Age and Ageing 1999; **28:** 385–391

Depressive illness, depressive symptomatology and regional cerebral blood flow in elderly people with sub-clinical cognitive impairment

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Abstract

Background: depressive illness in dementia is often assumed to be a unitary clinical phenomenon.
Aim: to describe changes in patterns of depressive symptomatology with time, and associated changes in cerebral blood flow to the frontal and temporal regions.
Method and results: 397 elderly people with sub-clinical cognitive dysfunction were observed over 3 years. Sixteen percent of them developed dementia during the study. The prevalence of depressive symptomatology was higher in this group than in the general population, especially in women, who also had higher recovery rates. A changing profile of depressive symptoms was found in depressed elderly people progressing to dementia, with fewer affective symptoms and increases in agitation and motor slowing. These changes were paralleled by greater reductions in left temporal regional cerebral blood flow than in non-depressed subjects with Alzheimer's disease.
Conclusion: in dementia, there may be two separate and interacting depressive syndromes whose differentiation may be clinically important.

Keywords: *Alzheimer's disease, cerebral blood flow, dementia, depression, elderly, prevalence, incidence*

Introduction

Depression and dementia in old age were once considered to be mutually exclusive. They are now known to occur together, but the relationship between them is unclear. Once categorized as 'pseudodementia' [1], depressive illness is now recognized as a common prodromal feature of dementia, occurring more frequently in those with dementia than in the normal elderly population [2, 3]. Wide variations in depression prevalence rates have been observed in clinical and population studies of dementing elderly subjects, ranging from 15 to 80% [4–7].

Kennedy *et al.* [8] found a relationship between depressive symptomatology and cognitive impairment in women only. Fuhrer *et al.* [9] found co-occurrence of depressive symptoms and cognitive impairment in only 5.5% of a French general population sample, with a higher rate in women. The prevalence of depression may decrease with the severity of the cognitive impairment, possibly due to loss of insight [4, 10, 11].

Does depression co-exist in dementia because of progressive deterioration of the limbic system? Is it a reaction to loss of competence? Do the conditions co-exist, their independent mechanisms masked by the use of the common classification of 'depression'? We have explored these questions by studying depressive symptomatology in a large group of elderly people with sub-clinical cognitive impairment over 3 years, comparing incident cases of dementia with and without depression in terms of symptom profiles and evolution.

Subjects

Subjects were recruited in 1992 from a representative general practitioner research network in the South of France as part of the Eugeria longitudinal

study of cognitive ageing. A proxy screening questionnaire on changes in different aspects of cognitive functioning over the past year, DECO (Détérioration Cognitive Observée), was sent to everyone over 60 in each general practice not meeting the criteria of American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (third version, revised; DSM-IIIR) for dementia. Ninety-three percent of the questionnaires given to the general practitioners were returned to the research centre. (This is likely to be a conservative estimate of refusal rate as it is not known whether all questionnaires were distributed.) This screening instrument, a 19-item Likert scale with a score range of 0–38 (38 indicating no change in any area of cognitive performance), is highly sensitive to early cognitive impairment from various causes [12, 13]. Eight hundred and thirty-three subjects were examined and 397 were found to have observable evidence of decline over the past year in at least one area of cognitive functioning. This cohort was followed for a further 2 years.

Methods

Subjects were visited annually in their homes by one of the project interviewers. A computerized neuropsychometric examination was administered along with a semi-standardized interview with both the elderly person and a nominated proxy. The interview included information on illnesses, medication and hospitalization over the past year, functional ability, family history of dementia and depressive symptomatology. Depressive symptomatology, as described in the Ninth Revision of the International Classification of Diseases (ICD-9) [14], was scored as absent, present or unknown. ICD-9 criteria define a depressive episode as the presence of two or three key symptoms (depression, lack of interest and reduced energy) plus two or more of the remaining symptoms (lack of confidence, guilt, suicide, poor concentration, motor slowing, agitation, sleep difficulties, early waking, loss of appetite and mood changes).

Following the final examination in the third year, subjects had a complete neurological examination based on DSM-IIIR criteria in a neurological clinic specialising in psychogeriatric disorders. All subjects were seen by the same neurologist (J.T.). Regional cerebral blood flow was examined using single-photon emission tomography (HMPAO SPECT). The utility of SPECT in monitoring the evolution of dementia has been consistently demonstrated [15]. However, its potential usefulness in monitoring changes related to depression is uncertain.

Eighty-five SPECT examinations had been conducted at the time of the present analysis. Data were analysed both on the basis of visual inspection and regions of interest (ROI) quantification. Four circular ROI were manually generated on the supra basal ganglia section corresponding to the frontal and the posterior parietal cortices. Two other circular ROI were positioned on the infra basal ganglia section corresponding to the posterior temporal cortices. Hippocampus free-hand ROIs were delimited on coronal slices. Mean counts of the cerebellar cortex (75% max isolevel) were taken for normalization of brain activity.

Results

In the 397 subjects followed longitudinally, the refusal rate was 4% (the most common reason being ill health; subjects often re-entered the study in the following year). Of those participating in all three waves of the survey, 274 (72%) had data recorded on all variables. Demographic variables are summarized in Table 1. Thirty-two percent of subjects were in institutional care in year 1, falling to 27% in year 3 (mainly because of deaths). Eighteen, 19 and 23% of subjects respectively were admitted to hospital in the 3 years of the study. The incidence of dementia between years 1 and 3 was 16% overall and 14% for subjects with Alzheimer's disease (AD). AD and co-existing depressive illness were found in 5% of the total cohort and 29% of those with dementia.

We found that 75.8% of the cohort experienced at least one depressive symptom during the first year, 67.7% in the second year and 75.6% in the third year, with a median of two symptoms being experienced per subject. Table 2 shows the prevalence of depressive symptoms. In this cohort, mood symptoms have a generally lower prevalence than symptoms relating to energy level, concentration and motor slowing, which are observed in about one-third of subjects.

The prevalence of depressive episodes (and exact Poisson 95% binomial confidence intervals; CI [16]) is 19.1% (95% CI: 15.2, 23.4) in the first year, 14.1% (95% CI: 10.5, 18.5) in the second year and 16.7% (95% CI:

Table 1. Demographic characteristics of the 397 people included in the Eugeria cohort

Characteristic	*n* (%)
Age (years)	
64–69	87 (22)
70–79	154 (39)
80–89	128 (32)
90–99	27 (7)
Sex	
Male	118 (30)
Female	278 (70)
Education	
Primary/secondary	306 (52)
Baccalaureat/tertiary	190 (48)

Table 2. Prevalence of depressive symptoms

	Prevalence (%)		
Symptom	Year 1	Year 2	Year 3
Depression	18.6	11.8	12.6
Loss of interest	18.7	14.2	16.2
Lack of energy	46.9	39.7	42.7
Reduced confidence	19.6	18.8	19.0
Guilt	7.9	7.5	5.9
Suicide	5.3	2.6	5.2
Poor concentration	36.6	32.5	34.9
Slowing	36.2	33.3	38.0
Agitation	7.7	6.6	11.3
Difficulty going to sleep	29.7	29.8	32.4
Early waking	28.3	26.0	28.8
Loss of appetite	15.7	18.4	17.1
Mood changes	24.4	25.5	22.1

12.6, 21.5) in the third year. The percentage prevalences of subjects experiencing depressive episodes are given by age and sex in Table 3. A higher prevalence of depressive episodes is found in women, but this finding remains tentative due to the small numbers of men. For this reason, interaction effects between gender and the other variables were not assessed. No difference was found in the prevalence rates between education levels [odds ratio (OR) = 1.0; 95% CI: 0.58, 1.72], however there was a markedly higher prevalence in elderly people living in institutions (OR = 2.4; 95% CI: 1.37, 4.19) and, to a lesser extent, in those with illness (OR = 2.29; 95% CI: 1.3, 4.05).

A logistic regression model [16] was used to demonstrate predictors of depressive episodes. A step-wise method was used for selecting variables (the explanatory variables selected being age-group, sex, place of residence, education, illness, hospitalization). Nested models were compared using the likelihood ratio test and terms were included in the logistic regression model if they reached a 10% level of significance. This procedure demonstrated institutionalization (adjusted OR = 2.55; 95% CI: 1.25, 3.72) and illness (OR = 2.36; 95% CI: 1.35, 4.00) to be the most important predictors of a depressive episode. (Not all subjects hospitalized were ill, so one is not a subset of the other.)

Of those subjects without depression, 9% became incident cases and 53.1% of those with depression recovered. The overall incidence of depression (and exact Poisson 95% CIs) was thus estimated as 90 cases per 1000 person-years (95% CI: 72.4, 110.6). Logistic regression demonstrated that the DECO score (adjusted OR 6.07; 95% CI: 2.99, 12.33) and institutionalization (adjusted OR = 1.85; 95% CI: 0.92, 3.71) were the most significant risk factors for incidence, while time from baseline (adjusted OR = 3.12; 95% CI: 1.18, 8.26) and female gender (adjusted OR = 3.07; 95% CI: 1.03, 9.17) were the most significant factors for recovery from depression.

Taking the 29/30 cut-off point for DECO (which gives 89% sensitivity and 90% specificity for detection of clinical levels of cognitive decline irrespective of cause), significant differences in depressive symptomatology

Table 3. Subjects experiencing depressive episodes

	No. of subjects (% prevalence)		
	Year 1 (n = 73/383)	Year 2 (n = 44/311)	Year 3 (n = 49/293)
Age (years)			
60–69	8 (19.6)	10 (12.7)	7 (9.3)
70–79	28 (19.0)	16 (13.4)	23 (18.9)
80–89	33 (26.4)	13 (13.8)	16 (19.9)
Sex			
Male	18 (15.5)	16 (16.8)	14 (16.1)
Female	55 (20.7)	28 (13.0)	35 (17.0)
Education			
Primary/secondary	38 (19.1)	22 (14.1)	26 (17.7)
Baccalaureat/tertiary	35 (19.1)	22 (14.3)	23 (15.8)
Residence			
Institution	35 (28.9)	20 (24.4)	20 (25.3)
Community	37 (14.5)	24 (10.6)	29 (13.6)
Illness			
Yes	33 (27.7)	24 (22.9)	26 (23.0)
No	36 (14.3)	20 (10.0)	23 (13.2)
Hospitalized			
Yes	18 (27.7)	13 (23.2)	19 (27.5)
No	53 (17.4)	30 (11.9)	30 (13.5)

Table 4. Depressive symptomatology (%) in sub-clinical cognitive impairment (SCCI), depressed and Alzheimer's disease (AD) subjects at years 1 and 3

	Depressive symptomatology (%)							
			Non-AD, depressed		AD			
	SCCI ($n = 232$)		($n = 19$)		Not depressed ($n = 33$)		depressed ($n = 15$)	
	Year 1	Year 3	Year 1	Year 3	Year 1	Year 3	Year 1	Year 3
Depression	1.8	8.9	78.8	25.1	33.0	6.7	100.0	24.8
Loss of interest	5.3	5.3	77.1	35.0	33.3	26.7	78.9	50.0
Lack of energy	14.0	9.3	94.2	65.0	60.0	53.9	100.0	48.0
Reduced confidence	5.3	4.0	55.1	42.5	40.6	19.9	100.0	0.0
Guilt	3.5	1.8	22.4	10.8	20.2	0.0	61.1	0.0
Suicide	1.8	0.0	19.6	15.4	13.3	6.7	40.3	25.0
Poor concentration	12.3	1.8	68.6	59.1	67.0	46.7	100.0	49.8
Slowing	10.5	16.0	65.4	53.8	40.0	46.7	79.7	75.2
Agitation	0.0	9.5	19.6	23.1	21.7	6.7	41.1	100.0
Difficulty going to sleep	17.5	5.8	55.1	43.6	33.0	26.7	42.0	24.9
Early wakening	18.0	15.3	52.0	41.0	20.0	13.3	41.9	25.0
Poor appetite	7.1	12.3	34.0	30.8	27.0	20.2	62.2	23.9
Mood change	7.0	10.5	52.1	35.9	33.3	19.8	80.6	22.8

prevalence were found according to degree of observed cognitive impairment. Overall, 71.6% of the high-scoring group and 88.9% of the low-scoring group experienced at least one depressive symptom. The prevalence of depressive episodes was 14% (95% CI: 10.5, 55.1) amongst high-scorers and 35.6% (95% CI: 26.4, 45.9) amongst low-scorers. The risk of developing depression is estimated to be three times higher in low-scorers than in those with high stability in cognitive functioning (OR = 3.32; 95% CI: 1.86, 5.92). Logistic regression revealed that poor concentration, agitation, lack of interest and age were the factors associated with poorer cognitive performance.

Taking the clinical diagnosis at year 3 as a starting point, depressive symptomatology could be traced back over the past 3 years in order to observe differences in evolution between subjects who subsequently developed dementia and those who did not. Table 4 compares the prevalence of depressive symptomatology at year 1 and year 3 (just before diagnosis) in those who were diagnosed as having depression without dementia, those with AD without depression and those with AD with depression (other forms of dementia were not examined as their prevalence was too low for meaningful analysis). The 'normal' comparison group consists of those people with sub-clinical cognitive impairment only at time one who, over the period of the study, develop neither depressive illness nor dementia. The overall frequency of depressive symptomatology in this sub-clinical cognitive impairment comparison group is far lower than in any of the other groups, and appears to remain stable over the 3 years—apart from some increase in agitation, lack of concentration and loss of confidence, which nonetheless remain much lower than for other groups.

When elderly people with depression only and those later developing depression with AD are compared, both groups show a high frequency of depressive affect with lack of interest, reduced energy and motor slowing in the first year (2 years before the diagnosis of AD). The AD group more frequently report lack of confidence, guilt, problems of concentration, mood change and suicidal ideation. Two years later, depressed elderly people both with and without AD show a drop in the reported frequency of depressive affect, lack of interest and energy, but these levels are still higher than those in subjects without either depression or dementia. In comparison with depressed subjects without AD, the depressed AD group show further reduction in the reporting of affective symptoms (confidence, guilt, depression). Mood swings are also much less commonly reported. In the period just before diagnosis, depressed subjects who develop AD show a marked fall in the reporting of lack of confidence and guilt and a marked increase in symptoms of agitation and motor slowing. Those with AD but without depression report higher rates of depressive symptomatology than the 'normal' group, but do not show the same changes in the patterns of depressive symptomatology (from mood disorders to motor symptoms) over time.

Regional cerebral blood flow examined in the third year within 3 months of the final clinical examination was compared in 'normal' and AD groups with and without depression in Table 5. To demonstrate differences in relative regional blood flow rates in

Table 5. Mean (standard deviation) regional cerebral blood flow (SPECT) in 'normal' (no depression or AD), and AD subjects with and without depression

		AD	
SPECT ROI	'Normal' ($n = 57$)	Not depressed ($n = 11$)	Depressed ($n = 17$)
Frontal left	89.2 (4.2)	83.5 (6.4)	72.0 (7.1)
Frontal right	92.0 (8.1)	89.0 (1.4)	87.0 (4.2)
Parietal left	94.0 (7.2)	91.5 (10.6)	84.5 (6.4)
Parietal right	91.8 (15.8)	93.0 (4.2)	89.5 (5.0)
Temporal left	91.5 (6.3)	84.5 (0.7)	76 (15.6)
Temporal right	89.3 (8.9)	85.5 (2.1)	80.5 (14.8)
Hippocampal left	67.5 (3.2)	62.5 (0.7)	63.0 (4.2)
Hippocampal right	68.0 (3.5)	62.5 (0.7)	60.5 (6.4)

each of the eight cortical regions, ANOVA analyses were conducted taking into account age, education and incident physical illness. No significant differences were found between the 'normal' group and the depressed group without AD. The depressed elderly subjects developing AD demonstrate lower activity in temporal and hippocampal regions than either normal subjects with AD or AD subjects without depression, reaching significance for the left posterior temporal region only ($F = 3.79$; $P < 0.03$).

Discussion

The prevalence of depressive symptomatology in a group of elderly people with sub-clinical cognitive impairment was higher (76% reporting at least one symptom) than the 10–40% reported in previous general population studies [9, 17–20]. In our cohort, the symptomatology reported was principally related to energy levels, concentration and motor slowing rather than mood. The prevalence of depressive illness was 19.1% in the first year, 14.1% in the second and 16.7% in the third year. The lower rate in the second year is probably partly due to drop out and mortality rates, which may in turn be related to depressive symptomatology.

This rate is much higher than that reported in general population studies, and approaches the depression prevalence rates reported in cohorts with dementia. The incidence rate of 90/1000 is also much higher than the rates of 24/1000 and 38/1000 reported for the general population [4, 21], suggesting that subjects with sub-clinical cognitive impairment are at greater risk of depression. The prevalence of depressive symptomatology and depressive illness increase with the severity of the cognitive deficit. Institutionalization and illness are the most important predictors of prevalent depression while institutionalization and rate of cognitive change the main predictors of incident cases. A high recovery rate over 3 years (53%) is also reported.

Elderly people with a recent change in ability to perform everyday activities are three times more likely to develop depressive illness over the next 2 years. Depressive symptoms predictive of poor cognitive performance are problems of concentration, lack of interest and agitation. Symptoms of slowing, guilt, suicide and difficulties in falling asleep were also associated with frontal hypo-metabolism. While depression is more prevalent in women irrespective of health status, women have higher recovery rates. Perhaps women with mild cognitive impairment are more likely to seek care. At clinical examination after 3 years, 16% had dementia. The co-occurrence of dementia and depressive illness is estimated at 5% of the total sample, similar to the proportion in a Bordeaux general population sample [9]. In a recent report we have demonstrated that the combination of depression with AD results in 'excess disability', with accelerated loss of ability to perform everyday activities over and above the disabilities caused by AD alone [22].

AD subjects were examined retrospectively in order to trace the evolution of depressive symptomatology. The group was divided into those with neither dementia or depression, those with depression alone, and those who developed AD with and without a depressive episode in the period before diagnosis. The 'normal' group shows much less reporting of depressive symptomatology. Two years before diagnosis, there is little difference between the depressive symptoms reported by those who do and those who do not go on to develop dementia, but the future AD group do have more problems related to confidence, guilt, concentration, mood change and suicidal ideation.

In the third year, when dementia has reached clinically identifiable levels, depressed subjects with and without dementia have less depressive affect, lack of interest and loss of energy, but still have more depressive symptoms than the non-demented non-depressed group. Depressed subjects who go on to

develop dementia had a change in the pattern of symptoms reported from year 1, with less depressive affect, guilt, lack of confidence and mood swings. Such changes are likely to accompany loss of insight [11, 23]. There is, however, also a marked increase in agitation and motor slowing. On the other hand, while non-depressed elderly people with AD still have more reported depressive symptomatology than those without either depression or AD, these symptoms appear to be relatively stable over time and there is no change in symptom profile from affective to motor symptoms—as seen in the AD plus depression group.

Even at this early stage of the disease, reductions in regional cerebral blood flow were observed in hippocampal, left frontal and left posterior temporal regions in AD subjects both with and without depression. This may be related to the increased reporting of loss of concentration, agitation and motor slowing. These symptoms are not reported as often as in non-depressed AD subjects with similar regional deficits. AD patients with depressive illness show greater deficits in regional cerebral blood flow in the left temporal area and left and right hippocampal regions than AD subjects without depression, although only in left temporal deficits does this reach significance. This may because of the lack of statistical power due to the small numbers examined. Förstl *et al.* [7] have attributed depression in old age to loss of noradrenergic neurons and Krishnan [24] observed lesions in frontal deep white matter in elderly depressed subjects. Our analysis has unfortunately been limited to cortical regions only.

Cerebral imaging was not possible in the first year of our study. This would have provided more reliable information on individual rather than group changes. The findings from this SPECT study should be interpreted with caution as only 85 observations were made. While inability to perform SPECT was principally due to problems of physical health, response bias cannot be excluded. It is not possible for us to assess to what extent the subjects receiving SPECT were representative of either the general population or of elderly people with depressive illness. Our observations should thus be considered tentative, and require confirmation from a larger number of depressed subjects with longitudinal follow-up.

These findings suggest that there may be a change in the nature of the depression in the course of cognitive decline from a principally reactive depressive syndrome, characterized by affective symptoms with loss of confidence (which often accompanies physical illnesses), and a second, principally organic syndrome, characterized by changes in concentration, motor performance and agitation. While this may be in part due to frontal and temporal lesions in AD, differences observed between AD subjects with and without depression suggest an interactive effect. Although depression occurring in a sub-clinical phase of AD may have a large affective and self-esteem component linked to awareness of loss of competence, these aspects may later diminish with lack of insight, and psychomotor and cognitive symptoms will then predominate. Although the one term 'depression' is used to describe the varied depressive symptomatology seen in AD, the single label may cover in fact two separate and interacting syndromes. Such changes in the symptomatic profile should be reflected in a nosological distinction, which may be of importance in the drug treatment of dementia-related depression.

Conclusion

Depressive symptomatology, prevalence and incidence of depressive illness are commoner in elderly people with sub-clinical cognitive impairment than in the general population. Depression progressing to AD initially resembles depression not leading to dementia, although the group that go on to develop AD more frequently report lack of confidence, guilt, mood change and suicidal ideation. Two years later, at the time of diagnosis, depressed subjects with AD report fewer affective symptoms and have higher rates of agitation and motor slowing. The change in the character of the symptoms raises the possibility of two separate interacting syndromes.

Key points

- Subjects with decline in everyday activities in the previous year are three times more likely to develop depressive illness in the following 2 years.
- Over time, elderly people with dementia and depression report fewer affective, reactive symptoms and greater agitation and motor slowing.
- These clinical changes are paralleled by greater reductions in left temporal regional cerebral blood flow compared with non-depressed subjects with Alzheimer's disease.
- The results suggest two separate and interacting depressive syndromes whose differentiation may be important for clinical management.

Acknowledgements

The authors wish to thank the Fondation de France, the French Social Security (CNAM-TS) and the Direction Générale de la Santé for their financial support of this project. We are also indebted to the Eugeria project interviewers J. Faurobert and C. Gonzalez who have ensured our high response rates.

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Received 16 October 1997; accepted in revised form 24 August 1998