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# **Neurological signs and late-life depressive symptoms in a community population: the ESPRIT study**

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## **Abstract**

### **Objective**

**Depression in the elderly is common and often resistant to treatment. It has been suggested that late-life depression may be related to underlying neurobiological changes, however these observations are derived from diverse clinical samples and as yet have not been confirmed in a more representative population study.**

**Our aim was to investigate associations between neurological signs as markers of underlying brain dysfunction and caseness for depression in an elderly community sample, controlling for physical health and comorbid/past neurological disorders.**

### **Method**

**A cross-sectional analysis of 2102 older people without dementia from the ESPRIT project. Depressive symptomatology was ascertained using the CES-D and abnormal neurological signs/comorbidity from a full neurological examination according to ICD-10 criteria.**

### **Results**

**Pyramidal, extrapyramidal, cranial nerve and sensory deficit signs were significantly associated with case-level depressive symptoms, but were more likely to be present in participants with a previous history of neurological disorder.**

### **Conclusions**

**We confirmed previous findings of an association between neurological signs and case-level depressive symptoms in late-life. However, this suggests that depression in late-life may reflect either the severity of comorbid neurological disorder or perhaps widespread neurodegeneration.**

**Author Keywords** Neurological signs ; Late-life Depression ; Depressive symptoms ; Old age ; Neurodegenerative theory

## **INTRODUCTION**

Depression occurring in late-life is common (estimated at 13.5% in community samples) (Beekman et al., 1997) and often resistant to treatment. Numerous studies have suggested that the causes of depression in the elderly may be different from that occurring in young adults, in that, depression in late-life is essentially related to neurobiological changes (Alexopoulos et al., 2005). Neuroimaging studies have suggested associations with brain atrophy and white matter hyperintensities (Baldwin and O'Brien, 2002; Ballmaier et al., 2004). Neurological signs are a further marker of underlying dysfunction but have received relatively little attention. Simpson et al. (Simpson et al., 1998) found that extrapyramidal, frontal, pyramidal signs and motor sequencing dysfunction were more likely to be found in people with late-life depression, particularly amongst those who were treatment resistant, compared to controls. More recently, Baldwin et al. (Baldwin et al., 2005) reported neurological signs consistent with subcortical-frontal (gaze impersistence and primitive reflex dysfunction) and frontal-striatal (motor sequencing) dysfunction in people with late-onset depression. These studies have suggested that such signs may be indicators of a vascular disorder and may point to a 'vascular hypothesis' for depression in late-life, but they have not ruled out the possibility that depression in late-life and the presence of neurological signs, may be symptomatic of wider neurodegeneration.

Such investigations have focused on clinical samples and have yet to be replicated in a community population. Furthermore, the extent to which these neurological signs are accounted for by comorbid neurological conditions has yet to be clarified. In a secondary analysis of data from a large community population who had received a comprehensive neurological examination, we investigated associations with case-level depressive symptoms and the extent to which these signs occurred in the absence of a formal neurological diagnosis.

## **METHODS**

The Enquête de Santé Psychologique – Risques, Incidence et Traitement (ESPRIT) study is an ongoing prospective population cohort study of late-life mental health that commenced in March 1999, sampling the elderly population of Montpellier in south east France ( Ritchie et al., 2004 ).

### **Study sample**

Random sampling was carried out separately for each of the 15 electoral registers of the Montpellier District between the dates of March 1999 and February 2001, in order to obtain 1/15 of the total population for the purposes of the ESPRIT study; an epidemiological study of psychiatric disorder in the elderly. Eligible people were those who were aged 65 years or older, community residents living in Montpellier's city or suburbs and registered on the electoral rolls, at the time of recruitment. Of those randomly selected, 24% did not participate and 3.3% were excluded on grounds of severe disability. Non-participants were replaced by other participants drawn from the same electoral register through an additional random sampling procedure so that each electoral division was equally represented. Non-participants were slightly older than participants and more likely to live alone (Ritchie et al., 2004 ). The study design and procedure was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and all participants gave written informed consent.

### **Measurements**

Participants were examined at a clinical research centre in the Gui de Chauliac Neurology Hospital, a research centre established for the purposes of the study. Housebound participants were visited and assessed at their homes, by a neurologist and a nurse, both with specialist geriatric training. Each participant's general practitioner was also contacted to verify information given by the participant. Participants with mild cognitive or sensory difficulties were assisted by a carer or close relative.

The neurological assessments were carried out by one of two neurologists. These consisted of a standardised neurological examination based on ICD-10 criteria (World Health Organization, 1992 ). Abnormalities were coded as present or absent in the following categories: motor deficits, coordination deficits, cranial nerve abnormalities, muscular tone abnormalities, abnormal movements, difficulty standing, gait abnormalities, reflex abnormalities, sensory system abnormalities, trophic and sphincter abnormalities. Extrapyramidal and pyramidal signs were also coded as present or absent. Information was also obtained by the neurologist on participants' lifetime histories (past and/or present) of neurological disorders with confirmation by general practitioners where necessary. Participants' scores on the depression scale were not known at the time of the neurological examination.

The Center for Epidemiologic Studies Depression scale (Radloff, 1977 ) was administered by a study interviewer (either nurse or psychologist with training in psychogeriatrics). Caseness for depressive symptoms was defined as a score of 16 points or above, which has been previously found to have a sensitivity of 100% and a specificity of 88% for major depression in an elderly Dutch (Beekman et al., 1997 ) and is now widely used.

Information was also collected on sociodemographic status, history of head trauma and all medical disorders currently being treated. Education was classified into four categories: low (5 years of schooling or less), medium low (6–9 years), medium high (10–12 years) and high (more than 12 years). The Instrumental Activities of Daily Living Scale (Lawton, 1988 ), was used as an assessment of disability and was entered into analyses as a binary variable using a 0|1 cut-off.

### **Statistical analysis**

All analyses were carried out with the Statistical Package for the Social Sciences Database (SPSS) version 12.1. Caseness on the CES-D was treated as a binary dependent variable and all analyses were restricted to participants with CES-D data. Participants with dementia ascertained in the study were excluded. For hypothesis testing, four independent variables were chosen a priori for primary analyses: i) motor deficits; ii) extrapyramidal deficits; iii) pyramidal deficits; and iv) coordination deficits. The following independent variables were considered in secondary analyses: cranial nerve abnormalities, muscular tone abnormalities, abnormal movement, difficulty standing, gait abnormalities, reflex abnormalities, sensory deficit, sphincter abnormalities and trophic abnormalities. Baseline characteristics were initially summarized for the total sample and for those with or without case-level depressive symptoms. Unadjusted associations were then investigated between the dependent variable and all primary and secondary independent variables. Further regression analyses were then carried out for all four primary independent variables and for any secondary independent variables which were significantly associated with case-level depressive symptoms in unadjusted analyses. These associations were then sequentially adjusted for potential confounders, age and sex (model 1), age, sex and education (model 2), model 2 and disability (model 3) and finally model 3 plus head trauma (model 4). As a secondary procedure, the final adjusted odds ratios from model 4 were further stratified by presence or absence of a lifetime history of neurological disorder.

## **RESULTS**

The sample consisted of 2234 participants. Of these, 132 participants ascertained to have dementia according to ICD-10 criteria ( World Health Organization, 1992 ), were excluded from the analysis, which resulted in a final sample of 2102 participants. Characteristics of the sample are summarised in Table 1 .

Prevalence of case-level depressive symptoms was 30.0%. This is in line with that reported previously for the same population ( Ritchie et al., 2004 ) and provides us with one of the best samples to investigate into depression in late life. Participants with case-level depressive symptoms were older, had lower education and were more likely to be female, to have IADL impairment and a previous neurological disorder. Characteristics of the sample are further described in Table 2 with respect to neurological signs in those with or without a lifetime history of diagnosed neurological disorder. Reflex, cranial nerve and sphincter abnormalities were the most commonly ascertained signs.

Associations between neurological signs and CES-D status are summarised in Table 3 . All neurological signs were more frequent in those with case-level depressive symptoms. Statistically significant associations were found for two of the four primary exposures (pyramidal and extra-pyramidal deficits) and for four of the secondary exposures (cranial nerve abnormalities, standing difficulty, gait abnormality, and sensory deficit).

Adjusted associations between neurological signs and CES-D status are summarised in Table 4 .

Both pyramidal and extra-pyramidal deficits remained significantly associated with case-level depressive symptoms after full adjustment (Model 4, total sample) with odds ratios little changed in strength. The same was the case for associations with cranial nerve abnormalities and sensory deficits. Associations with standing difficulty and gait abnormality were reduced substantially in strength following adjustment and were no longer significant in the fully adjusted model. In a final analysis, these associations were examined separately for those with or without a diagnosed lifetime history of neurological disorder. Upon stratification for a lifetime history of neurological disorder, all associations were most strong in participants with a lifetime history of neurological disorder and, apart from sensory deficits, all odds ratios were close to null values in those without a previous diagnosis.

## **DISCUSSION**

In a well-characterised community population, we investigated the association between neurological signs and case-level depressive symptoms in late life. We were able to confirm previous findings of associations for pyramidal and extra-pyramidal signs (two out of four signs investigated as primary hypotheses), and further secondary analyses identified associations with cranial nerve abnormalities and sensory deficits (two out of nine signs investigated). All these associations were independent of age, sex, education, disability and reported previous head injury. However, they appeared to be principally confined to those in the sample with a diagnosed lifetime history of neurological disorder.

### **Methodological issues**

Advantages of this study include the community-based sample which is likely to be representative of the source population. The sample size was large which allowed the population-level relationship between neurological signs and late-life depressive symptoms to be accurately quantified. Ascertainment of exposure status (neurological signs) was carried out by neurologists blind to outcome status (depressive symptoms), reducing the likelihood of information bias. Information on the most likely confounding factors was collected and taken into account in the analysis. Because this analysis is derived from a cross-sectional sample, prevalence bias cannot be excluded: associations between neurological signs and depression may therefore either represent an increased risk of incident depression in people with neurological signs, or a reduced risk of recovery, or both. The outcome measure used to ascertain depression status was a brief, albeit widely used, screening instrument rather than a diagnostic interview. It is possible therefore that misclassification may have obscured associations and negative findings should be viewed with caution. The neurological examination used in this study was based on ICD-10 criteria (World Health Organization, 1992 ). Other studies of neurological signs in late life depression (Baldwin et al., 2005 ; Simpson et al., 1998 ) have used the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989 ), which was primarily developed for assessment of neurological signs in schizophrenia and focuses on previous neurological findings for this particular disorder. The neurological examination in this study was designed to detect all pathologies, unlike the NES scale; however, greater detail was also given to motor signs, which may provide an unrepresentative picture of neurological abnormalities.

### **Primary analyses**

The findings in this study are at variance with those of Simpson et al. (Simpson et al., 1998 ) and Baldwin et al. (Baldwin et al., 2005 ) as motor deficits and coordination were not found to be significant even before adjustment for potential confounders. However, the finding of a significant association between extrapyramidal and pyramidal signs and case-level depressive symptoms, even after adjustment, were in accordance with the study reported by Simpson et al. (Simpson et al., 1998 ). With respect to the organic processes that may underlie at least some cases of late-life depression, the presence of pyramidal signs, as found in this study, have been hypothesised to indicate

cerebrovascular disease (Orell and Wade, 1996 ). Extrapyramidal signs have been linked to deep white matter hyperintensities and basal ganglia abnormalities and hence have also been hypothesised to have a vascular basis (Simpson et al., 1998 ). Extrapyramidal signs may be an expression of vascular disruption to limbic-cortical-striatal-pallidal-thalamic circuits (Simpson et al., 1998 ). Further neuroimaging research may be helpful to clarify the extent to which structural or functional abnormalities underlie the observed associations.

Significant findings between depressive symptomatology and extrapyramidal and pyramidal signs became non-significant upon stratification for a lifetime history of neurological disorder. Moreover, a trend was found that indicated that those who had case-level depressive symptoms were more likely to experience extrapyramidal and pyramidal neurological signs if they had a past or present history of neurological disorder. These findings suggest that extrapyramidal and pyramidal signs may not be risk factors in their own right, but may represent an underlying neuropathophysiology, an expression of which, is late-life depression.

### **Secondary analyses**

Considering findings from secondary analyses, Baldwin et al. (Baldwin et al., 2005 ) had found particular reflex abnormalities to be associated with depression, but we were not able to confirm this. Associations between sensory system abnormalities and case-level depressive symptoms were found in our study, similar to the findings by Negash et al. (Negash et al., 2004 ) for bipolar I disorder. Our finding of cranial nerve abnormalities associated with case-level depressive symptoms has, to our knowledge, not been identified before. Since it was derived from multiple analyses, it should be viewed with caution and requires replication in other samples. The neurological signs examined as part of the analyses also showed non-significance when stratified by lifetime history of neurological disorder. Again, higher associations were found in those with a lifetime history of neurological disorder which indicates that the relationship between neurological signs and case-level depressive symptoms in late-life can largely be explained by wider neurodegeneration.

### **Underlying causal pathways**

Cross-sectional data, such as that analysed here, cannot demonstrate causal relationships, merely correlation. As prospective neurological data are not yet available for analysis, it was impossible to draw firm conclusions regarding direction of causation. Neurological signs may be a manifestation of sub-clinical cerebrovascular disease. Stroke is associated with a high risk of depression ( Pohjasvaara et al., 1998 ) which appears to be sustained many years afterwards in survivors and which is not fully explained by associated disability (Stewart et al., 2001 ). White matter hyperintensities have also been found to be associated with late life depression (Herrmann et al., 2008 ) suggesting associations with sub-clinical cerebrovascular disease. However prospective studies are lacking to clarify the causal relationship between cerebrovascular disease and depression.

An alternative explanation for the association is that neurological signs represent a measure of the severity of a pre-existing disorder. In this respect, it is noteworthy that strengths of association were close to the null in the absence of a diagnosed lifetime history of neurological disorder (Table 4 ). For all exposures, the associations were stronger in those with a lifetime history of neurological disorder than in the group without. It is possible that this is an over-restrictive category since the most prominent neurological signs may have been taken to indicate a neurological disorder as part of the assessment. Firm conclusions are limited, as restricting analysis to those with neurological disorders would lead to a smaller sample and wider confidence intervals. However, neurological signs were not uncommon in participants without a lifetime history of neurological disorder (Table 2 ).

As neurological signs were more strongly associated with late-life depressive symptoms in the presence of other neurological disorders in this study, this may suggest that neurological abnormalities could more likely be explained by neurodegenerative changes. These may compromise key neural networks and eventually lead to vulnerability to depression as well as later dementia (Emery and Oxman, 1992 ). The association, therefore, between depression and neurological signs may simply be an expression of wider neurodegeneration that increases with age, providing support for a neurodegenerative aetiology theory of late-life depression. Prettyman (Prettyman, 1998 ) found that extrapyramidal signs were present in participants without neurological disease, and that the presence of these signs increased with age.

Further support for the involvement of degenerative processes has come from findings of associations between depression and general cognitive decline (Lyketsos et al., 2002 ; Yaffe et al., 1999 ), and those which suggest that late-life depression is associated with increased risk of later dementia (Geerlings et al., 2000 ; Green et al., 2003 ). For this reason, it has been hypothesised that depression in late-life may represent early neurodegeneration, culminating in dementia onset (Barnes et al., 2006 ; Chen et al., 1999 ). The functional impact of physical disorders is recognised to be an important component in risk of depression (Prince et al., 1998 ). Although several of the associations reported here remained significant after adjusting for functional status, it is possible that neurological signs are associated with other personal impacts of the underlying conditions which are not captured by conventional disability scales. Neurological signs may provide further insight into the pathophysiology of late-life depression and other psychiatric disorders. However causal pathways underlying this association remain unclear, and further research is required to clarify whether associations represent an underlying process with both physical and neurological manifestations or modifiable physical or psychological risk factors for depression.

### **Key points**

- Extrapyramidal, pyramidal, cranial nerve and sensory deficit signs were significantly associated with case-level depression but were more likely to be present in those with a lifetime history of neurological disorder.
- This suggests that neurological signs in those with case-level depressive symptoms, may better be explained by widespread neurodegeneration rather than being risk factors in their own right.
- Depressive symptomatology in late-life may therefore be a warning sign of early neurodegeneration, which is known to be an indicator for later dementia onset.

## Footnotes:

**CONFLICT OF INTEREST:** There is no conflict of interest.

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**Table 1**

Characteristics of the sample – demographic and health-related data

	Frequency (%)		
	Total sample (n=2102)	CES-D non-cases (n=1472)	CES-D cases (n=630)
Age:			
65–69 yrs	490 (23.3)	378 (25.7)	112 (22.9)
70–72 yrs	488 (23.2)	347 (23.6)	141 (22.4)
73–77 yrs	402 (19.1)	279 (19.0)	123 (19.5)
77yrs +	722 (34.3)	468 (31.8)	254 (40.3)
Gender:			
Male	875 (41.6)	694 (47.1)	181 (28.7)
Female	1227 (58.4)	778 (52.9)	449 (71.3)
Education:			
5 yrs or less	509 (24.2)	344 (23.4)	165 (26.2)
6–9 yrs	620 (29.5)	411 (27.9)	209 (33.2)
10–12 yrs	475 (22.6)	323 (22.0)	162 (24.1)
12 yrs +	497 (23.6)	393 (26.7)	104 (16.5)
IADL <sup>†</sup>			
No impairment	1938 (92.0)	1379 (93.9)	559 (88.9)
Impairment	160 (8.0)	90 (6.1)	70 (11.1)
Past head injury			
No	1912 (91.2)	1336 (91.1)	576 (91.4)
Yes	184 (8.8)	130 (8.9)	54 (8.6)
Lifetime history of neurological disorder			
No	1514 (72.0)	1124 (76.4)	390 (61.9)
Yes	588 (28.0)	348 (23.6)	240 (38.1)

(Data missing: education 1, IADL 4, past head injury 6)

<sup>†</sup> Instrumental Activities of Daily Living Scale (IADL) impairment

**Table 2**

Characteristics of the sample – neurological signs

	Prevalence of neurological sign (%)	
	No lifetime history of neurological disorder (n=1514)	Lifetime history of neurological disorder (n=588)
Motor deficit	1.3	7.3
Extra-pyramidal deficit	0.5	4.9
Pyramidal deficit	1.8	6.5
Coordination deficit	0.1	0.4
Cranial nerve abnormality	17.8	25.9
Muscle tone abnormality	3.5	8.7
Abnormal movement	10.0	21.9
Standing difficulty	5.7	11.9
Gait abnormality	9.3	19.6
Reflex abnormality	68.5	76.9
Sensory deficit	3.0	9.7
Sphincter abnormality	28.0	35.4
Trophic abnormality	4.3	3.4

**Table 3**

Frequencies of neurological signs by caseness by the CES-D

Neurological deficit	Frequency (%)			Odds ratio (95% CIs)
	Total sample (n=2102)	CES-D non-cases (n=1472)	CES-D cases (n=630)	
Primary analyses				
Motor deficit	3.0	2.7	3.5	1.29 (0.76–2.19)
Extra-pyramidal deficit	1.8	1.3	2.9	2.24 (1.17–4.30)
Pyramidal deficit	3.1	2.4	4.8	2.05 (1.25–3.36)
Coordination deficit	0.5	0.2	0.3	2.81 (0.86–9.25)
Secondary analyses				
Cranial nerve abnormality	20.1	18.8	23.2	1.31 (1.04–1.64)
Muscle tone abnormality	5.0	4.6	5.9	1.30 (0.86–1.97)
Abnormal movement	13.4	12.9	14.4	1.14 (0.87–1.49)
Standing difficulty	7.4	6.3	10.0	1.64 (1.17–2.29)
Gait abnormality	12.2	10.8	15.4	1.51 (1.15–1.98)
Reflex abnormality	70.8	70.3	72.2	1.10 (0.89–1.35)
Sensory deficit	4.9	4.1	6.7	1.68 (1.12–2.52)
Sphincter abnormality	30.1	30.2	29.8	0.99 (0.80–1.21)
Trophic abnormality	4.1	3.7	4.9	1.35 (0.86–2.13)

**Table 4**

Logistic regression analysis of the association between neurological signs and case-level depression (CES-D) after adjustment for other covariates. Odds ratios are displayed with 95% confidence intervals following sequential adjustment and stratification.

	Unadjusted	(1) Adjusted for age and sex	(2) Model 1 plus education	(3) Model 2 plus disability <sup>†</sup>	(4) Model 3 plus previous head trauma		
					Total sample	Lifetime neurological disorder absent	Lifetime neurological disorder present
Primary analyses							
Motor deficit	1.29 (0.76–2.19)	1.43 (0.83–2.47)	1.45 (0.84–2.50)	1.28 (0.73–2.25)	1.28 (0.73–2.25)	0.94 (0.32–2.80)	1.09 (0.54–2.17)
Extra-pyramidal deficit	2.24 (1.17–4.30)	2.19 (1.12–4.28)	2.16 (1.10–4.23)	2.04 (1.04–4.03)	2.04 (1.03–4.01)	0.79 (0.15–4.23)	1.80 (0.82–3.99)
Pyramidal deficit	2.05 (1.25–3.36)	2.10 (1.26–3.50)	2.07 (1.24–3.45)	1.93 (1.15–3.23)	1.92 (1.15–3.22)	1.06 (0.45–2.48)	2.47 (1.20–5.09)
Coordination deficit	2.81(0.86–9.25)	2.90 (0.84–10.01)	2.94(0.83–10.41)	2.55(0.70–9.30)	2.56(0.70–9.30)	1.21(0.09–16.56)	2.51 (0.54–11.76)
Secondary analyses							
Cranial nerve abnormalities	1.31 (1.04–1.64)	1.28 (1.01–1.61)	1.32 (1.04–1.67)	1.30 (1.03–1.65)	1.29 (1.02–1.63)	1.09 (0.80–1.48)	1.43 (0.97–2.12)
Difficulty standing	1.64 (1.17–2.29)	1.34 (0.95–1.90)	1.32 (0.94–1.87)	1.24 (0.87–1.76)	1.24 (0.87–1.76)	0.98 (0.59–1.60)	1.27 (0.73–2.21)
Gait abnormality	1.51 (1.15–1.98)	1.40 (1.10–1.86)	1.41 (1.10–1.88)	1.30 (0.97–1.75)	1.32 (0.98–1.77)	1.00 (0.66–1.53)	1.50 (0.95–2.39)
Sensory deficit	1.68 (1.12–2.52)	1.84 (1.21–2.79)	1.85 (1.21–2.81)	1.80 (1.18–2.75)	1.80 (1.18–2.74)	1.37 (0.70–2.66)	1.63 (0.91–2.91)

<sup>†</sup> Instrumental Activities of Daily Living Scale (IADL) impairment