



Neuroanatomical and neuropsychological features of elderly euthymic depressed patients with early- and late-onset

Christophe Delaloye ^{a,b,*}, Guenaël Moy ^a, Fabienne de Bilbao ^a, Sandra Baudois ^a, Kerstin Weber ^a, Françoise Hofer ^a, Claire Rago Paquier ^a, Alessia Donati ^c, Alessandra Canuto ^a, Umberto Gardini ^a, Armin von Gunten ^c, Raluca Iona Stancu ^c, François Lazeyras ^d, Philippe Millet ^e, Philip Scheltens ^f, Panteleimon Giannakopoulos ^{a,c}, Gabriel Gold ^g

^a Division of Geriatric Psychiatry, University Hospitals of Geneva and Faculty of Medicine, Switzerland

^b Faculty of Psychology and Science of Education, University of Geneva, Switzerland

^c Division of Old Age Psychiatry, University Hospitals of Lausanne, Hospices-CHUV, Switzerland

^d Department of Radiology, University Hospitals of Geneva, Switzerland

^e Clinical Neurophysiology and Neuroimaging Unit, University Hospitals of Geneva, Switzerland

^f Alzheimer Center and Department of Neurology, VU Medical Center, Amsterdam, The Netherlands

^g Department of Rehabilitation and Geriatrics, University Hospitals of Geneva, Switzerland

ARTICLE INFO

Article history:

Received 8 March 2010

Accepted 25 August 2010

Available online 17 September 2010

Keywords:

Depression

Onset age

Cognition

Neuroimaging

Older adults

Euthymia

ABSTRACT

Background: Whether or not cognitive impairment and brain structure changes are trait characteristics of late-life depression is still disputed. Previous studies led to conflicting data possibly because of the difference in the age of depression onset. In fact, several lines of evidence suggest that late-onset depression (LOD) is more frequently associated with neuropsychological deficits and brain pathology than early-onset depression (EOD). To date, no study explored concomitantly the cognitive profile and brain magnetic resonance imaging (MRI) patterns in euthymic EOD and LOD patients.

Method: Using a cross-sectional design, 41 remitted outpatients (30 with EOD and 11 with LOD) were compared to 30 healthy controls. Neuropsychological evaluation concerned working memory, episodic memory, processing speed, naming capacity and executive functions. Volumetric estimates of the amygdala, hippocampus, entorhinal and anterior cingulate cortex were obtained using both voxel-based and region of interest morphometric methods. White matter hyperintensities were assessed semiquantitatively.

Results: Both cognitive performance and brain volumes were preserved in euthymic EOD patients whereas LOD patients showed a significant reduction of episodic memory capacity and a higher rate of periventricular hyperintensities compared to both controls and EOD patients.

Conclusion: Our results support the dissociation between EOD thought to be mainly related to psychosocial factors and LOD that is characterized by increasing vascular burden and episodic memory decline.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Amongst patients who suffer from late-life depression, 30% to 50% display deficits across a wide range of cognitive domains [1]. Even more than in younger cohorts [2], some cognitive deficits in old age may represent trait characteristics of depression that persist despite the amendment of symptoms [3]. However, this viewpoint has been challenged by prospective studies showing that depression at baseline is not necessarily associated with an increased risk of subsequent cognitive decline [4]. These discrepancies might be partly explained by

age differences relative to the onset of depression among elderly patients. Recent studies suggest that the patterns of both neuropsychological deficits and structural imaging changes vary substantially between late-onset depression (LOD) and early-onset depression (EOD) [1,5,6]. LOD has been traditionally associated with more frequent and rapid cognitive decline as well as more severe structural brain abnormalities compared to age-matched controls and EOD patients [1,6]. In particular, literature reported executive dysfunction to be a characteristic of LOD whereas episodic memory dysfunction is present both in LOD and EOD [1]. Consistent with the presence of dysexecutive impairment in LOD, neuroimaging studies [7] revealed a frontostriatal disruption caused by subcortical, white matter and periventricular hyperintensities. In contrast, EOD cases display selective hippocampal volume loss [8] underlying the episodic memory impairment.

* Corresponding author. Service de Psychiatrie Gériatrique, Hôpitaux Universitaires de Genève, 2 Chemin du Petit-Bel-Air, 1225 Chêne-Bourg, Switzerland. Tel.: +41 22 305 51 30; fax: +41 22 305 50 44.

E-mail address: Christophe.Delaloye@hcuge.ch (C. Delaloye).

There are two main methodological limitations of these studies. Most of them explored separately structural changes and neuropsychological performances. Most importantly, they included acutely depressed patients and did not provide further insight into their persistent abnormalities. To address these issues, we performed a prospective group study (EOD, LOD and controls) including a detailed neuropsychological assessment and MRI investigation.

2. Methods

2.1. Participants

Thirty EOD patients (depression onset before 60), eleven LOD patients (depression onset after 60), and thirty healthy controls were included. The diagnosis of depression or the absence of a psychiatric condition was established using the Mini International Neuropsychiatric Inventory Interview. Euthymia was defined according to *DSM-IV* criteria, namely the absence of depressive symptoms for at least two months. In addition, all participants had to obtain a score below 5 on the 15 item Geriatric Depression Scale (GDS) at inclusion. Exclusion criteria for all groups were: 1) history of major neurological disorders, 2) the presence of a current or a past *DSM-IV* psychiatric diagnosis (other than depression), 3) the presence of dementia, and 4) current systemic medical disease requiring inpatient treatment. Physical health status was examined with the Charlson Comorbidity Index (CCI). Following the formal acceptance of the research protocol by the local ethics committee, written informed consent was obtained from all participants.

2.2. Cognitive measures

2.2.1. Processing speed

(I) In a simple reaction time test, participants had to press a key as quickly as possible when the visual signal stimulus appeared. The score of interest was the mean latency of the 120 test trials. (II) In the Color Trail Making Test part A, participants had to connect a series of 25 circled numbers in numerical order as quickly as possible. Time to complete the task was taken into consideration.

2.2.2. Working memory

(I) In a computerized reading span test, participants had to complete a single and a dual condition. In the single condition, participants had to decide whether each one of the 16 sentences, presented sequentially, was semantically correct as fast and accurately as possible. In the dual condition, the participants additionally had to memorize the final word of each sentence. Sixteen series, from two to five sentences, were presented. Recall took place at the end of each series. The retained score was the mean number of correctly recalled words; (II) In the Letter-number sequence task, participants had to listen to letters and numbers and then recall all the numbers in ascending order, followed by all the letters in alphabetical order. The score of interest was the number of correct sequences produced.

2.2.3. Executive function

(I) In the Stroop color, participants had to complete two subtests. The first subtask displayed solid color patches in one of four colors. The second subtask contained color words printed in an incongruous ink color. In each subtask, participants had to name the ink color of the stimuli as quickly and accurately as possible. Completion time for each subtask was the dependent measure. The score of interest was the interference effect which was computed by a relative ratio [(subtask 2 – subtask 1)/subtask 1]; (II) In the Color-trail making test part B (for part A see [Processing speed](#) section), participants had to shift sets by connecting numbers in an increasing order while alternating color-patterns. The time needed to complete each part

was the dependent measure. The score of interest was the flexibility cost [(part B – part A)/part A].

2.2.4. Episodic memory

(I) In the Cued recall 48 items test (CR 48), participants had to learn 48 different words, belonging to 12 different semantic categories, with the help of semantic cues. A cued recall task, using semantic categories as a cue, was performed. The score of interest was the number of words correctly recalled; (II) In the CERAD Word List Memory test, participants had to memorize a list of ten words that was presented over three trials. The total number of words recalled correctly across the three trials was the dependant measure.

2.3. MRI procedures

MRI imaging was performed at 3 T. Coronal slices were obtained from 3-dimensional MPRAGE sequence with the following parameters: TR 2500 ms, TE 2.94 ms, TI 1100 ms, flip angle 9°, isotropic resolution of 0.9 mm³, acquisition time 520 s. In addition, 3-dimensional T2 weighted imaging was obtained with the following parameters: TE = 383 ms, TR = 3200 ms, FOV = 230 mm, acceleration factor (parallel imaging) 2, matrix size 256 × 256 × 240.

2.4. Assessment of WMH

Assessment of white matter lesions was performed in T2-weighted sequences with the Scheltens semiquantitative scale [9].

2.5. ROI analysis

Anterior cingular and entorhinal cortices, as well as hippocampal and amygdala perimeters were traced manually on each contiguous coronal slice using a ROI procedure of ANALYZE software (version 8, Mayo Foundation). Neuroanatomic boundaries of the hippocampus and amygdala were based on those of Watson et al. [10]. Anatomic guidelines for outlining the entorhinal and anterior cingular cortices were those described by Bernasconi et al. [11] and Sassi et al. [12] respectively. Normalized volumes for brain regions of interest were determined by using the following formula: [absolute volume in mm³/intracranial volume (ICV) in mm³] × 1.000.

2.6. Voxel-based morphometry

Standard processing, using SPM5 software, was employed to analyze MRI for voxel-based morphometry (VBM) [13]. Images were segmented using the standard T1 template and a priori gray matter, white matter and CSF atlases provided by SPM. Spatially normalized (1 × 1 × 1 mm³) data were modulated to account for local volume changes due to non linear co-registration. Gray matter images were smoothed with a 8-mm Gaussian kernel.

2.7. Statistical analysis

Comparisons between groups for continuous variables were performed using a one-way independent analysis of variance. To respect assumptions of normality and homogeneity of variance data were modified prior to analysis by means of logarithmic or power 2 transformations. In the absence of normalisation, non-parametric tests were used. Comparisons of categorical variables were performed with a Pearson's Chi-Square. Linear regression models were also built with cognitive parameters or vascular lesions as the dependent variables and diagnostic group and age as the independent variables.

3. Results

3.1. Demographics and clinical characteristics

The demographic and clinical characteristics of the series are summarized in Table 1. Among the three groups there were no significant differences in gender, education and somatic comorbidity as assessed by the CCI. EOD patients were significantly younger than controls ($U=205.50$, $p<0.001$) and LOD patients ($U=22.00$, $p<0.001$). Patients were already under treatment at inclusion. We did not interfere with their medication as the treatment was prescribed naturalistically. 73% of LOD patients and 50% of EOD patients received regular antidepressant medication (selective serotonin reuptake inhibitors). This treatment was associated in 10% of the EOD cases and 27% of the LOD cases with benzodiazepines and in 3% of the EOD cases and 18% of the LOD cases with atypical antipsychotics. Only one LOD case received concomitantly antidepressants, antipsychotics, and benzodiazepines.

3.2. MRI data

Table 2 summarizes the mean rating score of WMH according to the Scheltens semiquantitative scale. Periventricular hyperintensities score differed among our three groups ($H(2)=13.00$, $p<0.01$) and were significantly higher in LOD patients compared to controls ($U=58.50$, $p<0.001$, $r=0.51$) and EOD patients ($U=57.00$, $p<0.001$, $r=0.52$). The severity of deep white matter and basal ganglia hyperintensities was comparable between the three groups. Except 2 LOD cases, there were no hyperintensities in infratentorial area in the present series.

The mean normalized volumes of each brain ROI by group of participants are reported in Table 2. There were no significant differences in entorhinal cortex and amygdala volume between our three groups. There was a trend for reduced hippocampal ($F(2, 68)=2.97$, $p=0.06$) and anterior cingulate ($F(2, 68)=3.03$, $p=0.06$) volume in LOD patients. However, this trend did not persist after adjustment for age in linear regression models. The VBM analysis confirmed the absence of statically significant difference in gray matter volumes between our three groups.

3.3. Cognitive test performance

Performances on cognitive tests are provided in Table 3. With respect to processing speed, the simple reaction time test and the part A of the color trail making test revealed no significant differences among our three groups. This was also the case for working memory assessed by the mean number of words correctly recalled in the reading span task and the score of the sequence-letter sequence test.

Table 1
Demographic and clinical characteristics.

Characteristics	Groups					
	Controls (N=30)		EOD (N=30)		LOD (N=11)	
	M	(SD)	M	(SD)	M	(SD)
Age in years	70.83	(6.78)	65.00	(4.24)	75.82	(6.48)
Education ^a	13.50	(3.68)	14.43	(3.31)	12.64	(4.20)
Score GDS (max 15) ^b	1.97	(1.52)	2.47	(1.63)	2.36	(1.63)
Score CCI (max 19) ^c	0.63	(0.85)	0.63	(0.85)	0.55	(0.82)
Age at depression onset (years)	–	–	35.67	(14.51)	74.09	(7.19)
Duration of depressive illness (years)	–	–	29.33	(14.72)	1.73	(1.42)
Gender (% women)	73.33	80.00	63.64			

^a Number of years of education completed.

^b Geriatric Depression Scale.

^c Charlson Comorbidity Index.

Table 2

White matter hyperintensity scores for EOD patients, LOD patients and controls.

	Groups						H/F ^a	p
	Controls (N=30)		EOD (N=30)		LOD (N=11)			
	M	(SD)	M	(SD)	M	(SD)		
<i>Scheltens' scale scores</i>								
Periventricular hyperintensities	0.83	(1.05)	0.80	(0.96)	2.45	(1.44)	13.00	0.002
WMH in deep white matter	2.87	(4.99)	3.23	(4.13)	6.45	(6.30)	5.39	0.068
Basal ganglia	0.40	(1.10)	0.13	(0.43)	0.73	(1.85)	0.94	0.625
Infratentorial	0.00	(0.00)	0.00	(0.00)	0.73	(1.68)	–	–
<i>Mean normalized volumes of the brain region of interest^b</i>								
Hippocampal Total	3.65	(0.53)	3.61	(0.43)	3.26	(0.37)	2.97	0.058
Entorhinal cortex Total	1.17	(0.20)	1.09	(0.23)	1.04	(0.15)	1.97	0.148
Anterior cingulate cortex Total	2.64	(0.49)	2.73	(0.64)	2.26	(0.33)	3.03	0.055
Amygdalar Total	1.70	(0.26)	1.69	(0.25)	1.63	(0.18)	0.34	0.519

^a Statistical comparisons were made using Kruskal–Wallis test/analysis of variance (ANOVA).

^b Mean normalized volumes: [(absolute volume of ROI in mm³/intracranial volume in mm³) × 1.000].

Executive functions were also preserved in EOD and LOD patients. The relative ratios measuring interference cost induced by the Stroop effect and switching cost evaluated by the color trail making test were not significantly different compared to controls.

For episodic memory, a significant group difference was observed for the cued recall score of the CR 48 items test ($F(2, 68)=4.16$, $p<0.05$) as well as for the total recall score of the CERAD word list memory test ($F(2, 68)=8.26$, $p<0.01$). Post-hoc analyses using the Bonferroni post hoc criterion for significance indicated that LOD patients ($M=17.73$, 95% CI [14.72, 20.73]) obtained a significantly lower total recall score on the CERAD word list memory test compared to controls ($M=22.17$, 95% CI [20.77, 23.56], $p<0.01$, $r=0.46$) and EOD patients ($M=22.70$, 95% CI [21.59, 23.81], $p<0.01$, $r=0.55$). Similarly, LOD patients ($M=23.55$, 95% CI [18.44, 28.65]) obtained a significantly lower cued recall score on the CR 48 items test compared to controls ($M=29.07$, 95% CI [26.96, 31.18], $p<0.05$, $r=0.37$) and EOD patients ($M=29.10$, 95% CI [26.78, 29.67], $p<0.05$, $r=0.39$). Importantly, linear regression analysis revealed that these differences were still present after adjustment for age. Among EOD patients, duration of illness had no impact on ROI volumes, WMH scores and cognition after control for age.

4. Conclusion

The preservation of both cognition and brain structures in euthymic EOD patients, in particular episodic memory capacity and hippocampal volume, as well as the absence of deleterious effect of the duration of illness does not support the hypothesis of a progressive neurotoxic effect of depression [8]. Our results parallel several lines of evidence supporting the preservation of cognitive abilities in elderly patients with EOD after remission [4,6]. In particular, Brodaty et al. [4] found no evidence for long-term cognitive deficits following depressive episodes even after 25 years of follow-up. It is worth mentioning that in the present study we carefully excluded all lifetime psychiatric comorbidities such as substance abuse, known to influence neuropsychological performances and hippocampal volumes [14]. This might explain the difference between our findings and those of certain previous studies in this field [3,8].

Unlike EOD, LOD patients showed decreased performances limited to episodic memory tasks. Although one could argue that this finding may be primarily due to confounding factors such as medication, this is an unlikely scenario since we indexed episodic memory capacity by

Table 3
Neuropsychological performances in EOD patients, LOD patients and controls.

Cognitive function	Task	Groups						H/F ^a	p
		Controls (N = 30)		EOD (N = 30)		LOD (N = 11)			
		M	(SD)	M	(SD)	M	(SD)		
Processing speed	Simple reaction time ^b	336.92	(74.77)	299.72	(48.48)	312.00	(54.22)	2.26	0.112
	Latencies in ms CTM part 1 ^{b,c}	59.03	(19.45)	52.80	(16.45)	60.55	(19.95)	1.03	0.361
Working memory	Latencies in sec. Reading span: Score	2.27	(0.54)	2.40	(0.59)	2.04	(0.38)	1.77	0.178
	Letter-number sequence Score	10.40	(2.72)	9.90	(1.83)	8.55	(2.16)	4.92	0.085
Executive function	Stroop color Relative ratio	2.00	(0.55)	2.45	(0.59)	2.10	(0.55)	2.48	0.091
	CTM ^c Relative ratio	1.04	(0.59)	0.91	(0.55)	1.33	(0.66)	3.66	0.161
Episodic memory	Cued recall 48 Score	29.07	(5.65)	29.10	(5.34)	23.55	(7.59)	4.16	0.020
	Cerad 10 words: Total recall score	22.17	(3.74)	22.70	(2.98)	17.73	(4.47)	8.26	0.001

^a Statistical comparisons were made using Kruskal–Wallis test/Analysis of variance (ANOVA).

^b Data were transformed prior to analyses (logarithmic or power 2 transformation).

^c CTM = Color Trail Making Test.

using the RI-48 item test that controls for cognitive processing during encoding. In contrast to free recall tests, this procedure involves cued recall and minimises the effect of impaired attention, inefficient strategies or reduced processing capacity that could result from these factors [15]. Moreover, the episodic memory impairment cannot be attributed to the co-existence of dementia since we carefully excluded all of these cases. In line with our results, two recent studies found a reduction of episodic memory capacity in LOD patients compared to controls and EOD patients [2,16]. Moreover, Thomas et al. [2] observed that none of their LOD patients developed dementia during a four-year follow-up suggesting that incipient Alzheimer's disease is not the explanation of the larger verbal memory impairment identified in LOD group. The significant increase of periventricular hyperintensities in our LOD group may partly explain the observed cognitive deficits. In fact, recent contributions pointed to a possible vascular origin of episodic memory impairment both in population-based samples and LOD cohorts [5,17].

To our knowledge, this is the only study that compared concomitantly the cognitive profile and the brain structural characteristics of elderly patients who recovered from EOD or LOD. Additional strengths of the present study include the careful exclusion of lifetime psychiatric comorbidities as well as physical burden, control for demographic variables and duration of depression, detailed assessment of cognitive performances, volumetric analyses as well as assessment of WMH. Two limitations should also be taken into account. First, we cannot exclude that the lack of significant between-group differences on some measures may be due to an insufficient sample size. Second, the effect of additional clinical parameters such as the number of previous episodes and history of psychotic symptoms was not addressed.

In conclusion, our observations support the distinction between the aetiological mechanisms implicated in the pathogenesis of LOD and EOD [1]. While LOD may be more driven by acquired pathology such as vascular burden, genetic background and personality dimensions may be the most important determinants of EOD.

5. Conflict of interest

This research was supported by the Swiss National Science Foundation (SNSF grant no 3200BO-112018). The SNSF had no further role in study design; in collection, analysis and interpretation of the

data; in the writing of the report; and in the decision to submit the paper for publication. All authors declare that they have no conflict of interest.

Acknowledgments

The authors thank Abba Moussa, Corina Meiler-Mittel, Karsten Ebbing, Montserrat Mendez Rubio, Françoise Lanet and Reto Meuli for their contribution to this work. This work was also supported by the Center for Biomedical Imaging (CIBM) of the Geneva-Lausanne Universities and the EPFL.

References

- [1] Herrmann LL, Goodwin GM, Ebmeier KP. The cognitive neuropsychology of depression in the elderly. *Psychol Med* 2007;37(12):1693–702.
- [2] Thomas AJ, Gallagher P, Robinson LJ, Porter RJ, Young AH, Ferrier IN, et al. A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychol Med* 2009;39(5):725–33.
- [3] Bhalla RK, Butters MA, Mulsant BH, Begley AE, Zmuda MD, Schoderbek B, et al. Persistence of neurocognitive deficits in the remitted state of late-life depression. *Am J Geriatr Psychiatry* 2006;14(5):419–27.
- [4] Brodaty H, Luscombe G, Anstey KJ, Cramsie J, Andrews G, Peisah C. Neuropsychological performance and dementia in depressed patients after 25-year follow-up: a controlled study. *Psychol Med* 2003;33(7):1263–75.
- [5] Takahashi K, Oshima A, Ida I, Kumano H, Yuuki N, Fukuda M, et al. Relationship between age at onset and magnetic resonance image-defined hyperintensities in mood disorders. *J Psychiatr Res* 2008;42(6):443–50.
- [6] Kohler S, Thomas AJ, Barnett NA, O'Brien JT. The pattern and course of cognitive impairment in late-life depression. *Psychol Med* 2009;1–12.
- [7] Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry* 2008;79(6):619–24.
- [8] Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry* 2004;161(4):598–607.
- [9] Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, et al. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci* 1993;114(1):7–12.
- [10] Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, et al. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 1992;42(9):1743–50.
- [11] Bernasconi N, Bernasconi A, Andermann F, Dubeau F, Feindel W, Reutens DC. Entorhinal cortex in temporal lobe epilepsy: a quantitative MRI study. *Neurology* 1999;52(9):1870–6.
- [12] Sassi RB, Brambilla P, Hatch JP, Nicoletti MA, Mallinger AG, Frank E, et al. Reduced left anterior cingulate volumes in untreated bipolar patients. *Biol Psychiatry* 2004;56(7):467–75.

- [13] Mechelli A, Price CJ, Friston KJ, Ashburner J. Voxel-based morphometry of the human brain: methods and applications. *Curr Med Imaging Rev* 2005;1:105–13.
- [14] Chanraud S, Reynaud M, Wessa M, Penttila J, Kostogianni N, Cachia A, et al. Diffusion tensor tractography in mesencephalic bundles: relation to mental flexibility in detoxified alcohol-dependent subjects. *Neuropsychopharmacology* 2009;34(5):1223–32.
- [15] Ivanoiu A, Adam S, Van der Linden M, Salmon E, Juillerat AC, Mulligan R, et al. Memory evaluation with a new cued recall test in patients with mild cognitive impairment and Alzheimer's disease. *J Neurol* 2005;252(1):47–55.
- [16] Dillon C, Allegri RF, Serrano CM, Iturry M, Salgado P, Glaser FB, et al. Late- versus early-onset geriatric depression in a memory research center. *Neuropsychiatr Dis Treat* 2009;5:517–26.
- [17] Potter GG, McQuoid DR, Steffens DC, Welsh-Bohmer KA, Krishnan KR. Neuropsychological correlates of magnetic resonance imaging-defined subcortical ischemic depression. *Int J Geriatr Psychiatry* 2009;24(3):219–25.