cut-off scores for the three measures are presented in Table 14. The difference between the low estimate (HRS_{EX}) and the high estimate (GDS) formed non-overlapping ranges between the diagnostic conditions with the following order: AD (6.7-26.7%), SVD (26.7-40.0%), and PD (50.0-73.0%). The overall effect of diagnostic condition was significant for each measure. The null hypothesis of equivalent frequency of significant depression for the three diagnostic conditions was therefore rejected. Specific group comparisons, however, indicated that this effect was primarily accounted for by the difference between AD and PD. The difference in frequency between AD and SVD was not significant for any measure. The comparisons between PD and SVD were significant for the GDS and

Table 13. Intercorrelations of measures of depression for (a) AD and (b) SVD patients. Patients with mild dementia (MMS ≥ 19) (N = 15) are presented in the upper diagonal and patients with moderate dementia (MMS < 19) (N = 15) are presented in the lower diagonal.

a. AD

	GDS	HRS_{EX}	HRS_{CG}
GDS	--	.48*	-.12
HRS_{EX}	.82*	--	.13
HRS_{CG}	.56*	.70*	--

b. SVD

	GDS	HRS_{EX}	HRS_{CG}
GDS	--	.80*	-.35
HRS_{EX}	.47*	--	-.17
HRS_{CG}	.05	-.01	--

*$p < .05$, one-tailed

Table 14. Frequency of clinically significant depression by diagnostic condition based on cutoff scores for each measure and DSM-III-R criteria.

	Group					
	AD		SVD		PD	
Criteria	N	%	N	%	N	%
GDS	8	26.7	12	40.0	22	73.0
HRS_{EX}	2	6.7	8	26.7	15	50.0
HRS_{CG}	4	13.3	10	33.3	19	63.3
DSM-III-R	3	10.0	7	23.3	16	53.3

approached significance for the HRS_{CG}. Thus, only the hypothesized difference between PD and AD was consistently supported.

A total of 10 AD patients, 22 SVD patients, and 22 PD patients were classified as "depressed" on at least one of the three measures. The congruence in classification between these measures is summarized in the venn diagrams in Figure 2. In AD, only one patient met criterion for depression on all three measures and two patients met criterion on two of three measures. The areas of intersection were also sparsely populated in SVD patients where 8 of 22 patients met criterion on multiple measures. In contrast, there was substantial agreement in classification between measures in PD.

The constellation of signs and symptoms required for major affective disorder (depressive episode) by DSM-III-R criteria was approximated using caregiver interview data. The convergent validity of ratings based on this source is supported by correlations with other measures of depression in nondemented PD patients (see Table 12). The frequency of depression based on DSM-III-R criteria are provided in Table 14 for each diagnostic condition. The pattern of effects for this criterion is consistent with mean scores and cut-off

a. Alzheimer's Disease

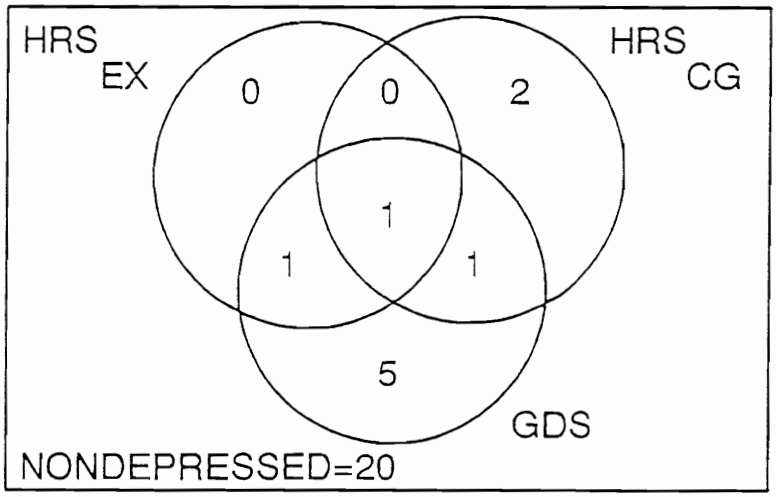

Figure 2. Agreement in classification between measures of depression by diagnostic condition. Numbers represent number of cases classified as depressed by each measure. Agreement is represented in overlapping regions.

b. Subcortical Vascular Dementia

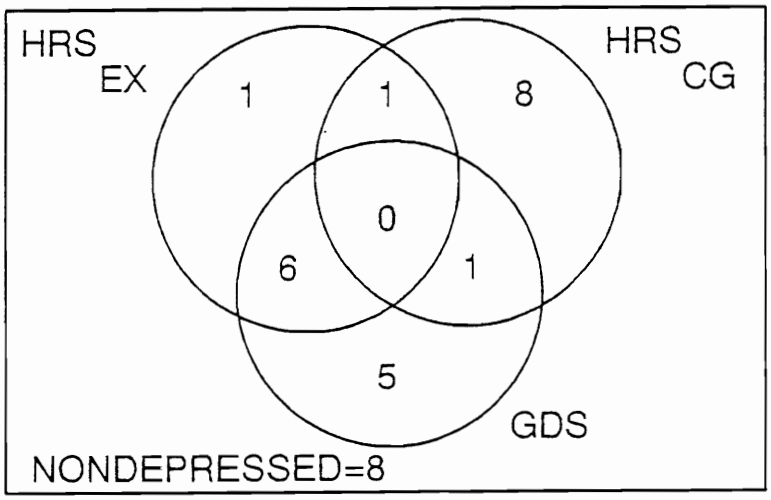

Figure 2. Agreement in classification between measures of depression by diagnostic condition. Numbers represent number of cases classified as depressed by each measure. Agreement is represented in overlapping regions - Continued.

c. Parkinson's Disease

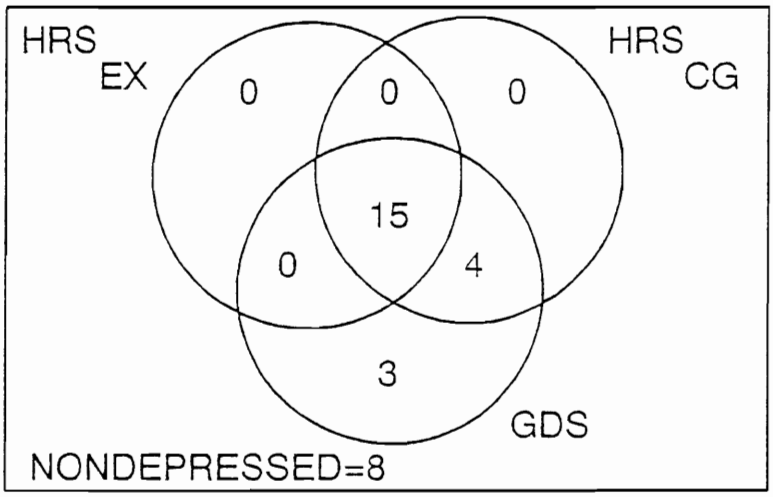

Figure 2. Agreement in classification between measures of depression by diagnostic condition. Numbers represent number of cases classified as depressed by each measure. Agreement is represented in overlapping regions - Continued.

scores for the individual measures. Fifty-three percent of PD patients were classified as depressed, followed by 23.3% of SVD patients and 10.0 percent of AD patients. The overall effect of diagnostic condition was significant (X^2=14.4, p<.001). Specifically, rates of depression in PD were significantly higher than the rates in AD and SVD. In contrast, rates of depression were similar between AD and SVD patients.

Symptomatology of Depression

The frequency of individual symptoms of depression covered by the Hamilton Rating Scale was evaluated in each diagnostic condition. Data on the caregiver- and examiner-based ratings are summarized in Tables 15 and 16, respectively. There were overall diagnostic condition effects for a total of ten symptoms on the HRS_{CG}. These symptoms were diverse, cutting across mood (item 1), activity patterns (items 2 & 9), abnormalities of thought (items 12, 14, & 16), and somatic symptoms (items 5, 7, 11, & 15). Most of the differences in symptom frequency were accounted for by higher rates in PD relative to AD, typically involving a two- to four-fold increase in frequency. PD and SVD patients were differentiated by higher rates of apathy

Table 15. Frequency of symptoms on the HRS_{CG} by diagnostic condition. Significant chi-square comparisons ($p < .0167$) are listed (trends, $.0167 < p .0333$, are in parentheses).

	AD	SVD	PD	Group Comparisons
1. Depressed mood	36.7	60.0	76.7	1 vs 3
2. Apathy	26.7	33.3	66.7	2 vs 3 1 vs 3
3. Libido	10.0	10.0	13.3	
4. Appetite loss	10.0	26.7	20.0	
5. Weight loss	0.0	20.0	30.0	1 vs 2 1 vs3
6. Insomnia - early	10.0	23.3	13.3	
7. Insomnia - middle	26.7	30.0	63.3	2 vs 3 1 vs 3
8. Insomnia - late	10.0	23.3	13.3	
9. Retardation	23.3	30.3	60.0	(2 vs 3) 1 vs 3
10. Agitation	33.3	43.3	23.3	
11. Somatic symptoms - general	46.7	46.7	83.3	2 vs 3 1 vs 3
12. Guilt	10.0	20.0	40.0	1 vs 3

Table 15. Frequency of symptoms on the HRS_{CG} by diagnostic condition. Significant chi-square comparisons ($p < .0167$) are listed (trends, $.0167 < p .0333$, are in parentheses) - Continued.

	AD	SVD	PD	Group Comparisons
13. Suicidal ideation	3.3	16.7	13.0	
14. Anxiety	33.3	53.3	70.0	1 vs 3
15. Anxiety - somatic	33.3	30.0	60.0	(2 vs 3)
16. Hypochondriasis	23.3	43.3	63.3	1 vs 3
17. Insight	0.0	3.3	3.3	

AD vs SVD = 1 vs 2

SVD vs PD = 2 vs 3

AD vs PD = 1 vs 3

Table 16. Frequency of symptoms on the HRS_{EX} by diagnostic condition. Significant chi-square comparisons ($p < .0167$) are listed (trends, $.0167 < p .0333$, are in parentheses).

				Group Comparisons	
	AD	SVD	PD		
1. Depressed mood	30.3	63.3	76.7	1 vs 2	1 vs 3
2. Apathy	10.0	33.3	93.3	(1 vs 2)	2 vs 3
				1 vs 3	
3. Libido	6.7	13.3	46.7	2 vs 3	1 vs 3
4. Appetite loss	13.3	16.7	26.7		
5. Weight loss	3.3	10.0	30.0	1 vs 3	
6. Insomnia - early	13.3	23.3	26.7	2 vs 3	1 vs 3
7. Insomnia - middle	10.0	13.3	66.7		
8. Insomnia - late	13.3	30.0	30.0		
9. Retardation	36.7	56.7	60.0		
10. Agitation	30.0	26.7	60.0	2 vs 3	1 vs 3
11. Somatic symptoms - general	26.7	56.7	86.7	(1 vs 2)	2 vs 3
				1 vs 3	

Table 16. Frequency of symptoms on the HRS_{EX} by diagnostic condition. Significant chi-square comparisons ($p < .0167$) are listed (trends, $.0167 < p .0333$, are in parentheses) - Continued.

				Group
	AD	SVD	PD	Comparisons
12. Guilt	6.7	30.0	33.3	(1 vs 2) 1 vs 3
13. Suicidal ideation	13.3	20.0	6.7	
14. Anxiety	40.0	43.3	63.3	
15. Anxiety - somatic	16.7	33.3	46.7	1 vs 3
16. Hypochondriasis	6.7	56.7	56.7	1 vs 2 1 vs 3
17. Insight	0.0	3.3	0.0	

AD vs SVD = 1 vs 2

SVD vs PD = 2 vs 3

AD vs PD = 1 vs 3

(item 2), sleep disruption (item 7), and complaints of fatigue (item 11) in PD; trends for higher rates of psychomotor retardation (item 9) and somatic symptoms associated with anxiety (item 15) were also observed. In contrast, only a higher rate of weight loss (item 5) in SVD differentiated these patients from AD.

The pattern of differences in symptom frequency using the HRS_{EX} was similar to the HRS_{CG}. There were overall diagnostic condition effects for ten symptoms including mood (item 1), activity patterns (items 2 & 10), abnormalities of thought (items 12 & 16), and somatic symptoms (items 3, 5, 7, 11, 15). The frequency of each of these symptoms was higher in PD than AD. Complaints of fatigue (item 11), apathy (item 2), and sleep disruption (item 7) along with examiner ratings of psychomotor agitation (item 10) differentiated PD and SVD patients. Depressed mood (item 1) and hypochondriasis (item 16) were significantly more common in SVD than AD patients; there were also trends for higher rates of apathy (item 2), fatigue (item 11), and guilt (item 12) reported by SVD patients.

The concordance between the HRS_{CG} and HRS_{EX} in terms of symptom ascertainment are presented in Table 17 for each diagnostic condition. The agreement between

Table 17. Agreement between the HRS_{CG} and HRS_{EX} in AD, SVD, and PD patient groups expressed as proportion agreement (P) and Yule's coefficient of colligation (Y). Y values reflecting chance level of agreement are underlined.

	AD		SVD		PD	
	P	Y	P	Y	P	Y
1. Depressed mood	.67	.28	.50	-.06	.93	.84
2. Apathy	.77	.45	.60	.09	.73	.41
3. Libido	.83	.33	.90	.67	.60	.34
4. Appetite loss	.83	.33	.60	.18	.93	.84
5. Weight loss	.97	.83	.77	.19	.93	.85
6. Insomnia - early	.83	.33	.60	-.19	.87	.69
7. Insomnia - middle	.70	.09	.63	-.07	.90	.80
8. Insomnia - late	.83	.33	.80	.55	.83	.64
9. Retardation	.73	.45	.67	.53	.93	.86
10. Agitation	.83	.49	.63	.26	.63	.48
11. Somatic symptoms - general	.67	.39	.57	.15	.90	.71

Table 17. Agreement between the HRS_{CG} and HRS_{EX} in AD, SVD, and PD patient groups expressed as proportion agreement (P) and Yule's coefficient of colligation (Y). Y values reflecting chance level of agreement are underlined - Continued.

	AD		SVD		PD	
	P	Y	P	Y	P	Y
12. Guilt	.90	.57	.83	.67	.87	.75
13. Suicidal ideation	.83	.42	.70	.00	.93	.76
14. Anxiety	.66	.30	.50	.01	.87	.75
15. Anxiety - somatic symptoms	.70	.33	.50	-.19	.87	.76
16. Hypochondriasis	.77	.33	.47	-.05	.73	.46
17. Insight	1.00	1.00	.93	.68	.97	1.00

the methods was adequate in PD patients with concordance of at least .80 for 13 of 17 symptoms. The only symptoms with marked disagreement involved examiner ratings of psychomotor agitation and patient complaints of decreased libido in the HRS_{EX} method relative to the caregiver-derived data. Concordance was also adequate in AD with agreement in .66 or more of the group for all symptoms. In contrast, near chance levels of agreement were found for the majority of items in SVD patients. Clearly, the low correlation in total scores between these measures cannot be accounted for simply by differences in symptoms severity.

Correction for chance level of agreement using Yule's coefficient of colligation, $\underline{Y}$, did not substantively alter the overall pattern of agreement between the HRS_{CG} and HRS_{EX} in different diagnostic conditions (see Table 17). Agreement beyond chance levels was obtained for all HRS symptoms in PD patients and for 16 of 17 HRS symptoms in AD patients. In contrast, the concordance between the HRS_{CG} and HRS_{EX} was poor in SVD patients. In SVD patients, chance level of agreement was observed for eight HRS symptoms and marginal agreement ($\underline{Y}<.20$) was found for three additional symptoms. These differences in the pattern

of agreement cannot be accounted for by differences in symptom base rates between these conditions. Methods which correct for chance level of agreement such as Yule's Y are most restrictive at the extremes of base rate or prevalence (Spitznagel & Helzer, 1985). As noted in Tables 15 and 16, the base rates for HRS symptoms in SVD were generally intermediate to those for AD and PD.

Covariates of Depression

Alzheimer's Disease.

Table 18 summarizes correlations between measures of depression and the patient's demographic and clinical characteristics. HRS_{CG} scores were significantly higher in female patients (7.3±5.9 vs 2.5±3.4) ($F(1,28)=5.9$, $p<.05$). This difference was not observed on the HRS_{EX} or GDS. Scores on the three measures of depression were uncorrelated with the patient's age, education, socioeconomic status, or estimated premorbid intellectual ability. Markers of disease severity, disease duration and MMS scores, were also unrelated to level of depression. Finally, measures of depression were not associated with age at onset or severity of extrapyramidal signs (EPS) on the NYU scale. Since age

Table 18. Correlations of measures of depression with demographic and clinical characteristics for (a) AD (N=30), (b) SVD (N=30), and (c) PD (N=30).

	GDS	HRS_{EX}	HRS_{CG}
a. AD			
Age	.09	.06	-.06
Sex	.27	.16	.42*
Education	-.16	-.09	-.12
Socioeconomic Status	.01	.12	.06
Premorbid IQ Estimate	.18	.10	.12
Age at Onset	.08	.09	.05
Duration	.03	-.11	.02
MMS	-.21	-.07	-.02
NYU	-.03	.21	.16
b. SVD			
Age	.14	.24	-.20
Sex	.09	.12	.16
Education	.01	-.12	.19
Socioeconomic Status	.08	-.04	.09
Premorbid IQ Estimate	.13	.17	.17
Age at Onset	.19	.27	-.23

*$p < .05$, one-tailed

Table 18. Correlations of measures of depression with demographic and clinical characteristics for (a) AD (N=30), (b) SVD (N=30), and (c) PD (N=30) - Continued.

	GDS	HRS_{EX}	HRS_{CG}
b. SVD - Continued			
Duration	-.16	-.13	.16
MMS	-.05	-.24	-.29
NYU	.35*	.62*	-.12

*p < .05, one-tailed

c. PD			
Age	-.28	-.20	-.21
Sex	-.10	-.12	-.08
Education	.12	.18	.16
Socioeconomic Status	.09	.07	.13
Premorbid IQ Estimate	.07	.12	.10
Age at Onset	-.35*	-.22	-.18
Duration	.23	.18	.19
NYU	.11	.03	.01

*p < .05, one-tailed

at onset and EPS mark important clinical subtypes of AD, a graded response between these variables and depression may not be meaningful. However, further analysis failed to yield differences in depression for early (<65 years) and late (≥65 years) onset groups or for EPS (present, absent) groups.

Subcortical Vascular Disease. Measures of depression were uncorrelated with the patient's demographic characteristics (see Table 18). Scores on the HRS_{CG} and HRS_{EX} were inversely related to dementia severity on the MMS, but this relationship did not reach statistical significance. Disease duration and age at onset were also not significantly related to any measure of depression.

The severity of EPS (total NYU score) was significantly correlated with scores on the GDS (r = .62, $p < .01$) and the HRS_{EX} (r = .35, $p < .05$), but not the HRS_{CG} (see Table 18). Given the emphasis on somatic and psychomotor symptoms in the HRS, correlations between the NYU total scores and individual HRS items were examined. Spearman rank correlations with total NYU score were significant for the following symptoms on the HRS_{EX}: insomnia - early (r = .34, $p < .05$), psychomotor retardation (r = .47, $p < .01$), fatigue (r =

.33, $p < .05$), anxiety ($r = .44$, $p < .01$), and suicidal ideation ($r = .37$, $p < .05$).

Parkinson's Disease. Measures of depression were unrelated to demographic characteristics, disease duration, or ratings of disease severity on the NYU scale (see Table 18). GDS scores were inversely related to age at onset ($r = -.35$, $p < .05$); a similar pattern was evident for the HRS_{CG} and HRS_{EX}, but did not reach significance.

DISCUSSION

The severity of current depressive symptomatology across the three neurodegenerative disorders followed a consistent pattern across each method of assessment. Specifically, scores on self-report (GDS), examiner ratings (HRS_{EX}), and caregiver ratings (HRS_{CG}) of depression were most severe in patients with Parkinson's disease (PD), intermediate in subcortical vascular disease (SVD), and least severe in Alzheimer's disease (AD). There were reliable differences between PD and AD patients for all measures; PD-SVD and AD-SVD comparisons were only significant for the HRS_{EX}. The presence of clinically significant depression based on cut-off scores and fit to DSM-III-R criteria also followed the same pattern. However, method variance in the measurement of depression cannot be discounted because of the three methods of symptom assessment were highly correlated only in Parkinson's disease. Exploratory analyses to identify possible covariates of depression suggested that depression was related to gender in AD, severity of extrapyramidal signs in SVD, and age of onset in PD.

Subcortical dementia and depression. This study was designed to evaluate the hypothesized association between depression and subcortical pathology based on the subcortical-cortical dementia framework (Albert et al., 1974; Cummings, 1986). There was consistent support for this hypothesis in all comparisons between AD and PD patients, the prototypical exemplars of cortical and subcortical dementia syndromes, respectively. Specifically, PD patients had significantly higher scores than AD patients on three measures of depression derived from different sources of information (caregiver ratings, examiner ratings, patient self-report). Rates of clinically significant depression also favored PD, regardless of whether based on standard cut-off scores for these measures or the constellation of symptoms required for a major depressive disorder according to DSM-III-R criteria. It is unlikely that these differences can be accounted for simply by measurement artifact secondary to the movement disorder associated with PD. In particular, the symptoms of depression with elevated frequency in PD were diverse and scores on the measures of depression were uncorrelated with the severity of the movement disorder.

The frequency estimates of depression for the AD and PD groups are generally consistent with previous work. With respect to PD, only the estimate based on the self-report GDS (73.3%) falls outside the range reported in outpatient PD samples (32-63%) (Mayeux et al., 1988; Starkstein et al., 1989; Santamaria et al., 1986; Gotham et al., 1986). Similarly, the diverse assessment methods in this study provided estimates of depression in AD well within the range of 0-40 percent described in the literature (Cummings et al., 1987; Kral, 1983; Knevesich et al., 1983; Lazarus et al., 1987; Reding et al., 1985; Reifler et al., 1986; Larsson, Sjogren, & Jacobson, 1963; Sulkava, 1982). Hence, it is difficult to argue that the differences between AD and PD can be accounted for by sampling extremes.

The association between subcortical pathology and depression, however, fared less well in comparisons involving SVD patients. All indicators of depression in SVD were intermediate to the AD and PD groups. The only significant difference between AD and SVD patients on all measures of depression and corresponding frequency estimates was on the HRS_{EX}. This evidence does not provide unequivocal support for the differentiation of

SVD and AD patients expected on the basis of the subcortical dementia hypothesis. Furthermore, there were significant differences between SVD and PD patients on a number of indicators of depression: means on the GDS and HRS_{CG}, and frequency estimates derived from GDS cut-off scores and DSM-III-R criteria based on HRS_{CG} data. Consequently, the expected similarity in depression for two exemplars of subcortical dementia did not receive substantial support.

The apparent failure to find SVD-AD differences in depression may relate to the probability of a Type II statistical error. If the sample size had been increased by as little as ten subjects per cell, all mean score and frequency comparisons would have reached statistical significance. However, it is equally true that all SVD-PD comparisons would also have reached significance with larger sample size. Therefore, even with improved statistical power, the overall pattern of the data would provide at best conflicting support for the pattern predicated by the subcortical-cortical dementia conceptualization.

Much of the criticism of the concept of subcortical dementia has been directed at the accuracy of anatomical characterization of subcortical and cortical disease

entities such as PD and AD (see Whitehouse, 1986). Recent reviews (e.g., Brown & Marsden, 1988; Cummings, 1986; Freedman & Oscar-Berman, 1986) have abandoned the underlying assumptions regarding neurophysiology in favor of more limited behavioral distinctions. However, the present data highlight another area of weakness in the conceptual framework, namely within-category heterogeneity. Differences in the frequency, severity, and symptomatology of depression were as large between SVD and PD as the differences between SVD and AD. As depression is the **sine qua non** of emotional sequelae associated with subcortical dementia, this pattern is difficult to meaningfully reconcile with the framework. This issue is not limited to depression or SVD-PD comparisons in general. In their exhaustive review of the neuropsychological data pertaining to the cortical-subcortical distinction, Brown and Marsden (1988) concluded that the performance of patients with Huntington's disease, another exemplar of subcortical dementia, was as different from PD as AD across a wide range of cognitive tasks.

Standards of comparison with respect to depression in SVD patients are few, but several lines of evidence are noteworthy. Estimates of the prevalence of

depression in single and multiple infarct patients range between 20 and 40 percent (Cummings et al., 1987; Folstein et al., 1977; Robinson et al., 1984; Sinyor et al., 1986). In patients with suspected vascular dementia, Erkinjuntti (1987) found higher rates of depression with subcortical (42.6%) than cortical (24.6%) infarcts. Hence, there is no reason to assume that rates of depression in patients with subcortical vascular pathology are actually lower than in cortical vascular disease. Further, disturbances of mood were reported in 20 of 30 patients with pathologically-verified subcortical vascular disease in one recent series (Ishii et al., 1986), but this categorization included diverse affective symptomatology. Likewise, high rates of affective disturbances have been described in patients with single subcortical foci (Fromm et al., 1985: 11/16 cases) and diffuse subcortical abnormalities (Loizou et al., 1981: 11/15 cases) of suspected vascular origin. These estimates are in accord with the high endorsement rate on the depressed mood item on the HRS_{CG} (60.0%) and HRS_{EX} (63.3%) in SVD, but they fail to address the prevalence of the syndrome of depression <u>per se</u>.

One potential criticism of the use of SVD to evaluate the subcortical-cortical dementia syndrome concerns the viability of SVD as a meaningful clinical entity. If the underlying neuropathology of this condition is heterogeneous, then its clinical manifestations may be similarly variable. The typical pathological features of SVD are (a) incomplete softening of the white matter in the frontal and parietal lobes, and (b) lacunes concentrated in the frontal periventricular white matter and the striatum (Fisher, 1982; Ishii et al., 1986). These changes affect both cerebral hemispheres, albeit not necessarily in symmetric fashion. This general constellation is thought to arise from the specific vulnerability of the longer branches of small penetrating arteries and arterioles due to arteriosclerosis or hemodynamic changes (e.g., hypertension, hypotension) (Olzsewski, 1962). Thus, SVD appears to represent a more homogeneous entity than large vessel occlusive disease where the location and size of the lesions are less predictable. However, relative to neurodegenerative processes affecting specific subcortical nuclei (e.g., PD), the "patchy," uneven distribution of pathology within the periventricular white matter and subcortical

gray matter in SVD represents a variable pathological substrate. The wide range of clinical manifestations of SVD is similarly well documented (e.g., Babikian & Roper, 1987; Caplan & Schoene, 1978; Fisher, 1982; Roman, 1987).

Predictors of depression. There is conflicting evidence regarding the relationship between depression and dementia severity. A higher rate of depression in less severe cases of dementia has been reported (Merriam et al., 1988; Reifler et al., 1982), but not replicated using similar patient populations (Lazarus et al., 1987; Reifler et al., 1986). The relationship between measures of depression and MMS scores in the present study was not significant for either AD or SVD patients. In both groups, the slope of the regression line was negative and may have reached statistical significance with larger sample sizes for some measures. Nonetheless, any variance in the frequency and severity of depression accounted for by the severity of cognitive dysfunction appears limited.

It is difficult to gauge the relationship between depression and disease progression from these cross-sectional studies. Longitudinal data on the development

and persistence of depression over the course of the disease in AD and SVD are not available. However, recent data suggest that depression in PD may be relatively stable over time (Mayeux, Stern, Sano, Williams, & Cote, 1988). Of 49 PD patients studied over a period averaging 2.5 years, remission of depression as measured by was observed in only 4 of 21 cases and no new cases of depression developed in the originally asymptomatic 28 patients.

The relationship between depression and the rate of disease progression in dementia syndromes is controversial. Nonprogression or reversal of cognitive dysfunction has been associated with depression in psychiatric inpatient populations (Folstein & McHugh, 1978; Nott & Fleminger, 1975; Rabins, Merchant, & Nestadt, 1984; Ron, Toone, Garralda, & Lishman, 1979). However, the rate of progression in outpatients with probable AD (Reifler et al., 1986) and mixed dementia syndromes (Reding et al., 1985) has been found to be unrelated to depression. Furthermore, long-term follow-up ($\geq$ 4 years) of 22 patients with reversible dementia syndromes associated with depression has revealed a surprisingly high rate (20/22: 91%) of AD (Kral, 1983).

Depression was unrelated to most demographic characteristics of the patient in each diagnostic condition. The only exception involved higher levels of depressive symptomatology among female AD patients. This finding is consistent with the results of community-based epidemiological studies of depression (Boyd & Weissman, 1981). This association in the present sample of AD patients, however, was confined to the HRS_{CG} measure. No relationship between depression and gender has been reported in most other studies of depression in AD (Cummings et al., 1987; Merriam et al., 1988; Reifler et al., 1986), but a similar pattern was found in Lazarus et al. (1987).

Age at onset was related to depression in PD, but not AD and SVD. An inverse relationship between depression and age at onset was evident in all measures but was only statistically significant for the GDS. This relationship has been found in some previous studies (Mayeux et al., 1981; Santamaria et al., 1989; Starkstein et al., 1989), but not others (Huber et al., 1989; Hietanen & Trevainen, 1988; Mayeux et al., 1983; Mayeux et al., 1988). Given the differences in the magnitude of association between age at onset and depression across different measures in this study, the

lack of consensus in the literature is not surprising. At best the effect appears small and its significance in understanding depression in PD is unclear.

There is no basis in the literature to expect any relationship between depression and age at onset in SVD (e.g., Babikian & Roper, 1987). Age at onset in AD, however, may mark an important subtype of the disease. Further, patients with early onset (< 65 years of age) appear to have greater reduction in the level of several aminergic neurotransmitters (Brane, Gottfries, Blennow, Karlsson, Lekman, Parnetti, Svennerholm, & Wallin, 1989; Bondareff, Mountjoy, Rossor, Iversen, & Reynolds, 1987) with putative relationship to depression (van Praag, 1982). The report by Zweig et al. (1988) of an association between depression in AD, higher neurofibrillary tangle counts in the serotonergic raphe and noradrenergic locus ceruleus, and early age at onset provides further evidence for the possible covariance among these variables. Our data, however, do not support any association between age at onset and depression, but must be interpreted with caution because only 6 of 30 cases had onset prior to age 65. This sampling fraction is lower than the AD population at the RADC where 42% of the cases have onset prior to 65.

The relationship between EPS and depression provides a secondary test of the cortical-subcortical dementia distinction. Parkinsonian features are thought to arise from disruption of a fronto-striatal-thalamic loop (Marsden, 1982). The presence of EPS were documented in 10 AD, 17 SVD, and all PD patients, which parallels the pattern of depression severity among these groups. In AD, the presence and severity of EPS on the NYU scale did not predict scores on any measure of depression. Similarly, the severity of EPS was uncorrelated with depression in PD. In SVD, EPS was significantly correlated with GDS and HRS_{EX} scores. The role of hypokinesis on ratings of some vegetative and psychomotor symptoms of depression cannot be discounted, but the GDS gives little weight to those symptoms.

The lack of congruence in the association between the severity of EPS and depression across these diagnostic conditions is puzzling. No consistent relationship between EPS and depression has emerged in numerous studies of PD (see Gotham, Brown, & Marsden, 1986). This relationship has not been evaluated in AD and SVD patients.

One difficulty in comparing the association between depression and EPS in these conditions concerns probable

heterogeneity in the etiology of EPS. EPS in PD is thought to arise from reduced availability of dopaminergic input from the substantia nigra to the putamen (Marsden, 1982). The source of EPS in AD is unclear, but nigral (coexistent PD; AD pathology in the substantia nigra) and extranigral (AD pathology in prefrontal mesocortical areas) factors have been described (see Morris, Drazner, Fulling, Grant, & Goldring, 1989). Infarction within the striatum and thalamus, and interruption of connections between the structures in the fronto-striatal-thalamic circuit is the likely source of EPS in SVD (Caplan & Schoene, 1978; Thompson & Marsden, 1987). It is tempting to speculate that these differences in pathology account for the inconsistent findings with respect to depression. However, it is clear that interuption of the fronto-striatal-thalamic circuit is neither necessary nor sufficient to produce depression in these disorders.

Measurement of depression. The second aim of this study was to evaluate measurement methods of depression in dementia syndromes. Most studies of depression in neurological disorders associated with dementia have relied on the patient as the principle source of data.

However, the ability of a patient with significant cognitive dysfunction to provide accurate information on the duration and intensity of depressive symptomatology is questionable. Even the validity of approaches which rely exclusively on self-reported current mood state (e.g., GDS) has been challenged (e.g., Burke, Houston, Boust, & Roccaforte, 1989; Norris, Gallagher, Wilson, & Winograd, 1987). Ratings based on observations of the patient's primary caregiver circumvent many of the limitations of self-report in dementia patients. The application of this approach in the HRS_{CG} appears to have adequate psychometric properties. The estimated interrater reliability based on the agreement between trained interviewers was .92 with similar scoring of individual items and composite total (see Appendix B). The convergent validity of the HRS_{CG} was supported by the concordance of this measure and two other measures of depression in PD patients with minimal cognitive dysfunction. This level of agreement was evident at the level of total scores, classification schemes based on this data, and individual symptoms covered by the HRS. Furthermore, there was substantial coverage of the entire spectrum of depression severity in this group which argues against spurious inflation of agreement due

to range restriction and base rate artifact. These data stand in marked contrast to the discordance among measures in the two patient groups with significant cognitive dysfunction.

The potential limitations of the HRS_{CG} fall into several general categories. First, there was evidence of asymptotic error at the upper range of scores in the original validation sample of PD patients (see Appendix A) and the current PD sample. This departure appeared to be based in part on greater subjective complaints of apathy, diminished libido, and hypochondriasis by patients not readily reflected in the behaviors observed by the caregivers. Caregivers also had a higher apparent threshold for rating psychomotor agitation than professional examiners.

The importance of the patient's verbalizations in the ascertainment of many internal states provides an additional constraint. The quantity and quality of verbal expression will be adversely affected by the presence of severe dementia. Thus, a reduction in the sensitivity of the HRS_{CG} is likely and countenance must be given to the adage "absence of evidence is not evidence of absence."

Measurement error secondary to caregiver variables cannot be discounted. Caregivers differ on numerous dimensions, including relationship to the patient, extent of daily contact with the patient, and various demographic characteristics. Variance in the HRS_{CG} accounted for by any of these variables results in nonparallel measurement and limits generalization of findings (Lord & Novick, 1968).

Finally, validity data for the HRS_{CG} is lacking for two salient groups: normal controls and neurologically normal patients with affective disorders. The factor structure of the HRS and consequent interpretation of scores is based on these populations (Hamilton, 1960, 1967). A number of symptoms covered by the HRS may be related to various neurological disorders independently of depression (e.g., apathy, sleep disturbances, psychomotor activity patterns). Therefore, the specificity and positive predictive value of HRS_{CG} scores in patients with coexistent dementia syndromes needs to be systematically evaluated.

These potential limitations further highlight the difficulties in the assessment of depression in neurological disorders associated with dementia. Caution in the interpretation of HRS_{CG} scores is

warranted, but this measure is more defensible that methods which depend on self-report in this patient population. Informant-based measurement of all noncognitive disturbances in dementia syndromes is a methodological necessity; continued evolution of the approach is needed to address these limitations and improve utility.

Limitations. The principle limitations of this study involve diagnostic accuracy and the representativeness of sampling. The general problem of diagnostic accuracy with respect to dementia syndromes revolves around the absence of noninvasive means for the detection of the underlying neuropathological process. As a consequence, it is difficult to identify "pure" cases of a given disease type. None of the target disease entities which produce dementia are mutually exclusive and it is not uncommon to find coexistent neuropathological processes (e.g., Joachim et al., 1988).

One partial exception to the problem of antemortem diagnosis is cerebrovascular disease. Existing technology (magnetic resonance imaging) has proven to be very sensitive to most vascular lesions (e.g., Revesz,

Hawkins, Boulay, Barnard, & McDonald, 1989). However, the concept of vascular dementia remains controversial primarily because of the presence of coexistent Alzheimer's type neuropathological changes in a significant proportion of cases reaching autopsy (Brust, 1983). The magnitude of this problem with respect to SVD is unknown. A total of seven clinically diagnosed SVD cases have reached autopsy from the RADC: four patients had multiple discrete lacunar infarctions, diffuse demyelination, and extensive astrocytic gliosis consistent with subcortical arteriosclerotic encephalopathy (Olszweski, 1965); two cases with mixed subcortical vascular pathology and AD; and one case of Cruetzfeldt-Jakob disease. Two SVD patients included in this study died 1-6 months after participation, but did not reach autopsy. It is safe to assume that some of the SVD cases had coexistent AD, a contamination which may attenuate the observed relationship between subcortical vascular disease and depression.

The accuracy of the clinical diagnosis of AD generally exceeds .83 in most studies (Martin et al., 1987; Molsa et al., 1985; Neary et al., 1986; Joachim et al., 1988; Sulkava et al., 1983; Tierney et al., 1989; Wade et al., 1987). This figure, while comforting, is

somewhat misleading. More than 83 percent of the cases had Alzheimer's type pathology, but 10-25 percent of these cases had other neuropathological features such as Lewy bodies and vascular disease. Diagnostic accuracy of the AD patients in this study is unknown; one patient died 5 months after participation with pathological verification of uncomplicated Alzheimer's disease. However, a total of 19 RADC patients with the clinical diagnosis of AD have reached autopsy with the following breakdown of neuropathological diagnoses: 13 cases of AD, 5 cases of AD with other neuropathological features (4 with Lewy bodies, 1 with subcortical infarcts), and 1 case of diencephalic sclerosis (probable encephalitis) with scattered neuritic plaques within the hippocampal formation. In addition, 16 RADC patients with the clinical diagnosis of AD have had cortical biopsy (typically right frontal lobe) with AD pathologically verified in 14 cases. These data provide no specific information on the patients in this study but suggest that the accuracy of clinical diagnosis of AD within the RADC is satisfactory.

Estimates of the accuracy of the clinical diagnosis of idiopathic PD generally exceed .90 (Gibb, 1988) but is unknown with respect to the patients drawn

from the movement disorders clinic at Rush-Presbyterian-St. Luke's Medical Center. Until recently, there was no systematic effort to obtain autopsy to provide pathological confirmation. The diagnosis reflects systematic exclusion of known risk factors for parkinsonism (drugs, encephalitis, cerebrovascular disease) and consensus appraisal of symptoms. Hence, the diagnosis of the PD patients in this study is reliable and presumed valid.

The prevalence of coexistent PD and AD is unknown, but assumed to account for a significant proportion of PD cases with severe dementia (Whitehouse et al., 1983). Coexistent PD and AD in the PD group in this study is likely to be rare because cases of significant dementia were excluded. The presence of coexistent PD and SVD cannot be ruled out in some cases, however, because participation did not require contiguous MRI scan.

The greatest threat to the external validity of this study concerns the representativeness of sampling procedures. It should be emphasized that all participants in this study, regardless of specific diagnostic condition, were drawn from tertiary diagnostic centers. These centers have the advantage of systematic diagnostic procedures applied by

specialized professionals but are subject to a number of referral biases. Cases with complicated medical management due to difficult diagnosis, treatment, or coexistent symptomatology are more likely to be represented in samples drawn from tertiary diagnostic centers. Subtle biases may also exist which result in the overrepresentation of particular socioeconomic and racial groups as well as urban living conditions.

The potential impact of these referral biases on the external validity of the study is twofold. First, point-prevalence and incidence estimates derived from these clinic-based samples are not readily generalizable to the population of cases with a given disease entity. Second, specific referral and selection biases may be differentially related to disease type. Interactions of this type could affect comparisons between diagnostic conditions. However, these factors are not endemic to the present study, but rather represent a significant limitation in all published evidence pertaining to the cortical-subcortical dementia framework.

Another sampling factor which may affect the external validity of this study is range restriction with respect to dementia severity. In AD and SVD groups, there were no MMS scores below 8. This

truncation of range limits inferences regarding the association between dementia severity and depression, and precludes the evaluation of method variance in the measurement of depression in severe dementia. The ascertainment of many symptoms of depression relies on verbalizations by the patient regardless of specific assessment method. Since the verbal output of patients with severe dementia is likely to be sparse, knowledge of the behavior of the three measures of depression is important.

Range restriction in the PD group consisted of eliminating patients with significant cognitive dysfunction. This selection factor improves internal validity at the possible expense of external validity. The use of nondemented PD patients protects the overall integrity of the diagnostic group by minimizing the inclusion of cases with coexistent PD and AD, and cases of AD with extrapyramidal signs. Likewise, the exclusion of PD cases with dementia improves the interpretability of the concordance between the HRS_{CG} and HRS_{EX}. However, the frequency of significant depression in PD could have been underestimated by this exclusion criteria because there is evidence that the severity of depressive symptomatology in PD may be at

least weakly correlated with dementia severity (Mayeux et al., 1981).

One further potential threat to the external validity of the study concerns the equivalence of depression in these three neurological disorders with depression as a psychiatric disorder. The syndrome of depression is conceptualized as a complex psychological and pharmacological disorder in structurally intact neural substrate with a characteristic pattern of signs and symptoms (e.g., Ross & Rush, 1981). Structural lesions may share information processing and neurotransmitter abnormalities with this matrix, but lack specificity. For example, most neurodegenerative disorders affect widely disparate structures and neurotransmitter systems through interconnectivity (e.g., Saper, Wainer, & German, 1987). Functional abnormalities dependent upon this network will be similarly diverse.

Irrespective of assessment method, patients in each diagnostic condition under study exhibited depressive symptomatology of sufficient magnitude to resemble the clinical syndrome of depression. However, the elevated base rate of some symptoms of depression in these neurological disorders (e.g., apathy, psychomotor

agitation, sleep disturbances) increases the risk of false positive classification. Further, Merriam et al. (1988) describe significant short-term fluctuations in depressive symptoms in AD patients. Marked end-of-dose fluctuations in mood have been reported in PD patients on dopaminergic replacement therapy (Hardie, Lees, & Smith, 1984). Taken together, these observations do not invalidate the use of the construct of depression but suggest the need for caution.

Beyond depression: Proposal for future study

Depression has been the primary focus of research on affective disturbances in dementia syndromes. This approach has important limitations. Inferences are constrained by the validity of the construct of depression in characterizing these affective disturbances. The construct of depression, even if valid, cannot account for the diversity and complexity of affective disturbances evident in the neurological disorders in question. For example, pronounced lability of affect and pseudobulbar-like episodes of forced laughter or crying are commonly described in SVD patients (Ishii et al., 1986; Roman, 1987). By definition, these conditions imply a dissociation

between affective behaviors and the patient's underlying emotional state (Lieberman & Benson, 1977).

The conceptual framework of Ross (Ross, 1981; 1985; Ross, Harney, DeLacoste, & Purdy, 1981; Ross & Rush, 1981; Ross & Stewart, 1987) may have heuristic value in organizing the diverse affective disturbances in dementia syndromes as well as generating testable hypotheses. This particular neurobehavioral system discusses different components of emotion with respect to the possible anatomic substrate based on available clinicopathological data. Deficits in the linguistic and behavioral components involved in the expression and comprehension of affect are characterized by different syndromes of aprosodia. These aprosodic syndromes parallel aphasic syndromes in terms of expressive and receptive features; the putative anatomic representation of these features in the right cerebral hemisphere also directly parallels the left hemisphere representation of language. The experiential aspects of emotion, like the content of language, is assumed to be moderated through limbic and paralimbic (mesocortical) structures.

The present study focused on three bilateral degenerative conditions with different distributions of underlying pathology. The pathological hallmarks of AD,

neuritic plaques and neurofibrillary tangles, are concentrated in the basal forebrain, hippocampal formation and other limbic structures, and heteromodal association neocortical areas (Pearson et al., 1985). In the Ross model, this disease should exert its primary effects on the experiential aspects of emotion. The model lacks detail on this component of emotion, but it seems reasonable to speculate that the content and organization of the patient's internal mood state should be adversely affected by the degeneration of the hippocampal formation and related limbic structures. That is, it may be difficult to form a coherent, persistent mood state. Impersistence of mood in AD patients has been described (Merriam et al., 1988). Further, the prevalence of the clinical syndrome of depression should be low in these patients, although vegetative and psychomotor symptoms normally associated with depression may continue to develop through other pathological mechanisms.

In PD, the primary lesion appears to involve a significant depletion of dopaminergic input to the striatum (Marsden, 1982). According to the Ross model, the experiential and receptive aspects of affective function should be preserved, but these patients may

lack the ability to moderate the motoric expression of affect. The sparing of the experiential components of affect suggests that the prevalence of depression should be no less than that seen in other chronic diseases (presumably reactive in nature) and higher if there is a disease-related biological component (see below). The affective display through gestures, facial expression, and intonation of voice should mirror the patient's internal mood state, but the intensity of this display would be disproportionate to the internal mood state. It is noteworthy in this regard that extreme affective displays in PD patients appear to be common during end-of-dose periods and during drug holidays (Hardie, Lees, & Smith, 1984) when dopaminergic replacement therapy effects are minimal. Mild emotional lability easily reversible with external stimulation characterizes the affective display of optimally treated PD patients (Taylor, Saint-Cyr, Lang, & Kenney, 1986).

Extranigral factors may also play a role in depression and other affective disorders in PD. Depression in PD has been tied to decreased serotonergic metabolism (Kostic, Djuricic, Covickovic-Sternic, Bumbasirevic, Nikolic, & Mrsulja, 1987; Mayeux, Stern, Cote, & Williams, 1984; Mayeux, Stern, Sano, Williams, &

Cote, 1988). Presynaptic serotonergic input to the limbic system and neocortex is thought to be affected by downregulation of the raphe by degeneration with the ventral tegmental area in PD (Raisman, Cash, & Agid, 1986), although direct pathological involvement of the raphe cannot be ruled out. These extranigral components of PD do not appear to be associated with the nigrostriatal dysfunction (Raisman et al., 1986). Hence, there is little reason to expect that the motor and cognitive deficits of PD patients would be correlated with depression. The presence of depression, however, may have an impact on the display of affective behaviors. Ross (1985) described a patient with mild premorbid depression who displayed pathological pseudobulbar-like forced crying, extreme irritability, and agitation after having an infarct in the right caudate.

Affective disturbances associated with SVD are likely to be diverse and complex based on Ross' model. First, diffuse softening of frontal periventricular white matter should result in prominent pseudobulbar-like affective displays. This has been described in single cases by Ross (1985) and by Babikian and Roper (1987) as well as in the 30 patients in the Ishii et

al. (1986) series. Release of inhibition of extreme affective displays can also result from disruption of the thalamo-cortical connections from the striatum either through infarction or white matter softening. Thus, an affective display similar to PD patients is possible and has been illustrated in a case by Ross (1985). The sensory receptive aspects of affective processing may also be affected by degeneration in the white matter underlying the parietal lobes. A mixed transcortical aprosodia secondary to white matter pathology in the right parietal lobes has been described by Ross (1981). Finally, the experiential aspects of emotion may be preserved in SVD due to relative sparing of the limbic structures, but disconnection of afferent and efferent connections of mesolimbic prefrontal areas may result in dissociations between the patient's internal mood state and affective display. This pattern has been described in a case by Ross & Rush (1984) and is particularly interesting in light of dissociations among measures of depression for SVD patients in the present study.

One potential limitation to the applicability of the Ross model to neurodegenerative conditions concerns laterality. The model and its supporting patient

material were restricted to right hemisphere lesions. Therefore, while parallels may exist between the observations of Ross and each of the neurodegenerative conditions under study, the presence of bilateral pathology is likely to result in a more complicated presentation. As noted by Ross (1985), both hemispheres appear to participate in affective processing but differ in the valence of affect (e.g., euphoria/indifference associated with the left hemisphere and dysphoria associated with the right hemisphere) and relative contribution of linguistic factors. Nonetheless, lateral asymmetries in the distribution of pathology in neurodegenerative disorders may provide an interesting test of predictions stemming from the Ross model.

Regardless of specific limitations of the model by Ross (1985), it is useful in drawing attention to the potential complexity of affective disturbances in AD, SVD, and PD. Affective disturbances in these conditions clearly warrant further investigation but at the level of specific affective processing tasks. Clinicopathological correlation is likely to be more meaningful at this level of analysis than broad characterization of affect in terms of constructs such as depression.

The following quote from Alois Alzheimer (1907/1987) characterizes our understanding of the emotional disturbances in neurological diseases as well as the progressive degenerative disorder that now bears his name.

> "On the whole, it is evident that we are dealing with a peculiar, little-known disease process. In recent years these particular disease-processes have been detected in great numbers. This fact should stimulate us to further study and analysis of this particular disease. We should not be satisfied to force it into the existing group of well-known disease patterns. It is clear that there may exist many more mental diseases than our text books indicate. In many such cases, a further histological examination must be effected to determine the characteristics of each single case. We must reach the stage in which the vast well-known disease groups must be subdivided into many smaller groups, each one with its own clinical and anatomical characteristics." (page 3)

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APPENDIX A

Validation of a measure of depressive symptomatology independent of patient self-report is essential for the study of depression in patients with significant dementia. The Hamilton Rating Scale (HRS; Hamilton, 1960) is typically completed by a clinician who rates individual items on the basis of a semi-structured interview with the patient. Since the symptoms covered by the scale are primarily the behavioral manifestations of depression, reliable and accurate estimates of the frequency, duration, and intensity of these symptoms should also be obtained from the patient's spouse or other informant with frequent contact with the patient. This study was designed to validate this modification of the HRS in a patient sample with a progressive neurological disorder (Parkinson's disease) without dementia.

The selection of idiopathic Parkinson's disease (PD) for study was based on the following considerations. Depression is common in PD (Mayeux, 1984), providing for adequate variation in level of depression in a relatively homogeneous sample. Further, restrictive selection criteria regarding mental status,

antidepressant therapy, and general physical health can be employed without confounding disease severity with depression. Depression appears to be unrelated to disease severity, concomitant disability, duration of illness, or treatment modality (see Mayeux, 1984). Finally, dementia is rare and antidepressant therapies are infrequently used.

Patients were selected to cover a wide range of depression severity on the basis of scores on the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Specifically, a similar number of patients at each of three levels of depression (none, mild, moderate-to-severe) were studied. The patient and an informant with frequent contact with the patient (typically spouse) were interviewed separately about the patient's depressive symptomatology in the past week. HRS scores completed from each source were compared.

METHOD

Subjects

Thirty-four community dwelling patients with idiopathic Parkinson's disease were evaluated at the Movement Disorders Clinic of Rush-Presbyterian-St.

Luke's Medical Center (RPSLMC). All patients met the selection criteria outlined in Table 19.

The sample was stratified on the basis of level of depression as measured by the total score on the Beck Depression Inventory (BDI). Level of depression was defined in accordance to guidelines suggested for medical patients (Schwab, Bialow, Clemmons, Martin, & Holzer, 1967): nondepressed (0-10), mild depression (11-17), and moderate-severe (>18). An attempt was made to cover all three levels equally in order to insure adequate range for statistical purposes. Table 20 presents demographic characteristics, measures of PD severity, and previous history of psychiatric disorders for each of the three subgroups.

Procedure

The patient and spouse were interviewed separately. The patient was examined by the principal investigator. Tests administered included the BDI, HRS_{EX}, and Mini-Mental State (MMS) Examination (Folstein, Folstein, & McHugh, 1975). These measures required 30-45 minutes and were administered during a routine clinic visit. The spouse was interviewed concurrently by a trained, independent research assistant, blind to the results of

Table 19. Selection criteria.

Inclusion Criteria

1. Diagnosis of PD based on the insidious onset of movement disorder consisting of at least two cardinal PD signs (bradykinesia, rigidity, rest tremor, postural instability, festinating gait).
2. Stable on anti-parkinsonian agents.
3. Information available on all relevant disease variables.
4. Spouse and patient willing to participate.

Exclusion Criteria

1. No history of vascular, encephalitic, or drug contribution to parkinsonism.
2. Dementia (MMS total score <24).
3. No current treatment with antidepressant agents, sedative-hypnotics (including sleep induction agents), or neuroleptics.
4. No major side effects on anti-parkinsonian agents (on-off fluctuations, nausea, hallucinosis, etc.).
5. No cardiovascular disease or other medical conditions requiring treatment.

Table 20. Demographic characteristics for PD patients by level of depression.

	Group		
Variable	Nondepressed	Mild Depression	Mod/Severe Depression
n	14	12	8
Age	61.4 (11.8)	64.5 (7.8)	64.8 (7.5)
Education	13.5 (2.6)	13.6 (0.9)	12.6 (3.5)
Sex Male	9	9	5
Female	5	3	3
Race White	14	12	8
Nonwhite	0	0	0
NYU	6.4 (2.3)	6.9 (2.1)	7.7 (4.1)
NW	9.8 (4.4)	9.8 (3.9)	11.1 (7.8)
Stage I	0	0	0
II	0	1	0
III	13	8	5
IV	1	3	3
V	0	0	0
Psychiatric History	5	2	3
Family Psychiatric History	3	3	1

the patient examination and the hypotheses under consideration. A second Hamilton Rating Scale (HRS_{CG}) was completed on the basis of this interview. Neurologist ratings of PD severity using the New York University PD scale (NYU; Lieberman et al, 1980), Northwestern University Disability Scale (NW; Canter et al, 1961), and Hoehn and Yahr stage (1967) were also obtained during clinic visit.

RESULTS

The two criterion measures of depression (BDI, HRS_{EX}) were strongly related ($r = .92$, $p < .001$). The HRS_{CG} was significantly correlated with the HRS_{EX} ($r = .88$, $p < .001$) and the BDI ($r = .87$, $p < .001$). None of the measures of depression were related to PD severity on the NYU scale (BDI: $r = -.004$; HRS_{EX}: $r = .03$; HRS_{CG}: $r = .05$) and NW disability scale (BDI: $r = .04$; HRS: $r = .10$; HRS_{CG}: $r = .01$).

Figure 3 presents the scatterplot of the HRS_{EX} and HRS_{CG}. There appears to be adequate agreement between the two scales across the range of the HRS_{EX}. The relationship between the HRS_{CG} and the BDI (see Figure 4) also indicates adequate responsiveness of HRS_{CG}

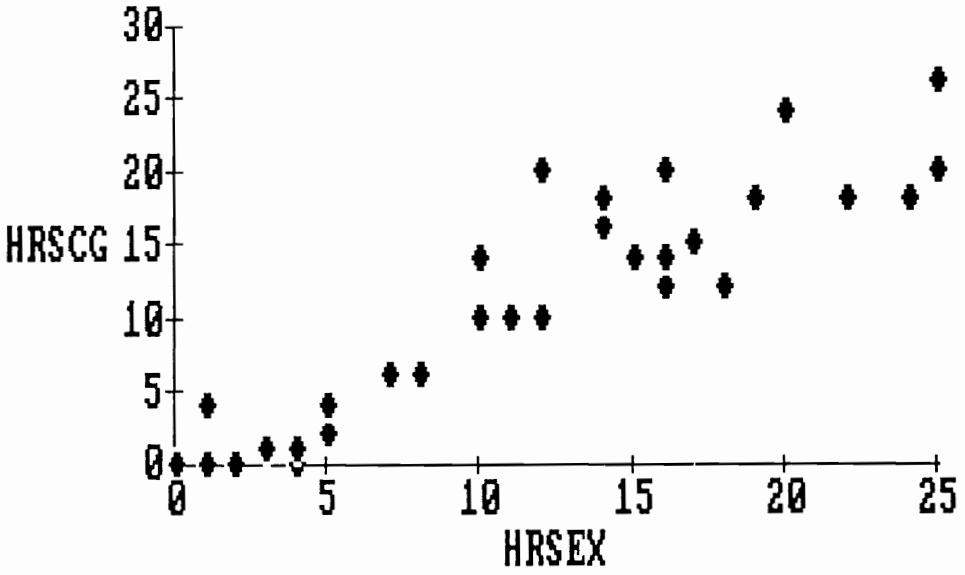

Figure 3. Relationship between HRS_{CG} (y axis) and HRS_{EX} (x axis).

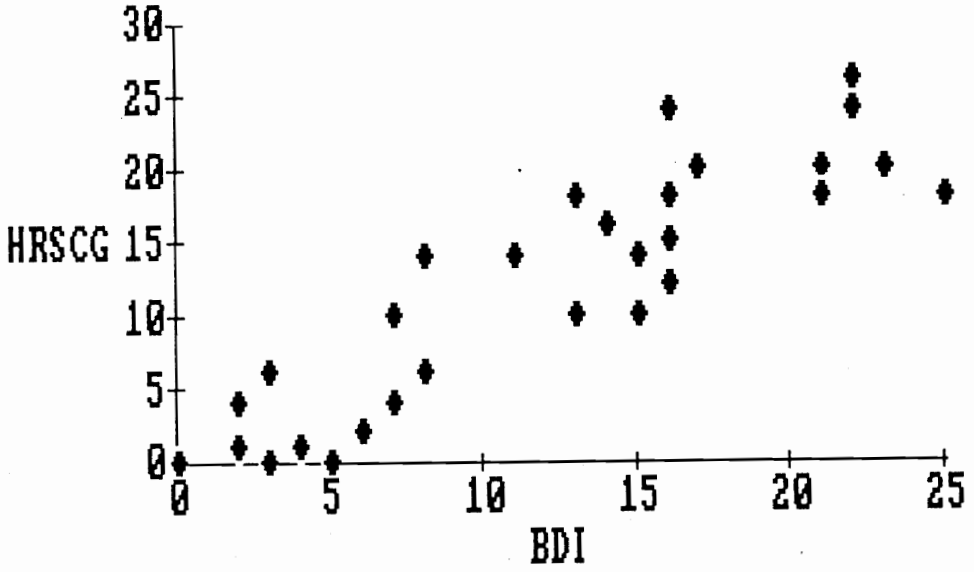

Figure 4. Relationship between HRS_{CG} (y axis) and BDI (x axis).

across a wide range of self-reported depression severity.

Regression parameters of the HRS_{CG} on the HRS_{EX} were examined in detail. Least squares fit of the equation ($Y = .8741*HRS_{CG} + 2.168$) yielded satisfactory R^2 (.81) with standard error of estimation of 3.33. There was, however, evidence of nonconstancy of error variance. Specifically, larger residuals were associated with increasing scores on the criterion (HRS_{EX}). This can be seen in the plot of unstandardized residuals against the criterion (Figure 5). The overall correlation between unstandardized residuals (difference between predicted and observed values) and the criterion was significant ($\underline{r} = .43$, $\underline{p} < .05$). The correlation between the residuals and the HRS_{EX} scores in the nondepressed range (0-10) was nonsignificant ($\underline{r} = .13$), $\underline{p} > .20$), but was significant for HRS_{EX} scores in the depressed range (11+) ($\underline{r} = .56$, $\underline{p} < .01$). Further, the plot of standardized residuals against the predictor (Figure 6) also suggests a trapezoidal dispersion of errors with outward flare toward extreme (large) values of the predictor. Spearman rank correlations between unstandardized residuals and individual items on the HRS_{CG} reached significance for three items: psychic

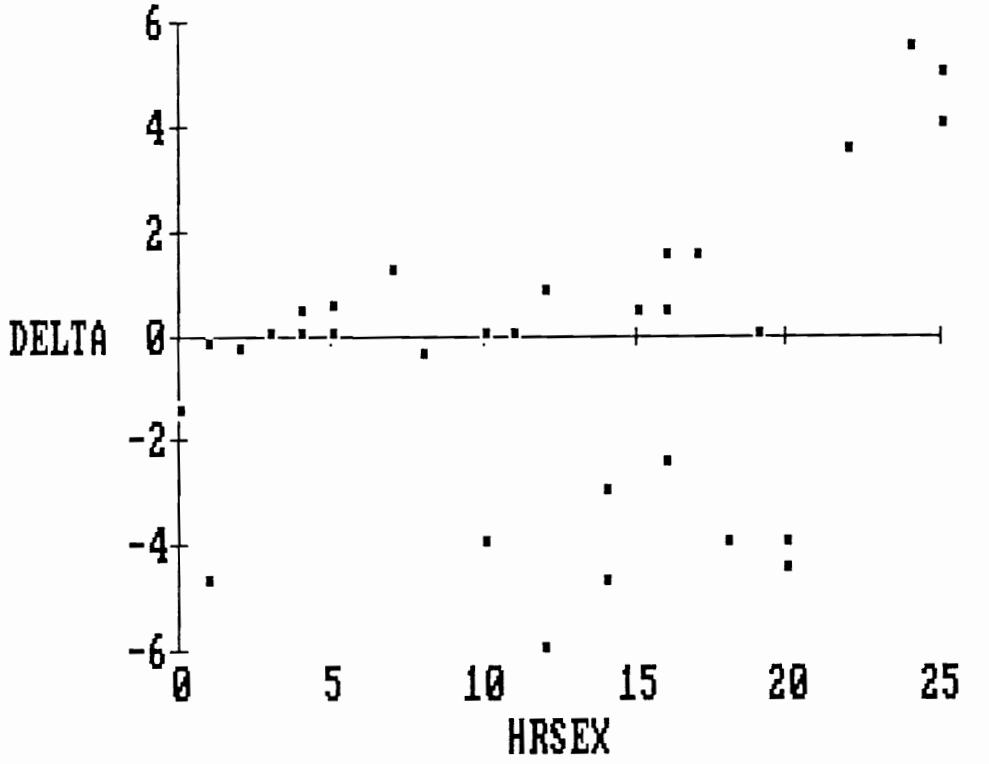

Figure 5. Plot of unstandardized residuals (Delta) against HRS_{EX} scores (x axis).

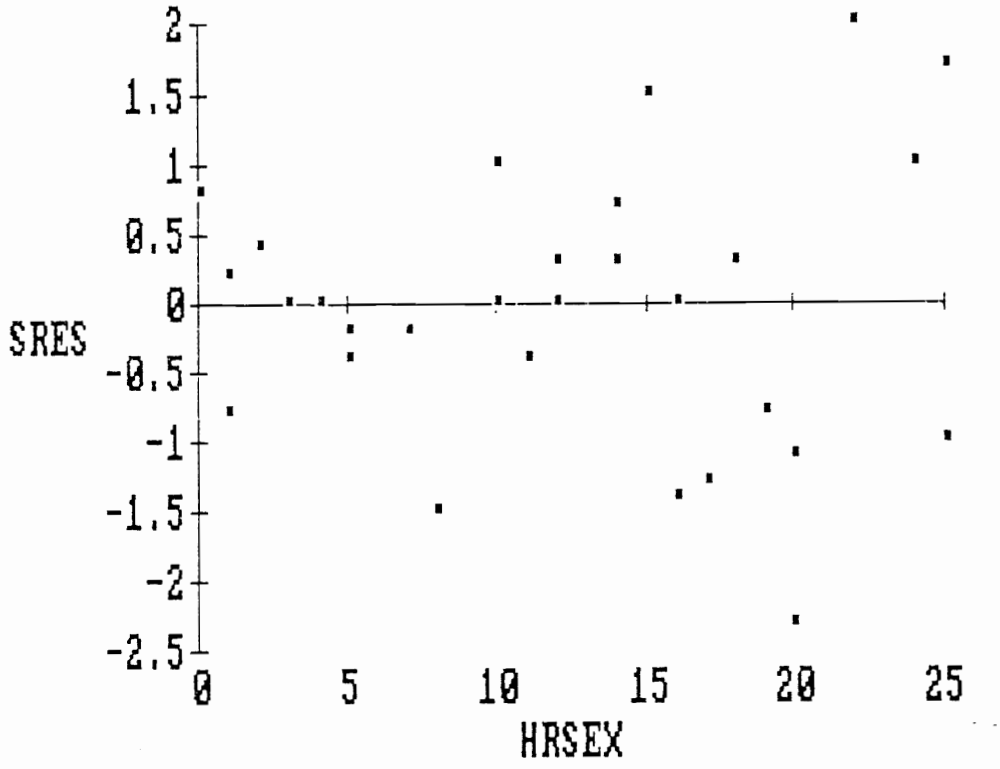

Figure 6. Plot of standardized residuals (y axis) against HRS_{CG} scores (x axis). Note the trapezoidal dispersion with larger residuals at higher HRS_{CG} scores.

anxiety (r = .33, p < .05), somatic anxiety (r = .44, p < .05), and hypochondriasis (r = .31, p < .05).

There was substantial agreement in the gross classification of depressed versus nondepressed between the HRS_{EX} and HRS_{CG}. Phi correlation between the two measures using dichotomous scores (1-10 = nondepressed; 11+ = depressed) was large (.93). Only one patient fell in the depressed range on the HRS_{EX} and in the nondepressed range on the HRS_{CG}.

DISCUSSION

This study generally supports the use of the HRS based on interview of the patient's primary caregiver (HRS_{CG}). This modification of the HRS had adequate product-moment correlations with the HRS_{EX} based on patient interview and the BDI, a self-report measure. The presence of large residuals at higher levels of depression is one potential limitation of the HRS_{CG}. It implies less agreement between the two measurement approaches at high levels of the construct of interest, namely, depressive symptomatology. In particular, the HRS_{CG} tended to underestimate the HRS_{EX} at scores greater than 24 (severe depression).

Attempts to correct for this bias either by transforming HRS_{CG} scores or computing different regression equations for two or three ranges of HRS_{CG} scores may be premature at this point. First the errors in prediction are fairly small (8 points or less). Second, eliminating the four most extreme cases vitiates the correlation between the predictor and size of residuals (r = .16, p >.20). Third, the misclassification rate for the depressed/nondepressed dichotomy was small for the HRS_{CG}. Only one patient with an HRS_{EX} score above 10 had an HRS_{CG} score in the normal range. Thus, for estimating overall prevalence of depression in patients with dementia, these data appear to support the use of HRS_{CG}.

The limitations of the present study are as follows. No information was obtained on interrater reliability on the HRS_{CG} and the exclusive use of PD patients. Interrater reliability was evaluated in Appendix B. The possibility of measurement bias associated with PD cannot be ruled out. The similarity between the motoric aspects of depression and the movement disorder of PD is one potential source of error. However, no study of depression in PD has established a relationship between severity of

depression and the severity of PD motor signs (see Mayeux, 1984). Therefore, the existence of any significant bias is unknown.

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APPENDIX B

One source of measurement error in observer rating scale concerns interrater agreement. Most estimates of interrater reliability for the Hamilton Rating Scale (HRS) have ranged from .85 to .90 (e.g., Hamilton, 1960, 1967; Waldron & Bates, 1965). Effective use of caregiver informants in completing the HRS is predicated upon adequate interrater reliability, in this case defined in terms of adequate agreement between different interviewers of the caregiver. This measurement property was investigated for the HRS based on caregiver report (HRS_{CG}) using 41 patients.

METHOD

Subjects

Participants were 41 patients and caregiver informants drawn from the Rush Alzheimer's Disease Center (RADC) and Movement Disorders Clinic (MDC) at Rush-Presbyterian-St.Luke's Medical Center in Chicago, Illinois. The patients had clinical diagnoses of Alzheimer's disease (AD), subcortical vascular dementia (SVD), idiopathic Parkinson's disease (PD), and other dementia syndromes (OD). AD patients (n=13) were

clinically typical and met all diagnostic requirements for probable AD according to NINCDS/ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price, & Price, 1984). Diagnostic criteria for SVD (n=5) are provided in Table 21. The diagnosis of idiopathic PD (n=10) was based on insidious onset and the presence of 2 or more cardinal PD signs (bradykinesia, cogwheel rigidity, resting tremor, festinating gait, postural instability) in the absence of other medical conditions or prior treatment with neuroleptics. OD patients (n=13) had evidence of significant cognitive impairment on standard psychometric measures. Psychometric evidence of dementia was defined as performance within the "impaired" range on either the Mini-Mental State (MMS) Examination (Folstein, Folstein, & McHugh, 1975) or the Dementia Rating Scale (DRS; Mattis, 1976). Standard cutoff scores for these measures were used: 23 or less on the MMS and 129 or less on the DRS. Of OD patients, 7 patients met NINCDS/ADRDA criteria (McKhann, et al, 1984) for possible AD, 3 patients had suspected mixed AD and vascular dementia, 1 patient had suspected Pick's disease, 1 patient had suspected aluminum toxicity, and 1 patient had atypical progressive dementia with no

Table 21. Criteria for SVD.

Inclusion criteria:

(a) the criteria for progressive dementia outlined above for AD patients;

(b) history of presentation suggestive of cerebrovascular disease based on at least two of the following five features from the Hachinski Ischemia Scale: abrupt onset of cognitive impairment, step-wise progression, focal neurological signs, focal neurological symptoms, history of stroke/transient ischemic attack;

(c) presence of one of the following cardiovascular risk factors: hypertension by history or examination, diabetes mellitus by history or examination, or evidence of cardiac disease (previous myocardial infarction, previous cardiac surgery, congestive heart failure, or angina pectoris);

(d) evidence on MR scan of either (1) three or more discrete bilateral foci or hyperintensity on T2 weighted images in the characteristic lacunar territories or (2) periventricular high signal throughout the entire centrum ovale on T2 weighted images.

Table 21. Criteria for SVD - Continued.

Exclusion criteria:

(a) no evidence of clouded consciousness;

(b) no concurrent systemic or neurologic illness other than those involving the cardiovascular system;

(c) no history of significant substance abuse, head trauma with loss of consciousness greater than one hour, or previous intracranial surgery;

(d) no history of major psychiatric disorder and not currently on psychoactive medications;

(e) no radiological evidence of focal pathology other than that listed above.

formal diagnosis. Descriptive information on the 4 diagnostic conditions is presented in Table 22.

Measures

Hamilton Rating Scale - Caregiver Ratings. The psychometric properties of the HRS have been studied and appear adequate. The HRS covers most symptoms in the psychiatric syndrome of depression (American Psychiatric Association, 1980), has relatively homogeneous item content (internal consistency estimates $\geq$ .82), and has adequate interrater reliability in most applications (.85-.90). However, interrater reliability may be somewhat lower in AD and related disorders (e.g., Lazarus et al., 1987). The validity of the HRS is supported by generally high correlations with other scales of depression (e.g., Zung Self-Rating Scale for depression, Beck Depression Inventory, Geriatric Depression Scale) and response to treatment (see Edwards et al., 1984).

The HRS is typically completed during interviews with the patient supplemented by clinical impressions. However, impaired cognition threatens the validity of patient self-report as the basis for ratings of the

Table 22. Descriptive information and HRS_{CG} scores for two interviewers by diagnostic condition.

	AD	SVD	PD	OD
N	13	5	10	13
Age	73.1±6.9	69.8 ±5.2	64.7±7.1	67.3±7.9
Sex				
Male	5	3	7	6
Female	8	2	3	7
Race				
White	11	5	10	12
Nonwhite	2	0	0	1
Education	11.7±3.1	12.7±2.1	13.1±2.3	12.4±2.4
MMS	17.9±4.9	19.8±3.7	28.7±1.1	15.6±5.2
Informant				
Spouse	9	4	10	8
Child	4	1	0	3
Other relative	0	0	0	2
HRS_{CG}-1	5.3±4.2	10.8±6.6	11.6±6.3	7.8±6.5
HRS_{CG}-2	5.7±3.7	11.0±5.1	11.9±4.7	6.6±4.8

presence and frequency of HRS symptomatology in dementia syndromes. As an alternative, it should be possible to obtain reliable and accurate estimates of HRS symptoms from the patient's primary caregiver. The HRS is appropriate for this approach given the reliance on the behavioral manifestations of depression. In fact, Hamilton (1960, 1967) recommended the use of supplementary information from other observers (e.g., family members, ward staff) in completing the HRS.

Preliminary data on the validity of the HRS based on the interviews with the patient's primary caregiver (HRS_{CG}) has been collected. In 34 PD patients, the correlation between the HRS_{CG} and HRS_{EX} was .89; the correlation between the HRS_{CG} and the Beck Depression Inventory was .87 (see Appendix A).

Procedure

The caregiver's primary caregiver was contacted for participation in a study on the "quality of interview data in patients with neurological disease." The interviews were conducted by two trained psychology technicians within a maximum of 5 days between interviews. Average separation between interviews was

1.6 (± 0.8) days. Interviewers were blind to all clinical data and the results of the other interview.

RESULTS

Mean HRS_{CG} scores were comparable between interviewers (8.3±6.1 vs 8.1±5.1) ($t_{(40)} = 0.4$, $p > .20$). The correlation between HRS_{CG} scores was .92 ($p < .0001$) and the scatterplot did not indicate any obvious departures from linearity (see Figure 7). There were also no differences in ratings for individual items (evaluated using Wilcoxon signed-ranks procedure). Agreement on the presence of individual HRS_{CG} items is summarized in Table 23. The level of agreement exceeded chance for all items with Yule's Y (see Spitznagel & Helzer, 1985) ranging from .56 to 1.00.

DISCUSSION

This study demonstrates adequate interrater reliability for the HRS_{CG} derived from informant data. HRS_{CG} scores from two separate interviewers had similar mean total scores and were highly correlated. Agreement on the presence of individual symptoms was also satisfactory. Thus, there was no evidence of

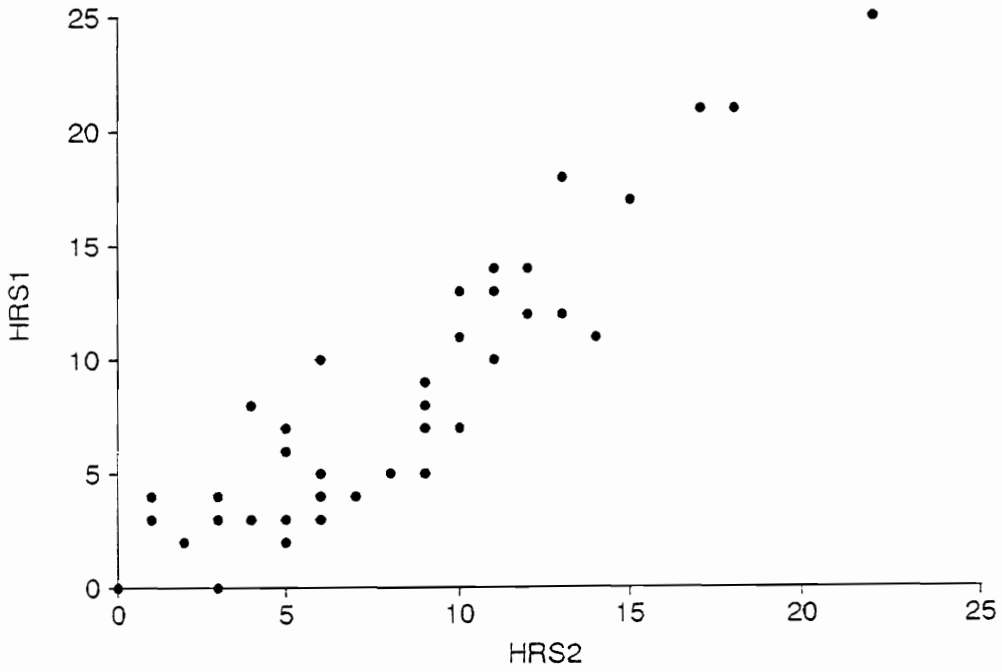

Figure 7. Relationship between HRS_{CG} scores derived from interviewer 1 (y axis) and interviewer 2 (x axis).

Table 23. Interrater agreement between two interviewers for the HRS_{CG} expressed as proportion agreement (P) and Yule's coefficient of colligation (Y).

		P	Y[1]
1.	Depressed mood	.93	.84
2.	Apathy	.76	.56
3.	Libido	.85	.69
4.	Appetite loss	.93	.82
5.	Weight loss	.80	.62
6.	Insomnia - early	.95	.80
7.	Insomnia - middle	.88	.66
8.	Insomnia - late	.88	.71
9.	Retardation	.90	.81
10.	Agitation	.93	.86
11.	Somatic symptoms - general	.95	.82
12.	Guilt	.93	.82
13.	Suicidal ideation	1.00	.96
14.	Anxiety	.90	.76
15.	Anxiety - somatic symptoms	.85	.60
16.	Hypochondriasis	.80	.62
17.	Insight	1.00	1.00

[1]All Y values significantly different from 0

systematic differences between interviewers in their HRS_{CG} ratings.

Two findings, however, are noteworthy as potential difficulties. First, the variability in HRS_{CG} ratings was slightly lower (s.d. = 5.1 vs. 6.1) for the second interviewer. There was also a small but consistent tendency for the second interviewer to produce slightly lower total HRS_{CG} scores. No systematic differences in item ratings were observed, but perhaps there was a slight overall bias against extreme ratings.

The second finding concerns mean differences between interviewers across diagnostic conditions (see Table 3). For AD, SVD, and PD conditions, the mean difference between HRS_{CG} scores was less than 1. However, the difference was 1.2 for OD patients. This asymmetry, while not large, raises the possibility that patient characteristics could contribute to differences between interviewers. Subjectively, interviewers reported some difficulty in rating symptoms for which the caregiver provided an apparent "explanation" based on medical conditions or other factors.

Differences between interviewers may have been minimized by their awareness of the purposes of the study. Awareness of reliability checks has been shown

to produce higher levels of interrater agreement (e.g., Romanczyk, Kent, Diament, & O'Leary, 1973). In this regard, the data in this study should be viewed as an index of "optimal" rather than typical agreement.

These factors do not invalidate the use of the HRS_{CG}, but suggest the need for systematic training and reliability checks to protect against observation "drift" and bias.

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Waldron, J., & Bates, T.J.N. (1965). The management of depression in hospital inpatients: A comparative trial of desipramine and imipramine. British Journal of Psychiatry, 111, 511-520.

CURRICULUM VITAE

DAVID W. GILLEY

Personal Data:

Birth Date:	September 23, 1957
Social Security No.:	
Home Address:	727 South Taylor Oak Park, Illinois 60304 (312) 383-7319
Office Address:	Rush Alzheimer's Disease Center Rush-Presbyterian-St. Luke's Medical Center 230 Johnston R. Bowman 710 South Paulina Chicago, Illinois 60612 (312) 942-2988

Education:

	Virginia Polytechnic Institute and State University Blacksburg, Virginia
1990	Ph.D. Degree in Psychology
	Dissertation: Depression in cortical and subcortical dementia syndromes
1983	M.S. Degree in Psychology
	Thesis: Effects of pre-exposure flavor concentration on conditioned aversion and neophobia
1979	B.S. Degree in Psychology; Minor in Sociology

Clinical Experience:

1987-present Director of Registry Operations

Rush Alzheimer's Disease Center
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL

Design and implementation of a microcomputer-based database for cross-sectional and longitudinal research on Alzheimer's disease and related disorders; training and supervision of data entry personnel; provide descriptive statistics and facilitate research on the database.

1986-Present Research Associate

Rush Alzheimer's Disease Center
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL

Supervisor: Robert S. Wilson, Ph.D.
(312) 942-4463

Neuropsychological evaluation of outpatients referred to the Rush Alzheimer's Disease Center. Coordination and supervision of patient assessments and family interviews. Evaluation of patients participating in multi-center experimental drug trials.

1984-1986 Clinical Intern

Department of Psychology and Social Sciences
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL

Supervisors: Robert S. Wilson, Ph.D.; David C. Garron, Ph.D.; Linas A. Bieliauskas, Ph.D.
(312) 942-5932

Neuropsychological and psychological evaluation of neurological, neurosurgical, psychiatric, geriatric, and general medical inpatients. Therapy experiences included stress management and supportive psycho-therapy with neurological, neurosurgical, and geriatric inpatients and outpatients.

1982-1984 Neuropsychology Technician

Veterans Administration Medical Center, Salem, VA

Supervisor: Leo Kormann, Ph.D.

Administration of neuropsychological tests to outpatient referrals to the Neuropsychology Laboratory. Reports written for approximately one-third of the evaluations.

Teaching Experience:

1990- Instructor

Chicago Medical School, North Chicago, IL

Introduction to Neuropsychology

1986-1988 Training Consultant for SPSS, INC

Taught public seminars on Introduction to SPSS/PC+ and SPSS/Data Entry. Also provided tailored seminars to private corporations and institutions on the use of SPSS/PC+.

1980-1983 Graduate Teaching Assistant

Virginia Polytechnic Institute and State University, Blacksburg, VA

Teaching and course management for: Introductory Psychology; Psychology of Aging; Methods of Assessment.

Professional Organizations:

American Geriatrics Society
Society for Industrial and Applied Mathematics
International Neuropsychological Society
Psychometric Society

Publications:

Gilley, D. W., & Franchina, J. J. (1985) Effects of pre-exposure flavor concentration on conditioned aversion and neophobia. Behavioral and Neural Biology, 44, 503-508.

Franchina, J. J., Gilley, D. W., Ness, J., & Dodd, M. (1985). Establishment and generalization of aversion effects to alcoholic beverages in rats. Behavior Research and Therapy, 23, 255-262.

Franchina, J. J., Dyer, A., Gilley, D. W., Ness, J., & Dodd, M. (1985). Role of ethanol in conditioning aversion to alcoholic beverages in rats. Behavior Research and Therapy, 23, 521-529.

Franchina, J. J., & Gilley, D. W. (1986). Effects of pretraining on conditioned-enhanced neophobia: Evidence for separable mechanisms of neophobia and aversion conditioning. Animal Learning & Behavior, 14, 155-162.

Gilley, D. W., Wilson, R. S., Tanner, C. M., Goetz, C. G., & Clark, D. C. (1987). Depression in Parkinson's disease. Journal of Clinical and Experimental Neuropsychology, 9, 61. (Abstract)

Tanner, C. M., Chen, B., Wang, W., Peng, M., Liu, Z., Liang, X., Kao, L. C., Gilley D. W., & Schoenberg, B. (1987). Environmental factors in the etiology of Parkinson's disease. Canadian Journal of Neurological Sciences, 14, 419-423.

Wilson, R. S., Gilley, D. W., Huckman, M. S., Fox, J. H., & Johnson, C. (1988). The pathophysiologic significance of ventricular enlargement in multi-infarct dementia. Journal of Clinical and Experimental Psychology, 10, 62.

Tanner, C. M., Goetz, C. G., Gilley, D. W., Shannon, K. M., Stebbins, G. T., Klawans, H. L., Wilson, R. S., & Penn, R. D. (1988). Behavioral aspects of intrastriatal adrenal medulla transplant surgery in Parkinson's disease (PD). Neurology, 38(1), 143-144.

Fox, J. H., Wilson, R. S., Gilley, D. W., & Huckman, M.S. (1988). Dementia, gait disorder and incontinence: A triad most commonly seen in subcortical multi-infarct dementia (SMID). Neurology, 38(1), 372.

Gilley, D. W., Wilson, R. S., Ristanovic, R. K., Stebbins, G. T. & Fox, J. H. (1988). Sleep disturbance in subcortical multi-infarct dementia and Alzheimer's disease. Annals of Neurology, 24, 134.

Wilson, R. S., Bennett, D. A., Fox, J. H., Gilley, D. W., Huckman, M. S., Crame, A. C. O., McCluney, K., & Geremia G. K. (1988). Alzheimer's disease: Prevalence and clinical significance of white matter lesions on magnetic resonance imaging. Annals of Neurology, 24, 160-161.

Koch-Weser, M. P., Garron, D. C., Gilley, D. W., Bergen, D., Bleck, T., Morrell, F., Ristanovic, R., & Whisler, W. (1988). Prevalence of psychologic disorders after surgical treatment of seizures. Archives of Neurology, 45, 1308-1311.

Goetz, C. G., Tanner, C. M., Shannon, K. M., Carroll, V. S., Klawans, H. L., Carvey, P. M., & Gilley, D. (1988). Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinsons's disease patients with and without motor fluctuations. Neurology, 38, 1143-1146.

Tanner, C. M., Chen, B., Wang, W., Peng, M., Liu, Z., Liang, X., Kao, L. C., Gilley, D. W., Goetz, C. G., & Schoenberg, B. S. (1989). Environmental factors and Parkinson's disease: A case control study in China. Neurology, 39, 660-663.

Gilley, D. W., Wilson, R. S., & Fox, J. H. (1989). Relationship between behavior disturbances and dementia severity in Alzheimer's disease. Journal of Clinical and Experimental Neuropsychology, 11, 20.

Koch-Weser, M. P., Gilley, D. W., & Garron, D.C. (1989). Change in perception of facial affect in patients with unilateral neurosurgical resections. Journal of Clinical and Experimental Neuropsychology, 11, 23.

Bernard, B. A., Wilson, R. S., Gilley, D. W., Waters, W. F., & Fox, J. H. (1989). Semantic encoding and episodic memory in Alzheimer's disease and multi-infarct dementia. Journal of Clinical and Experimental Neuropsychology, 11, 52-53.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Goetz, C. G., Tanner, C. M., Klawans, H. L., & Penn, R. D. (1989). Quality-of-life changes associated with adrenal medulla/caudate autograft surgery In Parkinson's disease. Neurology, 39(1), 200.

Fox, J. H., Bennett, D. A., Heyworth, J. A., Gilley, D. W., & Wilson, R. S. (1989). Primitive reflexes in Alzheimer's disease. Neurology, 39, 1001-1002. (Letter)

Goetz, C. G., Tanner, C. M., Gilley, D. W., & Klawans, H. L. (1989). Development and progression of motor fluctuations and side effects in Parkinson's disease: Comparison of Sinemet CR versus carbidopa/levodopa. Neurology, 39 (Suppl 2), 63-66.

Fox, J. H., Bernard, B., Gilley, D., Stebbins, G. T., Wilson, R. S., & Huckman, M. S. (1989). Multiple sclerosis: An unexpected cause of senile dementia. Archives of Neurology, 46, December, 1269. (Letter)

Stebbins, G. T., Wilson, R. S., Gilley, D. W., Bernard, B. A., & Fox, J. H. (1990). Use of the National Adult Reading Test to estimate premorbid IQ in dementia. The Clinical Neuropsychologist, 4 (1), 18-24.

Goetz, C. G., Tanner, C. M., Penn, R. D., Stebbins, G. T., Gilley, D. W., Shannon, K. M., Klawans, H. L., Comella C. L., & Witt, T. (1990). Adrenal medullary transplant to the striatum of patients with advanced Parkinson's disease: One year motor and psychometric data. Neurology, 40, 273-276.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Bernard, B. A., & Fox, J. H. (1990). Effects of language disturbances on premorbid estimates of IQ in mild dementia. The Clinical Neuropsychologist, 4 (1), 64-68.

Gilley, D. W., Wilson, R. S., Bernard, B. A., Stebbins, G. T., & Fox, J. H. (1990). Scaling severe dementia. Journal of Clinical and Experimental Neuropsychology, 12, 19.

Gilley, D. W., Bennett, D. A., Grosse, D. A., Wilson, R. S., & Fox, J. H. (1990). Risk factors and clinical features associated with depression in Alzheimer's disease. Neurology, 40 (Supplement 1), 447.

Tanner, C. M., Goetz, C. G., Penn, R. D., Stebbins, G. T., Gilley, D. W., Shannon, K. M., Klawans, H. L., Comella, C. L., & Witt, T. (in press). Autologous adrenal medullary transplant to the striatum of patients with advanced Parkinson's disease: 18 month follow-up. International Journal of Neurology.

Bennett, D. A., Wilson, R. S., Gilley, D. W., & Fox, J. H. (in press). Clinical diagnosis of Binswanger's disease. Journal of Neurology, Neurosurgery, and Psychiatry.

Penn, R. D., Kroin, J. S., Kroin, S. A., Klawans, H. L., Goetz, C. G., Tanner, C. M., Shannon, K. M., Comella, C. L., Carvey, P. M., Witt, T., Wilson, R. S., Stebbins, G. T., Gilley, D. W., Yaksh, T., O'Dorisio, T., & McRae-Degueurce, A. (in press). The adrenal medullary transplant operation - the Chicago experience. Progress in Brain Research.

Gilley, D. W., Wilson, R. S., Fox, J. H., & Kaszniak, A. W. (in press). Age at onset in Alzheimer's disease: Relationship to linguistic function and rate of progression. Cortex.

Gilley, D. W., Bennett, D. A., & Stebbins, G. T. (in press). Alzheimer's disease and psychiatric disorders. In R. W. Parks, R. F. Zec, & R. S. Wilson (Eds.), Neuropsychology of Alzheimer's disease and other dementias. New York: Oxford Press.

Koch-Weser, M., Garron, D. C., & Gilley, D. W. (in press). The DIS and outcome of surgical treatment of epilepsy. The DIS Newsletter.

Gilley, D. W., Wilson, R. S. Bennett, D. A., Stebbins, G. T., Bernard, B. A., Whalen, M. E., & Fox, J. H. (in press). Cessation of driving and unsafe motor vehicle operation by dementia patients. Archives of Internal Medicine.

Gilley, D. W., & Wilson, R. S. (in press). Nuisance parameters in the assessment of noncognitive manifestations of dementia. Psychology and Aging.

Gilley, D. W., Wilson, R. S., Bennett, D. A., Bernard, B. A. & Fox, J. H. (in press). Predictors of behavioral disturbance in Alzheimer's disease. Journal of Gerontology: Psychological Sciences.

Papers Presented

Silber, S., Gilley, D. W., May, B., Franchina, J., Perconte, S., & Butler, D. (March, 1980). Familiarity versus temporal contiguity in taste aversion learning. Paper presented at Southeastern Psychological Association, Washington, DC.

Gilley, D. W., & Bennett, B. (April, 1982). Stress management for organizations in transition. Paper presented at the Virginia Academy of Science, Blacksburg, VA.

Franchina, J. J., Gilley, D. W., Ness, J., Dyer, A., & Dodd, M. (March, 1984). Establishment and generalization of aversion effects to alcoholic beverages in rats. Paper presented at the Southeastern Psychological Association, New Orleans.

Dyer, A., Gilley, D. W., & Franchina, J. J. (March, 1984). Effects of pre-exposure flavor concentration on conditioned aversion and neophobia. Paper presented at the Southeastern Psychological Association, New Orleans.

Gilley, D. W., Wilson, R. S., Tanner, C. M., Goetz, C. G., & Clark, D. C. (February, 1987). Depression in Parkinson's disease. Paper presented at the 15th Annual Meeting of the International Neuropsychological Society, Washington, DC.

Tanner, C. M., Chen, B., Wang, W., Peng, M., Liu, Z., Liang, X., Kao, L., Gilley, D. W., & Schoenberg, B. (February, 1987). Environmental factors in the etiology of Parkinson's disease. Paper presented at the Canadian Neurological Association, Toronto, Canada.

Ristanovic, R., Gilley, D. W., Tanner, C. M., & Goetz, C. G. (April, 1987). Gilles de la Tourette's syndrome and sleep. Paper presented at the American Academy of Neurology Meeting, New Orleans.

Wilson, R. S., Gilley, D. W., Tanner, C. M., Goetz, C. G., Rapp, D. T., & Gans, S. L. (August, 1987). Ideational fluency in Parkinson's disease. Paper presented at the American Psychological Association Meeting, New York.

Grosse, D. A., Wilson, R. S., Gilley, D. W., Tanner, C. M., Goetz, C. G., Lazar, D. S., & Meyer, S. L. (August, 1987). Hallucinosis and cognitive functioning in Parkinson's disease. Paper presented at the American Psychological Association Meeting, New York.

Gilley, D. W., Wilson, R. S., Goetz, C. G., Tanner, C. M., & Fox, J. H. (August, 1987). Dissociation of depression and cognitive dysfunction in Parkinson's disease. Paper presented at the American Psychological Association Meeting, New York.

Wilson, R. S., Stebbins, G. T., & Gilley, D. W. (August, 1987). Short-term cognitive and affective changes following adrenal medulla transplant surgery in Parkinson's disease. Paper presented at the First Workshop on Adrenal Transplants in Parkinson's Disease, Chicago.

Tanner, C. M., Goetz, C. G., Gilley, D. W., Shannon, K. M., Stebbins, G. T., Klawans, H. L., Wilson, R. S., & Penn, R. D. (November, 1987). Psychiatric aspects of intrastriatal adrenal medulla transplant surgery in Parkinson's disease. Paper presented at the Movement Disorders Symposium, San Francisco.

Wilson, R. S., Gilley, D. W., Huckman, M. S., Johnson, C., & Fox, J. H. (January, 1988). The pathophysiologic significance of ventricular enlargement in multi-infarct dementia. Paper presented at the 16th Annual Meeting of the International Neuropsychological Society, New Orleans.

Stebbins, G. T., Wilson, R. S., Gilley, D. W., Bernard, B. A., & Fox, J. H. (January, 1988). Estimation of premorbid intelligence in dementia. Paper presented at the 16th Annual Meeting of the International Neuropsychological Society, New Orleans.

Stebbins, G. T., Wilson, R. S., & Gilley, D. W. (March, 1988). The impact of adrenal medulla transplant surgery on quality of life. Paper presented at the Second Workshop on Adrenal Transplants in Parkinson's Disease, Chicago.

Fox, J. H., Wilson, R. S., Gilley, D. W., & Huckman, M. S. (April, 1988). Dementia, gait disorder, and incontinence: A triad most commonly seen in subcortical multi-infarct dementia (SMID). Paper presented at the 40th Annual Meeting of the American Academy of Neurology, Cincinnati.

Tanner, C. M., Goetz, C. G., Gilley, D. W., Shannon, K. M., Stebbins, G. T., Klawans, H. L., Wilson, R. S., & Penn, R. D. (April, 1988). Behavioral aspects of intrastriatal adrenal medulla transplant surgery in Parkinson's disease. Paper presented at the 40th Annual Meeting of the American Academy of Neurology, Cincinnati.

Tanner, C. M., Chen, B., Wang, W. Z., Gilley, D. W., Peng, M. L., Liu, Z. L., Liang, X. L., Kao, L. C., Goetz, C. G., & Schoenberg, B. S. (April, 1988). Environmental factors and Parkinson's disease (PD): A case-control study in China. Paper presented at the 40th Annual Meeting of the American Academy of Neurology, Cincinnati.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Bernard, B. A., & Fox, J. H. (July, 1988). Premorbid IQ estimates and language disturbance in dementia. Paper presented at the Eleventh Annual European Conference of the International Neuropsychological Society, Lahti, Finland.

Stebbins, G. T., Wilson, R. S., Gilley, D. W., Goetz, C. G., Tanner, C. M., & Klawans, H. L. (August, 1988). The impact of adrenal/medulla transplant surgery on quality of life. Presented at the Second Annual Workshop on Adrenal Transplants in Parkinson's Disease, Chicago.

Stebbins, G. T., Wilson, R. S., & Gilley, D. W. (August, 1988). The national registry of autograft procedures in Parkinson's disease. Presented at the Second Annual Workshop on Adrenal Transplants in Parkinson's Disease, Chicago.

Gilley, D. W., Wilson, R. S., Ristanovic, R., Stebbins, G. T., & Fox, J. H. (October, 1988). Sleep disturbance in subcortical multi-infarct dementia. Paper presented at the American Neurological Association Meeting, Philadelphia.

Wilson, R. S., Bennett, D., Fox, J. H., Gilley, D. W., Huckman, M. H., Crame, A.C.O., McCluney, K., & Geremia, G. K. (October, 1988). Alzheimer's disease: Prevalence and clinical significance of white matter lesions on Magnetic Resonance Imaging. Paper presented at the American Neurological Association Meeting, Phildelphia.

Bernard, B. A., Wilson, R. S., Gilley, D. W., Waters, W. F., & Fox, J. H. (February, 1989). Semantic encoding and episodic memory in Alzheimer's disease and multi-infarct dementia. Paper presented at the Seventeenth Annual International Neuropsychological Society Meeting, Vancouver, Canada.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Goetz, C. G., Tanner, C. M., Klawans, H. L., & Penn, R. D. (February, 1989). Quality of life changes associated with adrenal medulla/caudate autograft surgery in Parkinson's disease. Paper presented at the Seventeenth Annual International Neuropsychological Society Meeting, Vancouver, Canada.

Koch-Weser, M. P., Gilley, D. W., & Garron, D. C. (February, 1989). Change in perception of facial affect in patients with unilateral neurosurgical resections. Paper presented at the Seventeenth Annual International Neuropsychological Society Meeting, Vancouver, Canada.

Bennett, D. A., Wilson, R. S., Gilley, D. W., & Fox, J. H. (April, 1989). Clinical diagnosis of Binswanger's disease. Paper presented at the 41st Annual Meeting of the American Academy of Neurology, Chicago.

Stebbins, G. T., Wilson, R. S., Gilley, D. W., Goetz, C. G., Tanner, C. M., Klawans, H. L., Shannon, K., & Penn, R. D. (April, 1989). Changes in quality of life at 12 months post-adrenal medulla/caudate autograft surgery in Parkinson's disease. Paper presented at the 41st Annual Meeting of the American Academy of Neurology, Chicago.

Gilley, D. W., Wilson, R. S., Bennett, D. A., Stebbins, G. T., Bernard, B. A., & Fox, J. H. (May, 1989). Assessment and significance of behavioral disturbances in Alzheimer's disease. Paper presented at the 46th Annual Meeting of the American Geriatric Society, Boston.

Gilley, D. W., Stebbins, G. T., Wilson, R. S., Bernard, B. A., Bennett, D. A., & Fox, J. H. (May, 1989). Driving among dementia patients. Paper presented at the 46th Annual Meeting of the American Geriatric Society, Boston.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Bernard, B. A., & Fox, J. H. (May, 1989). Impact of elderly dementia patient's functioning on caregiver distress. Paper presented at the 46th Annual Meeting of the American Geriatric Society, Boston.

Penn, R. D., Kroin, J. S., Kroin, S. A., Klawans, H. L., Goetz, C. G., Tanner, C. M., Shannon, K. M., Comella, C. L., Carvey, P. M., Witt, T., Wilson, R. S., Stebbins, G. T., Gilley, D. W., Yaksh, T., O'Dorisio, T., & McRae-Degueurce, A. (August, 1989). The adrenal medullary transplant operation - the Chicago experience. Paper presented at the Symposium on Neurotransplantation, Cambridge, MA.

Gilley, D. W., Wilson, R. S., Kaszniak, A. W., & Fox, J. H. (September, 1989). Age at onset of Alzheimer's disease: Relationship to linguistic function and rate of progression. Paper presented at the 114th Annual Meeting of the American Neurological Association, New Orleans, LA.

Gilley, D. W., Wilson, R. S., Bennett, D. A., & Fox, J. H. (September, 1989). Depression in putative Binswanger's disease. Paper presented at the 114th Annual Meeting of the American Neurological Association, New Orleans, LA.

Gilley, D. W., Wilson, R. S., Bernard, B. A., Stebbins, G. T., & Fox, J. H. (February, 1990). Scaling severe dementia. Paper presented at the 18th Annual International Neuropsychological Society Meeting, Orlando, FL.

Gilley, D. W., Wilson, R. S., Bennett, D. A., Bernard, B. A., & Fox, J. H. (February, 1990). Prediction of behavioral disturbances in Alzheimer's disease using dementia severity and clinical subtypes. Paper presented at the 18th Annual International Neuropsychological Society Meeting, Orlando, FL.

Gilley, D. W., Murphy, P., Wilson, R. S., Ivankovich, A., & Witt, T. (February, 1990). Memory for intraoperative stimuli. Paper presented at the 18th Annual International Neuropsychological Society Meeting, Orlando, FL.

Grosse, D. A., Gilley, D. W., Wilson, R. S., & Fox, J. H. (February, 1990). Episodic and semantic memory in early vs. late onset Alzheimer's disease. Paper presented at the 18th Annual Meeting of the International Neuropsychological Society, Orlando, FL.

Bernard, B. A., Wilson, R. S., Gilley, D. W., Grosse, D. A., Bennett, D. A., Whalen, M. E., & Fox, J. H. (February, 1990). Performance of patients with Binswanger's disease and Alzheimer's disease on the Mattis Dementia Rating Scale. Paper presented at the 18th Annual Meeting of the International Neuropsychological Society, Orlando, FL.

Tanner, C. M., Koller, W. C., Gilley, D. W., Goetz, C. G., Wang, W., Peng, M., Biao, C., Liu Z., & Liang X. (April, 1990). Cigarette smoking, alcohol drinking, and Parkinson's disease: Cross-cultural risk assessment. Paper presented at the First International Congress of Movement Disorders, Washington, DC.

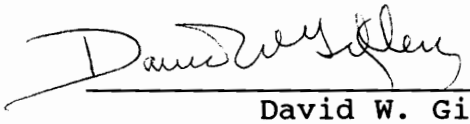
Gilley, D. W., Bennett, D. A., Grosse, D. A., & Wilson, R. S. (April, 1990). Risk factors and clinical features associated with depression in Alzheimer's disease. Paper presented at the 42nd Annual Meeting of the American Academy of Neurology, Miami, FL.

Bennett, D. A., Cochran, E., Saper, C. B., Gilley, D. W., & Wilson, R. S. (April, 1990). Pathological changes in frontal cortex from biopsy to autopsy in Alzheimer's disease. Paper presented at the 42nd Annual Meeting of the American Academy of Neurology, Miami, FL.

Bennett, D. A., Gilley, D. W., Wilson, R. S., Huckman, M., & Fox, J. H. (May, 1990). Clinical correlates of periventricular hyperintensity in Alzheimer's disease. Paper presented at the 47th Annual Meeting of the American Geriatrics Society, Atlanta, GA.

Gilley, D. W., Tanner, C. M., Stebbins, G. T., Goetz, C. G., Klawans, H. L., Penn, R. D., Shannon, K. M., & Comella, C. L. (June, 1990). Behavioral and cognitive function in patients undergoing intrastriatal adrenal transplant surgery. Paper to be presented at the Erik Fernstrom International Symposium on Intracerebral Transplantation in Movement Disorders, Lund, Sweden.

Tanner, C. M., Gilley, D. W., & Goetz, C. G. (October, 1990). A brief screening questionnaire for parkinsonism. Paper to be presented at the 115th Annual Meeting of the American Neurological Association, Atlanta, GA.



David W. Gilley