Title

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Journal

American Journal of Geriatric Psychiatry, 22(12)

ISSN

1064-7481

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Publication Date

2014-12-01

DOI

10.1016/j.jagp.2014.02.006

Peer reviewed

Published in final edited form as:
Am J Geriatr Psychiatry. 2014 December ; 22(12): 1633–1641. doi:10.1016/j.jagp.2014.02.006.

Association of Age of Depression Onset with Cognitive Functioning in Individuals with Late Life Depression and Executive Dysfunction

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Abstract

Objective—To compare patterns of cognitive performance in older adults with late-onset depression (LOD; ≥65 years of age) to that of older adults with early-onset depression (EOD; ≤65 years).

Method—Participants were 171 adults aged 60 years or older with major depression and executive dysfunction who were participating in a randomized psychotherapy trial. Participants included 72 LOD and 99 EOD individuals. Cognitive performance on measures of verbal learning, memory, and executive functioning were evaluated. Demographic and clinical characteristics, severity of cerebrovascular risk factors, and disability ratings were also compared between groups.

Results—The LOD group was older, and had fewer previous episodes of depression, and lower severity of depression compared to EOD participants. The LOD group demonstrated poorer performance on measures of verbal learning, $F(1,161) = 4.28$, $p = .04$ and memory $F(1,160) = 4.65$, $p = .03$, than the EOD group. Linear regression analysis demonstrated that LOD and fewer years of education were significant predictors of poorer verbal learning, $F(7,114)= 6.25$, $p < 0.001$ and memory, $F(7,113)=7.24$, $p < .001$. Performance on measures of executive functioning, severity of vascular risk factors, and disability ratings did not differ between the two groups.

Conclusions—In older adults with depression and executive dysfunction, LOD was associated with poorer performance on measures of verbal learning and memory. Aging related brain changes associated with LOD may play a more important role leading to dysfunction in these cognitive

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Disclosures: No other authors report competing interests.

domains than a history of recurrent depressive episodes in older adults with a dysexecutive syndrome.

Keywords

cognitive functioning; disability; late life depression; age of onset; late onset; memory; executive dysfunction; learning; vascular risk factors

INTRODUCTION

Major depression in older adults, or Late Life Depression (LLD), is a prevalent and debilitating psychiatric disorder that is commonly linked to a wide range of cognitive dysfunctions (1). LLD is most often associated with deficits of executive functioning, i.e. the depression dysexecutive syndrome of late life (2, 3), which is often conceptualized as representing individuals with concurrent cerebrovascular disease (4). However, cognitive impairments in the domains of verbal learning and memory are also frequently reported (1, 5). Further, there is considerable heterogeneity in the types, severity, and overall number of cognitive impairments reported in LLD samples (1, 6–8). While depression severity contributes to cognitive dysfunction in LLD (9), it is insufficient to explain the range of cognitive dysfunction reported. As cognitive dysfunction in LLD contributes to poor treatment adherence (10), increased cost of mental health treatment (11), and increased burden of disability (12), elucidating the impact of other LLD characteristics on cognitive functioning may represent a significant avenue to improve treatment and outcomes in these patients.

Age of depression onset is one clinical characteristic that has the potential to clarify the etiology of cognitive dysfunction in LLD. Two alternative, but not mutually exclusive, hypotheses have been suggested to explain cognitive dysfunction associated with LLD with respect of age of depression onset. Late onset depression (LOD), typically defined as onset of a first depressive episode after 65 years of age, occurs in approximately 30% of LLD individuals (13) and is often thought to be associated with aging related brain changes (14). This association is supported by consistent findings of cerebrovascular disease, specifically frontal striatal white matter abnormalities and executive dysfunction in LLD (15, 16). LOD has also been associated with temporal lobe atrophy and hippocampal volume loss, (17, 18) which are characteristics of incipient Alzhiemer's disease and are associated with memory impairment (19, 20). Together these findings suggest that LOD is associated with aging related brain changes that could adversely impact cognition. The alternate hypothesis suggests that cognitive dysfunction could be the result of damage suffered from repeated lifetime episodes of depression in those with EOD. Specifically, it has been suggested that repeated episodes of depression and associated hypercortisolemia (21, 22) and other factors could result in hippocampal damage and cortical abnormalities (23, 24) that contribute to learning and memory deficits in LLD. Complicating these hypotheses is the potential for cognition in individuals with EOD to be further impacted by neurodegenerative disease in later life. Despite the importance of clarifying the contributing factors to cognitive dysfunction in LLD relatively few studies have been conducted to evaluate these alternative hypotheses.

While early studies initially reported similar patterns of cognitive functioning in EOD and LOD (8), four recent studies reported that LOD was associated with poorer memory performance when compared to EOD (25–28). However, Rapp et al (29) did not find this association. Of note, there have been no previous studies which have evaluated verbal learning, a cognitive domain associated with memory performance, in LOD in contrast to EOD. Poorer performance on measures of executive functioning and information processing speed in LOD relative to EOD have also been reported in some studies (27, 30), but not others (5). These inconsistent findings may result from several factors. Many of these studies utilized small samples of LLD participants. Additionally, few studies controlled for the impact of depression severity on cognitive functioning and relied on dichotomous classifications of age of onset without accounting for the number of prior depressive episodes. Lastly, several previous studies have not controlled for the impact of education history on cognitive performance in LOD and EOD individuals (25, 26, 31). Given the potential for level of previous education, or "cognitive reserve", to impact cognitive performance in older adults (32), such investigations are particularly important.

This analysis evaluated cognitive functioning in LOD relative to EOD in a sample of older adults participating in a clinical trial of the efficacy of psychotherapy for patients with late life major depression and executive dysfunction. Evaluating the impact of age of depression onset on cognition in this sample, presumably at higher risk for aging related brain changes, offers a significant opportunity to clarify the role of age of depression onset on cognition. Based on the existing literature, we hypothesized that LOD participants would exhibit poorer performance on measures of learning and memory than EOD participants, and that LOD would be a stronger predictor of poor performance on measures of learning and memory than number of prior episodes after taking education level and current depression severity into account. We also examined if LOD was associated with greater burden of cerebrovascular risk factors when compared to EOD and if LOD patients differed from EOD patients on measures of disability status and executive functioning. To our knowledge, this is the first study to examine the effects of age of onset on cognitive functioning in older adults with depression and executive dysfunction.

METHOD

Participants

Data for this study were obtained for secondary analysis from a two-site, randomized controlled trial conducted to compare the efficacy of a modified version of Problem Solving Therapy (PST) to Supportive Therapy (ST) in patients ages 60 and over with major depression and executive dysfunction (33). Participants were recruited for participation in this study by community advertisements and referrals from psychiatry clinics at each study site. All participants provided informed consent to participate in the study and all study procedures were approved by a committee for human research institutional review board at each site. Psychiatric diagnoses were made by licensed psychologists utilizing DSM-IV criteria and the Structured Clinical Interview for the Diagnosis of DSM-IV Disorders, and were reviewed at a consensus conference comprised of psychologists, psychiatrists, and social workers. Depression severity at intake was evaluated with the 24-item Hamilton

Depression Rating Scale (HDRS) (34) and participants with moderate to severe depression severity (HDRS score of ≥20) were included in the study. Inclusion criteria with regard to executive functioning were based on screening performance on the Initiation/Perseveration index of the Mattis Dementia Rating Scale (DRS-IP; score ≤33) and the Stroop Word Color Test (SCWT; score ≤25) (33). Exclusion criteria consisted of current involvement in psychotherapy, currently on antidepressant medications or wish be treated with antidepressants, presence of psychotic depression (SCID-R), high suicide risk (i.e., intent or plan to attempt suicide in near future), any Axis I psychiatric disorder or substance abuse other than unipolar major depression or generalized anxiety disorder, antisocial personality (DSM-IV), history of head trauma, dementia (MMSE<24 or diagnosis of dementia by DSM-IV), acute or severe medical illness (i.e., delirium, metastatic cancer, decompensated cardiac, liver or kidney failure, major surgery, stroke or myocardial infarction during the three months prior to entry), drugs known to cause depression (e.g., reserpine, alpha-methyl-dopa, steroids), and inability to perform any activities of daily living even with assistance.

Of the 653 participants referred to the study, 29 either refused to be screened after explanation of the study or did not complete the screen. The remaining 624 underwent a structured interview, which led to exclusion of 345 individuals: 26% did not meet criteria for major depression; 12% did not have a HDRS score ≥20; 40% did not exhibit evidence of executive dysfunction, 1% had low MMSE scores, and 13% had another psychiatric diagnosis. Of the 279 who were eligible for the study, 58 (21%) were not included because they failed to complete baseline evaluation and did not return for further assessment or treatment. Of the 221 participants enrolled in the treatment study, age of depression onset was available for 171 participants.

Measures

All measures of depression severity, vascular risk factors, disability, and cognitive functioning were obtained for each participant during a single assessment. Late onset of depression (LOD) was diagnosed for individuals who reported a first episode of major depression meeting DSM IV criteria at 65 years of age or older. The specific measures utilized and outcome variables for each of these measures are described below. Additionally, demographic information (age, years of education, gender) and clinical history (age of depression onset, number of lifetime depressive episodes) was obtained for each participant.

VERBAL LEARNING AND MEMORY

Hopkins Verbal Learning Test - Revised (HVLT-R) (35)

The HVLT-R is a measure of verbal learning and memory for lists of verbally presented information. The outcome variable utilized for verbal learning performance was the total number of correct responses on the three learning trials of this test (HVLT-L). The total possible score on this measure was 36 points. The outcome variable utilized to evaluate memory (HVLT-M) was the total number of correct responses on the delayed free recall trial of this test and the total possible score was 12.

EXECUTIVE FUNCTIONING

Mattis Dementia Rating Scale-2 Initiation/Perseveration Scale (DRS IP) (36)

The DRS-IP is a measure of executive functioning for older adults with an information processing speed component; the total number of correct responses was utilized as the primary outcome variable. The total possible score on this measure was 37.

Wisconsin Card Sorting Test-64 Computer Version 2 (WCST-64) (37)

The WCST is a non-speeded measure of problem solving ability, cognitive flexibility, and ability to maintain a cognitive set; the outcome variable was the total number of correct responses. The total possible score on this measure was 64.

The Stroop Color and Word Test (SCWT) (38)

The SCWT is a timed measure of response inhibition, ability to maintain cognitive set, and information processing speed; the total number of correct responses on the color word trial was utilized as the outcome variable.

Trail Making Test Part B (TMT) (39)

Part B of the TMT is a timed measure of sequencing ability, visuomotor speed, and response inhibition. The time required to complete both trials was utilized as the outcome variables for this test.

DEPRESSION, VASCULAR RISK, DISABILITY

Hamilton Depression Rating Scale (34)

The 24-item HDRS assesses severity of depressive symptoms; high scores indicate greater severity of depression and the total possible score was 75.

Vascular Risk Scale (VRS): the VRS consists of 8 questions evaluating the presence of antihypertensive treatment, history of diabetes, smoking, congestive heart failure/myocardial infarction, atrial fibrillation, ventricular hypertrophy, stroke, and transient ischemic attacks. Scores ranged from 0–8 with high scores representing greater vascular risk.

World Health Organization Disability Assessment Scale (WHODAS II) (40)

The WHODAS II is a 36 item measure of disability and scores range from 0 to 100; higher scores represent greater disability.

Data Analysis

To evaluate clinical characteristics and cognitive functioning between the two groups analysis of variance models were estimated and tested. Evaluation of the assumption of normalcy for dependent measures was conducted and we did not find violations of this assumption. For low frequency count variables we retrospectively utilized non-parametric and our results did not change. Covariates analysis of variance models included age and education. Linear regression models were used to model factors associated with cognitive performance on measures differentiating the two groups. These factors included the effect of

age, education, depression severity, number of previous depressive episodes, vascular risk factors, and age of depression onset (EOD vs LOD). Given correlations among cognitive functioning variables colinearity thresholds were also evaluated for each model. Analyses were conducted using SPSS (version 20).

RESULTS

The mean age for the sample was 73.0 years (SD = 7.7), the mean years of education was 15.2 (SD = 2.8), the mean MMSE score was 27.8 (SD = 1.7), and 65% of the sample was female. The mean HDRS for the sample was 24.0 (SD=4.4), the average age of onset of depression was 55.9 years (SD=22.4), the mean number of previous episodes of depression was 2.3 (SD = 2.2, median = 2.0). The sample demonstrated relatively low ratings of vascular risk (mean = 0.90, SD = 1.1, median = 1.0) and moderate ratings of disability (WHODAS II mean =26.6, SD = 7.3). A high degree of correlation was found between measures of learning and memory and moderate correlations with these measures was seen with measures of executive functioning (Table 1). Forty-two percent of the sample reported late onset of depression (LOD; age of major depression onset ≥ 65 years) and age of onset groups did not differ with respect to gender (x^2=0.32, p=0.57).

With respect to group comparisons on clinical characteristics, the LOD group was significantly older, F(1,170) = 41.0, p <.001 and had lower depression severity ratings than the EOD group, F(1,170) = 6.4, p = .01 (Table 2). The LOD group also reported fewer previous episodes of depression, F(1,170) = 94.4, p < .001 but the two groups did not differ with respect to ratings of vascular risk or disability. With respect to cognitive performance (Table 3), after controlling for the effects of age and education, the LOD group performed significantly worse on measures of verbal learning F(1,162) = 4.3, p = .04 and memory F(1,162) = 4.7, p = .03. The two groups did not differ with respect to performance on measures of executive functioning. Linear regression analyses demonstrated that LOD and education were the only significant predictors of verbal learning, F(7,114) = 6.25, p < 0.001; and memory, F(7,113)=7.24, p < .001 in the sample (Tables 4,5) accounting for 4% and 5% of the total variance of these models respectively. In separate analyses EOD/LOD was replaced with age of depression onset and age of onset was not a significant predictor of either learning or memory performance.

DISCUSSION

Our study has two primary findings: 1) in patients with LLD and executive dysfunction, LOD was associated with poorer performance on measures of both verbal learning and memory when compared to EOD participants, 2) number of previous depressive episodes, current depression severity, and age of depression onset as a continuous measure were not associated with learning and memory performance. We also found that education was significantly associated with learning and memory performance and that the LOD and EOD depression groups did not differ with respect to ratings of vascular risk, disability, or performance on measures of executive functioning.

Our finding that LOD was associated with poorer performance on measures of memory is consistent with previous studies (25–28). However, our findings are important as our data suggest that LOD, i.e. onset on or after 65 years of age, is more strongly associated with memory performance than the specific age of first depressive episode, the number of lifetime depressive episodes, or depression severity in this sample. While we acknowledge a modest effect size in our statistical models, these results suggest that late onset of depression may play a more significant role in the development of memory impairment than the repeated insults associated with recurrent depressive episodes. Further, as memory disturbance has been shown to impact medical treatment adherence (10), our findings suggest that memory dysfunction in LOD may also impact both pharmacologic and psychotherapy treatment outcomes in LLD.

Our findings suggest that in addition to memory performance, LOD is also associated with poorer performance on measures of verbal learning. These findings represent an important extension of the prior literature which has primarily focused on memory performance (25–28). Specifically, verbal learning impairments may have important clinical implications particularly for psychotherapy interventions given the inherent learning requirements of these treatments for LLD. Given consistent findings that education level or “cognitive reserve” can impact cognitive performance in older adults (32), we statistically controlled for the impact of both age and education when performing our group comparisons. Our results, therefore, represent a more conservative statistical approach to evaluate differences in cognitive performance between the two depression onset groups across several cognitive domains than has been previously reported. Similarly, in contrast to previous studies (9), in our sample depression severity was not associated with measures of memory and learning. These results suggest that age of depression onset may be an important factor associated with verbal learning and memory dysfunction in older adults with LLD and concurrent executive dysfunction.

This is the first report of the influence of age of onset on cognition among older depressed patients presenting with executive dysfunction. In the current sample all participants were required to exhibit evidence of executive dysfunction, thus we likely limited our ability to detect group differences in this cognitive domain. Previous studies of patients with major depression not selected for executive dysfunction have demonstrated poorer performance on measures of executive functioning in LOD relative to EOD (27) (30). Further, the two depression groups in our sample did not differ with respect to burden of vascular risk factors which is consistent with a number of previous studies (13) (41–43). These findings are, however, relatively inconsistent with previous studies documenting a greater burden of MRI abnormalities associated with cerebrovascular disease in LOD (15, 44). Our findings provide further evidence to suggest that vascular risk measures similar to those utilized in our study may not be good indicators of MRI abnormalities associated with cerebrovascular disease in LLD. Also of interest, ratings of disability severity did not differ between depression groups suggesting that despite poorer cognitive performance, increased disability was not characteristic of LOD with executive dysfunction.

The degree to which verbal learning and memory functioning may represent a phenotypic marker of specific underlying neurodegenerative disease(s) in LOD is not well understood.

There is relatively consistent evidence supporting the impact of cerebrovascular disease on verbal learning and memory performance in LLD and non-depressed adults (45, 46). As such, cerebrovascular disease represents one possible etiology for the cognitive patterns we observed in LOD with executive dysfunction despite a lack of difference between the two groups on ratings of vascular risk factors. Additionally, reports linking LOD to hippocampal volume loss (17), and studies linking hippocampal atrophy to memory performance in LOD (42), suggest that our findings could be also interpreted as suggesting that LOD may be associated with incipient Alzheimer's disease. Our results did not support the role of repeated episodes of major depression as being a primary factor in cognitive dysfunction in this sample. Additional research will be necessary to clarify the etiology of memory and learning dysfunction in LOD.

Our study has several significant strengths including a relatively large sample of older adults with major depression and measures of cognitive functioning in executive functioning, verbal learning, and memory. Further, our statistical approach to control for the effects of education on cognitive performance and our evaluation of depression characteristics as predictors of cognitive functioning are relatively unique. Our study also has limitations. Our measure of vascular risk was not comprehensive, and as a result, the lack of difference on this measure between the two depression groups could reflect poor sensitivity of the measure in identifying cerebrovascular disease. Similarly, our measure of previous depressive episodes did not specify duration of lifetime depression which could be an important consideration for future studies. Additionally, the reliability and validity of self-reported history of age of depression onset, while commonly utilized (8), should be clarified in future studies. Further, our sample was highly selected and therefore our findings may not generalize to the larger population. Finally, nearly all of the cognitive tests we utilized were inter-correlated with each other. While these associations are not unexpected, we do acknowledge that our delineation of cognitive domains based on individual cognitive tests may have limited our ability to recognize broader patterns of differential performance between the two depression onset groups using multivariate analyses.

Conclusions

Among older patients with major depression and executive dysfunction, late onset of depression was associated with poorer memory and verbal learning performance when compared to individuals with early onset of depression, while number of prior depressive episodes and current depression severity was not associated with cognition. Further, in our sample education level was significantly associated with cognitive performance in these domains. The implications of poor memory and learning performance in LOD on treatment outcomes are yet to be demonstrated. However these cognitive characteristics of LOD may be important factors influencing psychotherapy outcomes as psychotherapy interventions require patients to learn and remember information. Similarly these cognitive characteristics may also influence pharmacological interventions given studies documenting the impact of cognitive dysfunction on treatment adherence.

Acknowledgments

Grant support: NIMH grants K08 MH081065, R01 MH063982, R01 0977669, R01 MH064099, P30 MH068638; UCSF Leon J. Epstein Endowment and the Sanchez Foundation.

Dr. Alexopoulos received grant support from Forest and has been a member of speakers' bureaus of Forest, Lilly, Merck, Sunovion, and Novartis.

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Table 1

Pearson Correlations Coefficients Between Cognitive Tests (n=171)

	HVLT-L	HVLT-M	DRS-IP	TMT B	WCST	SCWT
HVLT-L	1.00					
HVLT-M	.734**	1.00				
DRS-IP	.404**	.277**	1.00			
TMT B	−.337**	−.283**	−.245**	1.00		
WCST	.295**	.314**	.108	−.243*	1.00	
SCWT	.270**	.202**	.007	−.189*	.228*	1.00

SCWT = Stroop Color Word Test, DRS-IP = Dementia Rating Scale – Initiation/Perseveration, WCST = Wisconsin Card Sort Test, TMT B= Trail Making Test Part B, HVLT-L = Hopkins Verbal Learning Test-Learning, HVLT-M = Hopkins Verbal Learning Test - Memory

* $p < .05$

** $p < .01$

Table 2

Demographic and Clinical Characteristics of Early and Late Onset Depression groups (n=171)

	Early Onset		Late Onset		Test	*p*
	n	**M (SD)**	**n**	**M (SD)**		
Age	99	70.2 (8.0)	72	77.1 (5.0)	F(1,170) = 41.0	< **0.001**
Education	96	15.7 (2.8)	71	14.9 (2.7)	F(1,166) = 3.0	0.09
HDRS	99	24.7 (4.8)	72	23.0 (3.3)	F(1,170) = 6.4	**0.01**
Age at first MDD Episode	85	39.7 (18.1)	72	75.0 (5.4)	F(1,156) = 254.0	< **0.001**
Number of MDD Episodes	89	2.6 (1.4)	71	1.3 (0.8)	F(1,159) = 94.4	< **0.001**
CMCI	43	38.7 (3.6)	31	38.2 (2.8)	F(1,111) = 0.35	0.55
Vascular risk	68	0.88 (1.2)	56	0.91 (.98)	F(1,124) = 0.02	0.88
WHODAS	94	26.2 (7.3)	66	27.7 (7.4)	F(1,159) = 1.4	0.23

HDRS = Hamilton Depression Rating Scale, CMCI = Charlson Medical Comorbidity Index, WHODAS = World Health Organization Disability Assessment Scale, MDD=Major depression

Table 3

Cognitive Performance for Early and Late Onset Depression Groups (n=171)

	Early Onset (n= 99)		Late Onset (n=72)		Test	*p*
	N	**M (SD)**	**N**	**M (SD)**		
MMSE	95	27.7 (1.6)	70	27.8 (1.7)	F(1,164) = 0.02	0.89
SCWT	95	22.7 (7.4)	71	21.1 (9.1)	F(1,165) = 1.32	0.25
DRS IP	96	32.6 (3.5)	70	32.0 (3.8)	F(1,165) = 1.04	0.30
WCST	94	26.2 (11.1)	66	27.7 (10.9)	F(1,159) = 1.44	0.23
TMT B	87	127.6 (54.7)	57	148.5 (68.0)	F(1,143) = 3.36	0.07
HVLT L	94	21.9 (5.3)	68	19.9 (5.7)	F(1,161) = 4.28	**0.04**
HVLT M	94	7.5 (3.6)	67	6.2 (3.0)	F(1,160) = 4.65	**0.03**

MMSE = Mini Mental State Exam, SCWT = Stroop Color Word Test, DRS-IP = Dementia Rating Scale – Initiation/Perseveration, WCST = Wisconsin Card Sort Test, TMT B= Trail Making Test Part B, HVLT-L = Hopkins Verbal Learning Test-Learning, HVLT-M = Hopkins Verbal Learning Test – Memory.

Note: F Statistic corresponds with the group effect of age of depression onset

Table 4

Summary of Multivariate Regression Analysis for Prediction of Memory Performance in LLD Participants (n=160)

Variable	B	Std. Error	Std. Beta	Test	*p*
Age	−.010	.037	−.026	t(159) = −0.279	.781
Education	.533	.100	.450	t(158) = 5.317	**<.001**
HDRS	−.013	.072	−.016	t(159) = −0.185	.854
Number of previous depressive episodes	−.064	.219	−.027	t(154) = −0.293	.770
Vascular risk factors	−.227	.230	−.082	t(124) = −0.984	.327
Early vs late depression onset	−1.437	.660	−.229	t(159) = −2.176	**.032**

HDRS=Hamilton Depression Rating Scale

Table 5

Summary of Multivariate Regression Analysis for Prediction of Verbal Learning Performance in LLD Participants (n=161)

Variable	B	Std. Error	Std. Beta	Test	*p*
Age	−.086	.070	−.118	t(160) = −1.226	.223
Education	.785	.188	.359	t(159) = 4.174	**<.001**
HDRS	.072	.135	.046	t(160) = 0.534	.594
Number of previous depressive episodes	−.295	.408	−.069	t(155) = −0.722	.472
Vascular risk factors	.016	.431	.003	t(125) = 0.036	.971
Early vs late depression onset	−3.031	1.227	−.265	t(160) = −2.470	**.015**

HDRS=Hamilton Depression Rating Scale