Psychiatry Research: Neuroimaging 222 (2014) 1–9

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

The structure of the geriatric depressed brain and response to electroconvulsive therapy ☆

Mardien L. Oudega [a,b,h,*], Eric van Exel [a,b,c], Max L. Stek [a], Mike P. Wattjes [d], Wiesje M. van der Flier [e,f], Hannie C. Comijs [a,c], Annemieke Dols [a], Philip Scheltens [b,e], Frederik Barkhof [b,d], Piet Eikelenboom [a,g], Odile A. van den Heuvel [a,b,h]

[a] Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
[b] Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[c] EMGO Institute for Health and Care Research and VU University Medical Center/GGZ inGeest, Amsterdam, The Netherlands
[d] Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands
[e] Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands
[f] Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[g] Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands
[h] Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 3 April 2013
Received in revised form
25 February 2014
Accepted 6 March 2014
Available online 14 March 2014

Keywords:
Voxel-based morphometry
Magnetic resonance imaging (MRI)
Geriatric depression
Depression with psychotic symptoms
Late onset depression

ABSTRACT

Electroconvulsive therapy (ECT) is the treatment of choice in severe geriatric depression. High remission rates may be influenced by specific brain morphology characteristic of geriatric depression. Our objective was to identify the relationship between brain structure, symptom profile, and ECT response. In a naturalistic cohort of 55 patients with a major depressive disorder, structural magnetic resonance imaging (MRI) was performed before ECT. Voxel-based morphometry was applied to determine regional differences in gray matter (GM) volume between patients and 23 matched healthy controls. Depressed patients with psychotic symptoms showed significantly higher remission rates and smaller regional GM volume of the left inferior frontal gyrus (IFG). Patients with late onset depression showed smaller regional GM volume of the bilateral lateral temporal cortex. Larger size of response in the whole patient group was related to smaller pretreatment regional GM volume of the right lateral temporal cortex, whereas faster speed of response was related to smaller pretreatment regional GM volume of the right IFG. ECT is most effective in depressed patients with psychotic symptoms. In this study the presence of psychotic symptoms was related to pretreatment smaller GM volume of the left IFG and bilateral temporal cortex. Smaller volume of the IFG pretreatment was related to faster treatment response, and smaller volume of the right lateral temporal cortex pretreatment was related to larger response to ECT. These results are possibly explained by the connectivity between these brain regions and an interconnected network that is particularly activated by the ECT-induced seizures.

1. Introduction

Electroconvulsive therapy (ECT) is a safe and effective treatment in severe geriatric depression (Stek et al., 2007) with remission rates ranging from 50% to 70% (Tew et al., 1999; Oudega et al., 2011). Accumulating evidence suggests that differences in symptom profiles of geriatric depressed patients contribute to ECT response, i.e., geriatric depressed patients with psychotic symptoms (PS) have higher response rates to ECT than do geriatric depressed patients without PS (Parker et al., 1992; Birkenhäger et al., 2003). It is unclear, however, whether differences in symptom profiles and ECT response relate to specific neurobiological characteristics, such as differences in brain structure. The combined study of symptom profile, brain structure, and ECT response may add to our understanding of this differential ECT response and its underlying mechanisms of effect.

The mechanism of action in ECT is yet to be discovered. A previous study of our group showed an association between medial temporal

☆An earlier version of this report was presented at the meeting of the Dutch Society of Psychiatrists (NVVP) in Maastricht on 3 April 2012.

* Corresponding author at: Department of Psychiatry VU University Medical Center (VUmc) and GGZ inGeest. VU University Medical Center, Medical Faculty room C457 van der Boechorststraat 7, 1007 MB, Amsterdam, the Netherlands. Tel.: +31 6 18479865; fax: +31 20 444 0197.
E-mail addresses: M.Oudega@ggzingeest.nl, m.oudega@vumc.nl (M.L. Oudega).

http://dx.doi.org/10.1016/j.pscychresns.2014.03.002
0925-4927/

lobe atrophy (MTA) and poor ECT response (Oudega et al., 2011), suggesting that the medial temporal lobe is involved in the ECT mechanism. Furthermore, single photon emission computed tomography (SPECT) studies evaluated the network that is activated during ECT, showing specific strong activation of the frontal, parietal and temporal cortices after initiation of ECT-induced seizures (Blumenfeld et al., 2003; McNally and Blumenfeld, 2004).

Structural magnetic resonance imaging (MRI) studies in patients with geriatric depression compared with healthy subjects, using the region of interest (ROI) approach, showed smaller gray matter (GM) volume of the medial temporal (Steffens et al., 2000), parietal (Andreescu et al., 2008), and prefrontal (Kumar et al., 2000) cortices. Results of whole-brain voxel-based morphometry (VBM) studies in patients with geriatric depression, compared with healthy subjects, are inconclusive, showing no difference at all (Koolschijn et al., 2010) or smaller GM volume of the lateral (Yuan et al., 2008) and medial (Bell-McGinty et al., 2002; Egger et al., 2008) temporal cortices, mygdala, orbitofrontal (Egger et al., 2008), superior frontal, and postcentral cortices (Yuan et al., 2008).

Studies of brain structure in geriatric depression in relation to specific symptom profiles such as the presence of PS or late onset depression (LOD) (age of onset above 55 years of age) are sparse. Only one study, using a ROI approach, evaluated 19 geriatric depressed patients with PS versus 26 geriatric depressed patients without PS (Kim et al., 1999), finding smaller GM volume of the prefrontal cortex in psychotic depression. Other studies found no difference between elderly patients with LOD and healthy controls (Colloby et al., 2011) or smaller GM volume of the insula and posterior cingulate gyrus (Hwang et al., 2010).

So far, no study has reported on the relationship between symptom profile, brain structure, and ECT response in severe geriatric depression. We used VBM in a naturalistic cohort of 55 patients with severe geriatric depression to evaluate this relationship. We hypothesized that alterations of frontal, parietal, and temporal GM volume would relate to ECT response, since these regions are involved in the network that is activated during ECT-induced seizures (Blumenfeld et al., 2003; McNally and Blumenfeld, 2004).

2. Methods

2.1. Study design

This naturalistic study on ECT response in severe geriatric depression was conducted at the clinic for Geriatric Psychiatry of GGZ inGeest/VU University Medical Center (VUmc), Amsterdam, the Netherlands. Inclusion criteria were age of 55 years and over, referral for ECT, and a diagnosis of DSM-IV unipolar depression. From 2001 through 2006, 97 patients diagnosed with unipolar depression provided written informed consent. Excluded patients were: unavailable or had poor quality MRI data ($n=24$), scan from a different MR instrument ($n=6$), movement artifacts ($n=5$), brain pathology, e.g., large brain infarct ($n=3$), dementia ($n=3$), and meningioma ($n=1$). In total 55 patients were included in the present analysis, based on the same cohort of 81 patients described in our previous study (Oudega et al., 2011).

Two experienced geriatric psychiatrists (M.L.S., P.E.) confirmed a diagnosis of depression or depression with PS, according to *DSM-IV* criteria. Depression with PS required the presence of delusions. LOD was defined as age of onset above 55 years. Healthy controls were recruited among spouses of patients from the Alzheimer Center of the VUmc and matched manually for mean age and gender. In total 23 healthy controls were matched for this study, based on age and gender, and underwent brain MRI scanning. Excluded were healthy controls who could not be matched due to a young age. The local institutional medical ethical review board approved the study, and all participants provided written informed consent.

2.2. Administration of ECT

The ECT protocol has been described in detail previously (Oudega et al., 2011). In short, ECT was applied twice weekly using an age-dosing protocol. Treatment started with right unilateral stimuli to diminish cognitive side effects. Two patients, who stopped eating and drinking, received bilaterally treatment initially. During treatment, 12 patients who started with unilateral ECT switched to bilateral ECT because of a deteriorating clinical condition or after six unilateral treatments because of lack of effect. We observed no significant difference in pretreatment (T_0) Montgomery–Åsberg depression rating scales (MADRS) (Montgomery and Åsberg, 1979) score or ECT response between patients who were treated unilaterally and/or bilaterally. ECT was terminated (T_1) if patients remitted or showed no further improvement during the last 2 weeks of ECT.

Psychotropic medication was tapered off 2 weeks before ECT began. Patients were not treated with any antidepressants or mood stabilizers during ECT or during MRI scanning. Antipsychotic medication was allowed for severe agitation that hampered ECT procedures. In total, seven patients with a depression with PS received antipsychotics during the period in which the MRI scan was performed and during ECT.

2.3. Clinical evaluations

The same research nurse obtained MADRS scores for all patients within 5 days before ECT began, weekly, exactly in between sessions, and 1 week after the final session. Remission was defined as a score below 10 points on the MADRS (Hsieh et al., 2002; Corya et al., 2003). Size of response was defined as delta MADRS ($[(\text{MADRS } T_1 - \text{MADRS } T_0)/\text{MADRS } T_0] \times 100\%$), i.e., symptom reduction corresponded with a negative delta MADRS score. Speed of response was defined as delta MADRS per week ($[\text{MADRS } T_1 - \text{MADRS } T_0]$/weeks of ECT), i.e., symptom reduction corresponded with a negative delta MADRS per week score. The trained research nurse was blind to ECT modality.

2.4. MRI acquisition

All patients ($n=55$) and controls ($n=23$) underwent MRI scanning following a standard protocol, with a 1.0-T scanner (Magnetom Impact, Siemens, Erlangen, Germany). The series included coronal 3D T1 sequence images (flip angle$=15^\circ$; repetition time$=15$ ms, echo time$=7$ ms; matrix 256×256, voxel size $1 \times 1 \times 1.5$ mm; 168 slices).

2.5. Voxel-based morphometry (VBM)

Imaging data were analyzed using optimized VBM analysis, following anatomical registration through exponentiated Lie algebra (DARTEL) using Statistical Parametric Mapping software (SPM8) implemented in MATLAB (Mathworks, Natick, MA, USA). First, MRI scans were manually reoriented, and quality was visually checked. Second, images were segmented into GM, white matter (WM) and cerebrospinal fluid (CSF) using the standard unified segmentation model in SPM8 (Ashburner and Friston, 2000). Third, GM and WM population templates were generated from the entire dataset through diffeomorphic anatomical registration using DARTEL (Ashburner, 2007). Fourth, after an initial affine registration of the GM and WM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/), non-linear warping of GM and WM images was performed using DARTEL GM and WM templates in MNI space. Fifth, images were modulated to ensure that relative volumes of GM and WM were preserved following the spatial normalization procedure. Lastly, images were smoothed with a 10 mm full width at half maximum Gaussian kernel.

2.6. Statistical analyses

The Statistical Package for the Social Sciences software (SPSS version 15) was used for statistical evaluation of data. Demographics and clinical characteristics of patients and healthy controls are reported as means with standard deviations or as numbers with percentage of total group. Patients and healthy controls were compared using an independent sample *t*-test or a Pearson chi-square test. Two-sample *t*-tests or one-way analysis of variance (ANOVA) in SPM8 assessed regional differences in GM volumes between groups (patients vs. healthy controls, depression with PS vs. without PS, and LOD vs. early onset patients (EOD)) estimating the significance of each effect from the distributional approximations of Gaussian random fields (Friston et al., 1994). An absolute threshold mask of 0.2 was used for the GM analyses. To correct for global GM differences, total GM volume was added as a regressor (covariate) in the models. Linear regression models were used to evaluate the correlations between regional GM volumes, of peak coordinates of the voxels as identified with the group comparisons, and delta MADRS scores and delta MADRS scores per week, with total GM volume and initial MADRS score as covariates.

Significant effects were assessed using an uncorrected threshold of $p < 0.001$ with an extent threshold of 50 voxels for the *a priori* defined brain regions (prefrontal, temporal, and parietal cortices) (Van Tol et al., 2010) and $p < 0.05$ family-wise error (FWE)-corrected for brain regions that were not defined *a priori*.