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Research report

Volumetric MRI changes, cognition and personality traits in old age depression

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ABSTRACT

Background: The presence of cognitive and structural deficits in euthymic elderly depressed patients remains a matter of debate. Integrative aetiological models assessing concomitantly these parameters as well as markers of psychological vulnerability such as persistent personality traits, are still lacking for this age group.
Methods: Cross-sectional comparisons of 38 elderly remitted patients with early-onset depression (EOD) and 62 healthy controls included detailed neuropsychological assessment, estimates of brain volumes in limbic areas and white matter hyperintensities, as well as evaluation of the Five-Factor personality dimensions.
Results: Both cognitive performances and brain volumes were preserved in euthymic EOD patients. No significant group differences were observed in white matter hyperintensity scores between the two groups. In contrast, EOD was associated with significant increase of Neuroticism and decrease of Extraversion facet scores.
Limitations: Results concern the restricted portion of EOD patients without psychiatric and physical comorbidities. Future longitudinal studies are necessary to determine the temporal relationship between the occurrence of depression and personality dimensions.
Conclusions: After remission from acute depressive symptoms, cognitive performances remain intact in elderly patients with EOD. In contrast to previous observations, these patients display neither significant brain volume loss in limbic areas nor increased vascular burden compared to healthy controls. Further clinical investigations on EOD patterns of vulnerability in old age will gain from focusing on psychological features such as personality traits rather than neurocognitive clues.

1. Introduction

Early-onset depression (EOD) is usually defined by an onset of the first major depressive episode before 60 years of age. In older adults, EOD has been described as a distinctive phenomenological entity as opposed to late-onset depression (Brodaty et al., 2001; Rapp et al., 2005), reflecting possible differences in

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aetiology, neurophysiological patterns and guidance of antidepressant treatment. Depression in old age is a multi-facet disorder that may affect not only mood regulation but also cognition, brain structure and personality. During acute depressive phases, deficits in processing speed, working memory (Nebes et al., 2000), executive function (Baudic et al., 2004), and episodic memory (Rapp et al., 2005) have been described in the elderly. Even more than in younger cohorts (Paelecke-Habermann et al., 2005; Paradiso et al., 1997), some cognitive deficits in old age may represent trait characteristics of depression that persist despite the amendment of symptoms (Lee et al., 2007; Rapp et al., 2005). 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 (Brodaty et al., 2003; Dufouil et al., 1996). Consistent with the presence of state-independent memory impairment (Rapp et al., 2005), a substantial loss of hippocampal volume bilaterally has been described in elderly patients with early-onset depression compared to age-matched controls (Bell-McGinty et al., 2002; Sheline et al., 1999). This finding might reflect decreased neurogenesis (Kempermann and Kronenberg, 2003) or toxic effect of glucocorticoids on the hippocampus (Campbell and MacQueen, 2004; Post, 1992). In the same line, studies in both younger and elderly patients with a history of recurrent depression reported reduced frontal and parietal lobe volumes as well as frontal and anterior cingulate cortex hypometabolism (Ballmaier et al., 2004; Drevets et al., 1997; Martinot et al., 1990). In contrast to volumetric changes, vascular pathology and in particular deep white matter hyperintensities (WMH) have been traditionally associated with late-onset depression in hospital-based samples (Takahashi et al., 2008). However, a community-based study reported no difference in vascular burden between patients with EOD and late-onset depression (Janssen et al., 2006).

Besides its cognitive and neuroanatomical correlates, EOD is thought to be associated with persisting changes of personality dimensions (Brodaty et al., 2001). Referring to the Five-Factor Model of personality (Costa and McCrae, 1992), high levels of Neuroticism not only predispose to depressive reactions (Kendler et al., 1993; Liang-Lin et al., 2007), but may be present even in remitted young patients (Maier et al., 1992). However, other studies reported that Neuroticism and Extraversion were unrelated to depression (Santor et al., 1997; Shea et al., 1996). In young cohorts, recovered EOD patients showed decreased Extraversion, Conscientiousness, and increased Agreeableness (Anderson and McLean, 1997; Bagby et al., 1997; Barnett and Gotlib, 1988). In older patients, similar data are still rare. In a 6 year follow-up on 1511 elderly, Steunenberg et al. (2006) showed that Neuroticism was a main predictor of the onset of depressive symptoms in late life and that personality was a more powerful determinant of depression than physical health-related and social factors. Neuroticism has been shown to remain significantly higher in elderly patients who recovered from depression (Abrams et al., 1991).

Two main limitations explain the difficulty to draw definite conclusions about the long-term impact of EOD on cognition, brain structure and personality in the elderly. First, the vast majority of earlier studies in younger cohorts were based on routine neuropsychological measures, such as the Mini-Mental State Examination, which often fail to identify changes in restricted cognitive sub-domains (Royall and Mahurin, 1994), and have demonstrated a relatively low sensitivity to detect cognitive impairment associated with sub-cortical vascular lesions (Nys et al., 2005). Most importantly, studies in geriatric populations mostly focused on late-onset depression and limited their analysis on neuropsychological and neuroimaging parameters, neglecting psychological vulnerability markers. No study attempted to explore the relationship of these three trait characteristics in the same EOD sample.

The main goal of this study was to investigate concomitantly the neurocognitive and psychological characteristics of euthymic patients with EOD. In particular, we aimed to explore whether the long-term evolution of EOD is associated with persistent cognitive deficits and MRI structural alterations. We also hypothesized that changes in personality dimensions occur in EOD patients in the absence of acute depressive symptoms. The cross-sectional comparison between euthymic EOD and healthy elders included detailed neuropsychological evaluation, assessment of both volumetric changes in limbic areas and vascular burden and extensive investigation of personality profiles according to the Five-Factor Model. The statistical analysis included three parts. The first concerned group comparisons for each of the three sets of data (i.e. cognitive, MRI and personality factors and facets). Subsequently, covariates that are known to influence cognitive performances, brain volumes and personality (such as age, gender, education, nature and severity of depressive illness) were introduced in multivariate linear regression models. Finally, the possible correlations between the three sets of data were also explored.

2. Methods

2.1. Participants

Inclusion criteria for both groups were defined as 60 or more years, good French-speaking capacities, and absence/presence of EOD. Diagnosis of EOD and absence of psychiatric disorder in healthy controls was established using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) administered by a senior psychiatrist. Patients were recruited in geriatric psychiatry divisions of the University Hospitals of Geneva and Lausanne (Switzerland). Controls were recruited in elderly-specific clubs (such as gym classes, social and leisure activities, etc.) and via advertisements in local newspapers. Following the formal acceptance of the research protocol by the local ethics committee, written informed consent was obtained from all participants before inclusion in the study. Participation was voluntary and unpaid.

Subjects with history of major neurological disorders or head trauma, current or a past DSM-IV psychiatric diagnosis (other than depression), or systemic medical disease requiring inpatient treatment were excluded. Absence of dementia was defined according to DSM-IV criteria and a Mattis Dementia Rating Scale (DRS) total score lower than 1.5 standard-deviation below the mean. The final series included 38 patients with EOD and 62 healthy controls. Current euthymia was also defined according to the DSM-IV criteria, namely the absence of depressive symptoms for at least two months. Physical health status was examined with the Charlson Cormorbidity Index (Charlson et al., 1987) encompassing 19 medical conditions weighted 0–6.

2.2. Neuropsychological evaluation

A comprehensive neurocognitive battery was administered in two sessions of 1.5 h each and included the global Mattis Dementia Rating Scale (DRS, Mattis, 1976) as well as specific measures of processing speed, working memory, episodic memory and executive functioning. Interviewers and raters were blind to the participant's group, as well as to the neuroimaging data and personality profiles.

Processing speed was assessed with a computerized simple reaction time task adapted from Hultsch et al. (2000), composed of 5 blocks of 24 trials each. Participants were invited to press a key button as quickly as possible after a visual signal stimulus had appeared on the screen. A warning stimulus pseudo-randomly preceded the signal stimulus according to five inter-stimulus intervals to avoid response learning.

Working memory was evaluated in two different tasks. A computerized adaptation of the reading span test (De Ribaupierre and Ludwig, 2003) assessed participants' ability to perform active processing of a target stimulus while simultaneously buffering other information in working memory. Subjects were asked to maintain in memory the last word of a series of two to five sentences while judging whether each sentence was semantically correct or not. The Corsi Block-Tapping Task (Wechsler Memory Scale, Wechsler, 1997), a nonverbal analogue of the digit span, measuring visuo-spatial memory, was used to assess subject's ability to reproduce a sequence of locations in an array as previously tapped by the investigator, both in forward and backward order.

In respect to episodic memory, a memory test based on delayed cued recall (Ivanoiu et al., 2005), the CR48 Test, has been developed to distinguish between poor memory due to concurrent factors such as depression and impairments related to neurodegenerative processes such as Alzheimer disease. The task comprises 48 different items, belonging to 12 different semantic categories, and participants were asked to encode items with the help of semantic cues, followed by immediate cued recall, and to perform a delayed cued recall using the categories, on completion of an interference task.

Executive functioning assessment included measures on inhibition, mental flexibility, updating and verbal fluency. A computerized version of the Stroop colour-naming task (Stroop, 1935) recorded participants' response latencies in three conditions (congruent, incongruent and control), measuring inhibition of word reading in favour of colour naming. Stroop effect was calculated by a relative ratio controlling for overall speed differences between subjects (De Frias et al., 2006). Mental flexibility was assessed by a computerized version of the number–letter measure (Rogers and Monsell, 1995), a task-switching paradigm, which requires participants to alternate as quickly and accurately as possible between two tasks, namely deciding whether a number is odd or even or whether a letter is a consonant or a vowel, depending on the position of a number–letter pair on the computer screen. A computerized consonant updating task (De Ribaupierre et al., 1999), inviting subjects to update and monitor working memory contents, presented 12 lists of 4, 6 or 8 consonants. Subjects were not informed about the length of the list, yet they were asked to rehearse only the last four items in their correct order. Again, relative ratio was used to determine switching and updating costs. Verbal fluency (adapted from Cardebat et al., 1990) required subjects to generate in a limited amount of time as many words as possible beginning with a phonemic (P) respectively a semantic (animals) cue.

2.3. Structural imaging assessment

For each subject, a third session included MRI scans, which were acquired with a 3 T device (Siemens). Coronal slices were obtained from a 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 mm^3, acquisition time 8 min 40 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 $256 \times 256 \times 240$.

Volumetric estimates of the amygdala, hippocampus, anterior cingular and entorhinal cortices were determined both by morphometric and voxel-based methods. The perimeters of these areas were defined using a region of interest (ROI) procedure of ANALYZE software (version 8, Mayo Foundation). Neuroanatomic boundaries of the hippocampus and amygdala were based on those of Watson et al. (1992). Anatomic guidelines for outlining the entorhinal and anterior cingular cortices were those described by Bernasconi et al. (1999) and Sassi et al. (2004) respectively. References to sagital and horizontal planes were performed whenever necessary to improve identification of structure boundaries. Each brain structure was delimited by a manual contour from which the corresponding volume was calculated using the Analyze software. The total volume of each structure was calculated by summing all values obtained from ROIs applied on consecutive slices. Intracranial volumes (ICV), defined as all gray and white matter in the cerebrum (including cerebellum and stem) as well as the cerebrospinal fluid, were measured automatically from the segmented images. Normalized volumes for brain regions of interest were determined by using the following formula: (absolute volume in mm^3/ICV in mm^3) × 1.000. All measurements were performed by a trained rater blind to the participant's group. SPM5 software was used to analyze MRI for Voxel-Based Morphometry (VBM) (Mechelli et al., 2005). Images were segmented with SPM5 using the standard T1 template and a priori gray matter, white matter and CSF atlases provided by SPM. Spatially normalized ($1 \times 1 \times 1$ mm^3) 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.

Periventricular and deep white matter lesions were assessed in T2-weighted sequences with the Scheltens semiquantitative scale (Scheltens et al., 1993). Periventricular hyperintensities were rated as 0 = absent, 1 = ≤5 mm, or 2 = >5 mm and <10 mm. WMH were rated as 0 = no abnormalities, 1 = <3 mm and $n \leq 5$, 2 = <3 mm and $n > 6$, 3 = 4–10 mm and $n \leq 5$, 4 = 4–10 mm and $n > 6$, 5 = ≥11 mm and $n > 1$, 6 = confluent, in frontal, parietal, occipital and temporal white matter. Basal ganglia (caudate nucleus, putamen, globus pallidus, thalamus and internal capsule) and infratentorial foci hyperintensities were similarly rated from 1 to 6.

2.4. Personality assessment

Personality was self-assessed with the French NEO-Personality Inventory (Rolland, 1998). Based on the Five-

Factor Model, the NEO PI-Revised (Costa and McCrae, 1992) is an empirically derived assessment tool that explores five personality traits. *Neuroticism* is defined as the tendency to experience negative affect. Subjects who score high on Neuroticism are prone to experience feelings such as anxiety, angry hostility, depression, self-consciousness (emotions of shame or embarrassment), impulsiveness, and vulnerability to environmental stress. *Extraversion* includes interpersonal traits such as degrees of warmth, gregariousness (desire to be with other people), and assertiveness, as well as temperamental traits such as intensity of activity, excitement seeking and experiencing of positive emotions. The *Openness to experience* factor focuses on six different areas: fantasy and imagination, aesthetics, feelings, actions, ideas and values. Individuals with marked *Agreeableness* are trusting, believe the best of others, and rarely suspect hidden intents, just as they are themselves straightforward, compliant, modest, and tender minded. *Conscientiousness* characterizes individuals who think of themselves as being competent, ordered, achievement striving, self-disciplined, thinking carefully before acting, and having a strong sense of dutifulness.

The NEO PI-R consists of 240 statements, rated on a five-point agreement scale, which are organized into five personality traits (factors), each factor being subdivided into six facets. Widely used in the general population, its utility has also been demonstrated in psychiatric samples (Bagby et al., 1999). Each subject received the personality questionnaire during the interview and returned it after completion.

2.5. Statistics

Comparisons between patients and controls for continuous variables were performed using two-sample *t*-test with unequal variances. The normality of data distribution was verified with skewness and kurtosis tests. To normalize the distribution of data, usual logarithmic transformations were applied. In the absence of normalisation, Wilcoxon rank-sum test was used. Comparisons of categorical variables were performed with Fisher's exact test. Linear regression models were also built with cognitive parameters, volumetric estimates, vascular lesions, and NEO-PI factor/facet scores as the dependent variables and diagnostic group, socio-demographic (age, gender, education), history of depression (length of disease, age of onset), and number of depressive episodes (single/recurrent) as the independent variables. In order to avoid a significant reduction of our sample, we did not adopt the strategy of age matching. Importantly our previous study on neurocognitive and neuroimaging features in bipolar populations (see Delaloye et al., 2009) indicated that the choice to work on pair-wise age-matched groups dramatically reduced sample sizes, but led to similar conclusions as multivariate analysis including age as additional independent variable. Spearman rho correlation coefficient was used to examine the relationship between ROI and NEO-PI data in our EOD sample. To limit multiple comparison biases, only p values smaller or equal to 0.01 were considered statistically significant. Data were analyzed with Stata statistical computer software, version 10.1 (Stata Statistical Software: Release 10.1 [computer program]. College Station, Texas, USA: Stata Corporation; 2007).

3. Results

3.1. Demographics and clinical characteristics (Table 1)

As summarized in Table 1, no group differences were observed for education and gender, participants being predominantly women with 13–14 years of education. Controls were significantly older than EOD patients ($Z=3.67$, $p<0.001$). Both groups did not differ in respect to their score on the Charlson Cormorbidity Index, indicating an overall good physical health status in both samples. 27 patients (71%) had two or more depressive episodes, while the remaining 11 (29%) patients showed one single episode. 89% (34 patients) followed a pharmacological treatment. 47% (18 patients) received regular anti-depressant medication (selective serotonin reuptake inhibitors), while 23% (9) took benzodiazepines and 13% (5) hypnotics.

3.2. Cognitive test performance (Table 2)

The DRS showed no significant difference ($Z=-0.007$, $p=0.994$) in overall cognitive performance between depressed patients and healthy controls (Table 2). In respect to processing speed, the simple reaction time task ($t(90)=-1.06$, $p=0.289$) revealed no significant group differences. This was also the case for working memory performances assessed by correctly recalled words ($Z=-0.29$, $p=0.770$) and number of errors ($Z=1.02$, $p=0.305$) in the reading span task, and the visuo–spatial forward ($t(77)=0.51$, $p=0.611$) and backward ($Z=-0.33$, $p=0.738$) memory spans. Similarly, there were no differences in the number of correctly listed words in the CR48 delayed recall ($t(75)=-0.03$, $p=0.973$).

Executive functions were also preserved in EOD patients. The relative ratios measuring additional cost induced by the Stroop effect ($t(84)=0.05$, $p=0.957$), and switching costs evaluated by the number–letter task ($Z=-0.03$, $p=0.973$), were not significantly different from healthy controls. Likewise, updating and monitoring of working memory did not distinguish the two groups, neither for the 6 ($t(72)=0.03$, $p=0.974$) nor the 8 ($t(80)=0.09$, $p=0.925$) consonants lists or the cost ratio. Finally, there were no significant differences neither for phonemic cue ($t(76)=-1.23$, $p=0.219$) nor semantic cue ($t(69)=-0.36$, $p=0.715$) verbal fluency.

3.3. MRI characteristics (Table 3)

Group comparisons showed no significant differences between EOD patients and healthy controls for the whole

Table 1
Demographic and clinical characteristics.

	EOD ($N=38$)		Controls ($N=62$)	
	Mean	(SD)	Mean	(SD)
Age (years)	66.11	(6.22)	71.10	(7.26)
Education (years)	14.24	(3.18)	12.92	(3.30)
Charlson Comorbidity Index (scores 0–6)	0.74	(1.03)	0.55	(0.82)
Age at depression onset (years)	37.76	(14.75)	–	–
Duration of depressive illness (years)	28.45	(15.79)	–	–
Gender (% women)	81%	($N=31$)	77%	($N=48$)

Table 2
Cognitive test performances in EOD patients and healthy controls.

		EOD ($N=38$)	Controls ($N=62$)		
Cognitive function	Task	Mean (SD)	Mean (SD)	t/Z [a]	p
Overall cognition	DRS [b] (total score) [c]	139.08 (5.13)	139.65 (3.13)	$Z=-0.007$	0.994
Processing speed	Reaction time (ms) [c]	301.26 (51.59)	319.84 (72.89)	$t=-1.06$	0.289
Working memory	Reading span (words) [c]	2.36 (0.58)	2.33 (0.51)	$Z=-0.29$	0.770
	Reading span (errors) [c]	0.74 (1.70)	0.87 (1.23)	$Z=1.02$	0.305
	Block-tapping (forward) [c]	7.37 (1.40)	7.52 (1.42)	$t=0.51$	0.611
	Block-tapping (backward) [c]	6.63 (1.82)	6.81 (1.63)	$Z=0.33$	0.738
Episodic memory	CR48 (delayed recall)	28.39 (5.98)	28.35 (5.74)	$t=-0.03$	0.973
Executive functioning	Stroop (cost ratio) [c]	0.26 (0.11)	0.26 (0.13)	$t=0.05$	0.957
	Number–letter (cost ratio)	0.26 (0.17)	0.25 (0.12)	$Z=-0.03$	0.973
	Updating (6 consonants) [c]	12.37 (2.71)	12.47 (2.27)	$t=0.03$	0.974
	Updating (8 consonants) [c]	12.24 (2.85)	12.29 (2.81)	$t=0.09$	0.925
	Verbal fluency (phonemic)	23.47 (7.31)	21.63 (7.10)	$t=-1.23$	0.219
	Verbal fluency (semantic)	31.95 (9.59)	31.26 (8.31)	$t=-0.36$	0.715

[a] Statistical comparisons were made using t-test/Wilcoxon test.
[b] DRS = Mattis Dementia Rating Scale.
[c] Data were transformed prior to analysis.

brain volume ($t(61)=1.42$, $p=0.158$), nor for the different regions of interest, namely the total hippocampus ($t(71)=0.48$, $p=0.632$), amygdala ($t(67)=0.13$, $p=0.897$), entorhinal cortex ($t(62)=1.31$, $p=0.193$), and anterior cingulate cortex ($t(64)=-0.57$, $p=0.568$). Separate analyses in each hemisphere led to the same conclusions (see Table 3). The VBM analysis confirmed the absence of statistically significant difference in gray matter volumes between EOD patients and healthy controls (height threshold: $T=5.19$ (for $p<0.05$), extent threshold: $k=0$ voxels; degrees of freedom = [1.0, 82.0]). The severity of periventricular ($Z=0.58$, $p=0.560$), deep white matter ($Z=-0.03$, $p=0.975$), basal ganglia ($Z=1.48$, $p=0.137$), and infrantentorial foci ($Z=1.0$, $p=0.620$) hyperintensities were also comparable between the two groups.

3.4. Personality profiles (Table 4)

Contrasting with the negative neuropsychological and MRI data, group comparisons revealed significant differences between healthy controls and EOD patients for Neuroticism and Extraversion facets (Table 4). Patients scored significantly higher than controls on Neuroticism ($t(69)=-2.62$, $p=0.010$) and two of its facets, namely Anxiety (N1, $t(68)=-2.61$, $p=0.011$) and Depression (N3, $t(66)=-3.10$, $p=0.002$). In respect to Extraversion, patients scored significantly lower on two facets: Warmth (E1, $t(89)=2.96$, $p=0.003$) and Positive Emotions (E6, $t(64)=2.93$, $p=0.004$). Factor and facet scores for Agreeableness, Conscientiousness and Openness to experience were not significantly different between the two groups.

Table 3
MRI data in EOD patients and healthy controls for regions of interest.

		EOD ($N=38$)	Controls ($N=62$)		
		Mean (SD)	Mean (SD)	t/Z [a]	p
Whole brain (ICV) [b]		1525.60 (162.88) [c]	1578.48 (148.33)	$t=1.42$	0.158
Hippocampus	Total [b]	3.58 (0.45) [d]	3.63 (0.52)	$t=0.48$	0.632
	Left [b]	1.74 (0.23)	1.76 (0.26)	$t=0.30$	0.759
	Right [b]	1.83 (0.23)	1.87 (0.27)	$t=0.62$	0.536
Amygdale	Total	1.67 (0.25)	1.68 (0.27)	$t=0.13$	0.897
	Left [b]	0.83 (0.15)	0.83 (0.13)	$t=-0.06$	0.949
	Right [b]	0.84 (0.13)	0.85 (0.15)	$t=0.15$	0.874
Entorhinal cortex	Total [b]	1.08 (0.23)	1.14 (0.21)	$t=1.31$	0.193
	Left [b]	0.54 (0.13)	0.56 (0.12)	$t=-0.60$	0.550
	Right [b]	0.54 (0.11)	0.59 (0.12)	$t=1.78$	0.079
Anterior cingulate cortex	Total [b]	2.72 (0.62)	2.63 (0.63)	$t=-0.57$	0.568
	Left [b]	1.37 (0.33)	1.26 (0.37)	$t=-1.44$	0.152
	Right [b]	1.39 (0.39)	1.37 (0.41)	$t=-0.27$	0.787
Hyperintensities (Sheltens' scale scores)	Periventricular	0.70 (0.95)	0.89 (1.13)	$Z=0.58$	0.560
	Deep white matter [b]	3.00 (4.11)	3.36 (4.73)	$Z=-0.03$	0.975
	Basal ganglia [b]	0.15 (0.46)	0.48 (1.02)	$Z=1.48$	0.137
	Infratentorial	0.00 (0.00)	0.02 (0.15)	$Z=1.0$ [e]	0.620

[a] Statistical comparisons were made using t-test/Wilcoxon test.
[b] Data were transformed prior to analysis.
[c] ($mm^3 \times 10^3$).
[d] Corrected volumes (absolute volume in mm^3/ICV in mm^3) $\times 1.000$.
[e] Statistical comparison was made using Fisher's exact test.

Table 4
Personality factor and facet scores in the present series.

		EOD ($N=38$)	Controls ($N=62$)		
Factor	Facet	Mean (SD)	Mean (SD)	t [a]	p
Neuroticism [b]		88.50 (27.62)	74.16 (22.21)	−2.62	**0.010**
	Anxiety (N1)	17.32 (7.31)	13.60 (6.20)	−2.61	**0.011**
	Angry hostility (N2) [b]	12.76 (5.29)	11.45 (4.98)	−1.25	0.214
	Depression (N3) [b]	16.97 (6.50)	12.97 (4.79)	−3.10	**0.002**
	Self-consciousness (N4) [b]	16.13 (6.01)	13.73 (3.88)	−1.92	0.059
	Impulsiveness (N5)	14.76 (5.30)	13.79 (4.29)	−0.95	0.342
	Vulnerability (N6) [b]	12.39 (5.84)	9.87 (4.69)	−2.09	0.039
Extraversion		92.34 (24.09)	101.19 (21.66)	1.85	0.068
	Warmth (E1) [b]	21.37 (4.35)	23.74 (4.09)	2.96	**0.003**
	Gregariousness (E2)	14.26 (5.83)	14.94 (5.26)	0.58	0.563
	Assertiveness (E3)	13.24 (6.25)	14.66 (5.07)	1.18	0.240
	Activity (E4)	16.45 (5.54)	17.76 (5.33)	1.16	0.247
	Excitement seeking (E5) [b]	11.74 (4.94)	11.74 (4.93)	0.04	0.960
	Positive emotions (E6) [b]	16.42 (6.32)	19.95 (4.93)	2.93	**0.004**

[a] *T*-test comparisons were made between EOD patients and healthy controls. Statistically significant differences (p threshold value of 0.01) are in bold.
[b] Data were transformed prior to analysis.

Importantly, linear regression analysis revealed that the diagnostic group effect (as well as the lack of group differences) persisted after adjustment for age, gender and education. As for cognitive, volumetric and WMH data, duration of EOD, age at disease onset, medication and the number of depressive episodes (single/recurrent) had no impact on NEO PI-R factors (and facets) scores. In the EOD subgroup, a significant positive correlation was found between the left amygdala and the N factor ($r_s=0.48$; $p=0.005$) as well as one of its facets (Vulnerability N6; $r_s=0.52$; $p=0.002$). No other significant correlations between NEO-PI and MRI data were found in the present series.

4. Discussion

From a neurocognitive perspective, the present study shows that euthymic EOD patients are preserved both in terms of global functioning and depression-specific cognitive domains. This sparing concerns processing speed, working memory and executive function but also episodic memory performances thought to be particularly vulnerable in the long-term evolution of EOD (Rapp et al., 2005). As already suggested (Biringer et al., 2005, 2007), this vulnerability may concern the acute stages of the disease and be reversible. These results parallel several lines of evidence supporting the preservation of cognitive abilities in elderly patients with EOD (Brodaty et al., 2003; Dufouil et al., 1996). In particular, Brodaty et al. (2003) found no evidence for long-term cognitive deficits following depressive episodes even after 25 years of follow-up. Interestingly, this protection seems to be confined to unipolar patients. In fact, in a recent study of euthymic bipolar patients, we found reduced processing speed as well as episodic memory impairment in the absence of executive dysfunction (Delaloye et al., 2009). Taken together these results suggest that episodic memory impairment may be characteristic of bipolar disorder rather than EOD in old age.

In line with the cognitive preservation, our MRI data documented both intact volume in the main limbic areas and absence of significant vascular burden in EOD cases. After adjustment for age differences, euthymic EOD patients were comparable to healthy elderly controls in respect to hippocampal, amygdala, anterior cingulate and entorhinal cortex volumes, as well as total brain ICV. This observation was valid for patients having experienced one single depressive episode as well as to the majority of patients, who had experienced two or several depressive episodes over the past thirty years. Consistent with the neurotoxic theory of depression, one would expect significant hippocampal volume loss at least among the most chronic and severely depressed patients (Campbell and MacQueen, 2004). This was clearly not the case in this cohort showing an impressive resistance of brain structures despite the recurrent nature of the depressive disorder. In conjunction with several recent contributions (for review see Herrmann et al., 2008), our observations support the distinction between the aetiological mechanisms implicated in the pathogenesis of late- and early-onset depression. As postulated by Brodaty et al. (2001), while late-onset depression may be more driven by acquired pathology such as vascular burden, genetic background and personality dimensions may be the most important determinants of EOD.

And indeed, the only markers that significantly differentiated EOD cases from controls were their personality traits. Even in euthymic state, scores on Neuroticism and two of its facets (Anxiety and Depression) were significantly higher in EOD patients. These results are consistent with previous observations indicating an increase of Neuroticism both in younger (Maier et al., 1992; Bagby et al., 1995) and older (Abrams et al., 1991) recovered EOD patients. Depressed elderly individuals showed a tendency to be shy, fearful, and anxious (N1). They also experienced more feelings of guilt, sadness, helplessness and loneliness (N3). The relationship between the persistent increase of Neuroticism and recurrent depression reported here also agrees with the dynamic stress-vulnerability model proposed by Ormel et al. (2001). The scores of the EOD group on the Warmth (E1) and Positive Emotions (E6) facets were significantly lower than those of controls. Patients tended to be more introverted, less sociable and naturally active, confident and optimistic. They were less interested and showed less sympathy to other people and they also failed to experience positive emotions such as joy and happiness. As for Neuroticism, these observations are

consistent with previous reports in younger cohorts and imply that the decreased Extraversion of euthymic patients with mood disorders is a consistent finding across the age spectrum (Maier et al., 1992; Barnett and Gotlib, 1988). Interestingly, our study revealed a significant positive association in these patients between the N factor and volume of the left amygdala, a key structure in the processing of affect in mood disorders. In younger cohorts, although chronic depression has been associated with decreased amygdala volume (Hamilton et al., 2008), increased left amygdala volume has also been reported in remitted patients (Lorenzetti et al., 2010). Omura et al. (2005) suggested that differences in levels of emotion-related personality traits, such as Neuroticism, may partly determine these variances in amygdala volume. Based on these findings, the authors stress the need to control for personality when assessing neuroanatomical correlates of depressive disorders. Yet, neuroanatomical correlates of the Five-Factor Model of personality in EOD remain largely unexplored in old age. Our preliminary findings may generate hypotheses for further research into the biological background of personality changes in this particular group of patients.

To our knowledge, this is the first comprehensive analysis of elderly patients who recovered from EOD combining detailed neuropsychological assessment, MRI analysis of volumetric changes in key cortical areas and vascular burden as well as psychological evaluation of personality dimensions. Additional strengths of the present study include the careful exclusion of lifetime psychiatric comorbidities (which could affect both cognitive performances and structural imaging data, Basso et al., 2007; Jorm et al., 2005) as well as physical burden, control for demographic variables and duration of depression, detailed assessment of cognitive performances, volumetric analyses using both ROI and VBM methods as well as concomitant assessment of WMH. These strict criteria of inclusion may have induced a selection of patients with less severe EOD (e.g. lower number and intensity of depressive episodes). Several limitations should, however, be taken into account. Although an effect size may mask significant differences in cognitive and MRI measures, the absence of trends in almost all of our comparisons did not support this scenario. Given the limited number of cases, it was not possible to perform separate comparisons for EOD cases with a single versus recurrent episodes. However, the absence of significant relationships between our measures and the number of episodes in our EOD sample does not support the presence of distinct cognitive, MRI and NEO-PI patterns for these subgroups. Similarly, the observed floor effect in respect to vascular comorbidities did not allow for investigating their impact on the present findings. However, the absence of group differences in MRI hyperintensities did not support a major role of vascular factors in the present study. Although, our observations may support the idea that higher levels of Neuroticism and lower levels of Extraversion facets are associated with increased vulnerability to depression, the cross-sectional design of the study does not allow for drawing definite conclusions on this matter. In addition, the extent to which previous depressive episodes may alter the post-morbid personality remains unknown. Future longitudinal studies in larger series of elderly EOD patients addressing these limitations are clearly needed to further confirm these observations.

In conclusion, our data suggest that unlike late-onset depression that is predominantly characterized by neurocognitive markers such executive dysfunction and vascular pathology (Rapp et al., 2005), studies on EOD in old age may gain from shifting their focus on psychological features such as personality. Despite their psychological vulnerability, old EOD patients without major psychiatric nor somatic comorbidities remain preserved from cognitive impairment as well as from structural and vascular abnormalities. From this point of view, the present results clearly convey a message of hope for patients suffering from EOD.

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Conflict of interest

All authors declare that they have no conflict of interest.

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