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Determinants of brain SPECT perfusion and connectivity in treatment-resistant depression

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ABSTRACT

This study aims to characterize and compare functional brain single photon emission tomography (SPECT) perfusion and connectivity in treatment-resistant depression (TRD) according to distinct demographic or clinical profiles (male vs. female; old vs. young; unipolar vs. bipolar) and to study their relationship to the severity and the duration of episode/illness. We retrospectively included 127 consecutive patients who met DSM-IV criteria for a nonpsychotic major TRD episode. All patients were studied using ^{99m}Tc-ethyl cysteinate dimer SPECT. Whole-brain, voxel-based, between-groups analyses were performed according to demographic and clinical data and in comparison to 37 healthy subjects. Voxel-wise interregional correlation was also performed to compare functional SPECT connectivity. Finally, relationships were searched for regarding severity and duration of episode/illness. The whole group of patients exhibited significant hypoperfusion within bilateral fronto-temporal, insular, and anterior cingulate cortices, as well as within the left caudate. Functional connectivity between left frontal and left cerebellar regions was higher in patients than in healthy subjects. Gender, age, and type of mood disorder did not influence these SPECT patterns. A significant relationship was found between brain SPECT perfusion and either duration or global severity of illness in particular frontal areas. Our data support the hypothesis of a shared SPECT pattern, whatever the profile of TRD, involving fronto-temporal regions and the cerebellum.

1. Introduction

Depression has many profiles. Even though the core symptoms are characterized by persistently depressed mood or anhedonia, demographic features are linked to varying patterns of symmptomatology. Among younger depressed patients, the predominant symptoms are loss of interest, feelings of guilt or of being a burden, suicidal thoughts, and depressed mood, whereas the elderly minimize or deny depressed mood, and present more cognitive impairment or hypochondriacal symptoms (Shahpesandy, 2005). Women report more distress, lack of energy, and bulimia associated to weight gain and anxiety, while men report more decreased appetite, psychomotor retardation, substance abuse, and suicidal ideation (Marcus et al., 2005). Moreover, the type of mood disorder may influence the course of depression. In this line, bipolar depression is related to higher rates of psychomotor retardation, cognitive difficulty, or early awakening while unipolar depression is characterized by vegetative and psychomotor symptoms and anxiety (Mitchell et al., 2008). Finally, treatment-resistant depression (TRD) is unfortunately common, afflicting 10–30% of treated-patients (Souery et al., 2006).

Functional neuroimaging provides valuable information in psychiatric diseases. Single photon emission tomography (SPECT) is, for example, useful in the differential diagnosis of depression, particularly in distinguishing it from neurodegenerative diseases (Cho et al., 2002). Neuroimaging has also been used as a means to investigate the predictive/prognostic value of specific cortico-limbic patterns (Richieri et al., 2011; Richieri et al., 2012) as well as to aid in the understanding of neural mechanisms underlying

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antidepressant effects (Richieri et al., 2012). More recently, neuroimaging studies have explored functional connectivity using magnetic resonance imaging (MRI), and have identified cortico-limbic abnormalities (Alalade et al., 2011; Ma et al., 2013).

Those different demographic/clinical profiles of depression may impact functional neuroimaging findings, as much as factors such as age and gender also cause variations in healthy subjects, within structural (Leonard et al., 2008; Gong et al., 2009) and functional brain networks (Luders et al., 2009; Tian et al., 2011; Tomasi and Volkow, 2012). However, based on the clinical characteristics and course of TRD, and specific neurobiological profiles derived from neuroimaging or genetic studies, Fagiolini and Kupfer (2003) have suggested that TRD may be a unique subtype of depression.

Functional neuroimaging could be used to understand the mechanisms of TRD, and especially to determine if there are functional brain abnormalities that are distinctive within the clinical profile of TRD. In the current retrospective study, we used ^{99m}Tc-ethyl cysteinate dimer SPECT to characterize and compare cerebral perfusion and functional connectivity in a wide range of TRD patients, taking into account several covariables, including demographic (age, gender) or clinical characteristics (type, severity, and episode/illness duration), in order to determine functional substrates of TRD.

2. Methods

2.1. Subjects

One hundred and seventy-one consecutive outpatients with a current diagnosis of TRD were admitted from June 2008 through March 2012 into a referral center for Depression in the Sainte Marguerite University Hospital, Marseille, France. This unit provides psychiatric, physical and neuropsychological assessment to confirm diagnoses, eliminate differential diagnoses, and evaluate medical comorbidity. In addition to clinical evaluation, we routinely perform routinely brain MRI, brain perfusion SPECT, electroencephalography, and clinical laboratory measures, including thyroid function tests. Indeed, SPECT is a complementary strategy to deal with diagnostic uncertainties and can be used to define a patient's pathological status when neurological or psychiatric symptoms cannot be explained by structural neuroimaging findings. For example, brain perfusion SPECT can be a useful tool for the differential diagnosis between depression and Alzheimer's disease (Vercelletto et al., 2002; Hanada et al., 2006), or between depression and chronic fatigue syndrome (MacHale et al., 2000). In the present study, patients had to satisfy criteria for a diagnosis of unipolar or bipolar depression, as assessed by a psychiatrist through clinical interview and confirmed with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV-TR (American Psychiatric Association, 1994). Patients must also satisfy criteria for TRD, which was defined as a failure to respond to at least two different classes of antidepressants given for an adequate duration and dose (Berlim and Turecki, 2007). One hundred and twenty-seven patients were selected after consideration of exclusion criteria (age less than 18 years, left-handed, chronic neurological illness, psychotic depression and a major psychiatric illness other than depression as assessed with the Mini-International Neuropsychiatric Interview).

Thirty-seven healthy and non-depressive participants (20 women; age = 53.0 years $\pm$ 13.8) were also included. They were screened for anxiety and depression using the Hospital Anxiety and Depression Scale (subscores < 8). Control subjects who had first or second-degree relatives with unipolar or bipolar disorder were excluded. These investigations were approved by the local ethics committee. The project was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practice (World Medical Association, 2008).

2.2. Data collection

Data recorded included demographic characteristics (gender and age). Clinical assessments included duration of illness (years) and episode duration; chronic depression was defined as a major depressive episode lasting at least 2 years (DSM-IV-TR). Depression severity was assessed using the 21-item Beck Depression Inventory (BDI) (Beck et al., 1988) and the Clinical Global Impression scale (CGI) (Guy, 1976); anxiety severity, using the State-Trait Anxiety Inventory, state form (STAI) (Spielberger et al., 1983).

All patients with unipolar TRD were receiving antidepressants. Almost all patients with bipolar TRD (43 of 44) were on mood stabilizers; among them, 38 were being treated with antidepressants.

2.3. SPECT protocol

A brain SPECT was performed for all subjects, with the same camera, and under the same conditions (Richieri et al., 2011; Richieri et al., 2012). The subjects received an injection of 740 MBq of ^{99m}Tc-ECD and were placed at rest for 1 h, in quiet surroundings with their eyes closed. SPECT image acquisition was performed using a double-headed rotating gamma camera (ECAM, Siemens) equipped with a fanbeam collimator. Thirty-two 40-s projections per subject were collected in 128×128 format. Tomographic 3D reconstruction was performed using a filtered back-projection algorithm. A voxel-by-voxel group study was then performed using SPM8 (Welcome Department of Cognitive Neurology, University College, London), running on Matlab (Mathworks Inc,, Natick, MA).

Images were initially converted from the DICOM to the Analyze format using MRIcro (*www.mricro.com*) and transferred to SPM. Data were then standardized with the Montreal Neurological Institute (MNI) atlas. Dimensions of resulting voxels were $2 \times 2 \times 2$ mm^3. Standardized data were then smoothed with a Gaussian filter (full-width at half-maximum = 8 mm) to blur individual variations in gyral anatomy and to increase signal-to-noise ratio. The "proportional scaling" routine was used to check for individual variations in global brain perfusion. The SPM (T) maps were obtained at a height threshold (voxel level significance) of $p < 0.001$, corrected for the volume of the cluster. Montreal Neurological Institute (MNI) coordinates were converted into Talairach coordinates, and brain structures were identified using the Talairach Daemon database (⟨http://ric.uthscsa.edu/projects/talairachdaemon.html⟩).

2.4. Statistical analyses

Data were expressed in proportion or mean and standard deviation. The clinical characteristics were compared between patients according age, gender, and the type of depression using the Student t-test or the Mann–Whitney U-test for continuous variables, a chi-square test, or Fisher's exact test for categorical variables.

The following SPECT analyses were performed with SPM8 ($p < 0.001$, corrected for the volume of the cluster):

(1) Comparisons (T-contrast) between the whole-group of patients and healthy subjects, using age and gender as nuisance variables.
(2) Interactions (F-contrast) comparing
   (a) SPECT profile obtained between patients and healthy subjects younger than 65 years, with those obtained between patients and healthy subjects older than 65 years (nuisance variables tested: none; gender; gender, type, Beck depression, anxiety, illness duration, episode duration). This cut-off was selected as previously suggested (Giron et al., 2005).
   (b) SPECT profile obtained between male patients and male healthy subjects, to those obtained between female patients and female healthy subjects (nuisance variables tested: none; age; age, type, Beck depression, anxiety, illness duration, episode duration).
   (c) SPECT profile of patients with unipolar and bipolar TRD (nuisance variables tested: none; age and gender; age, gender, Beck depression, anxiety, illness duration, episode duration).
(3) Functional SPECT connectivity from the significant perfusion clusters identified in the between-group comparisons was studied using voxel-wise interregional correlation analysis (IRCA), as previously described (Morbelli et al., 2012). Briefly, mean values of extracted perfusion clusters were used as covariates to find regions showing significant voxel-wise positive/negative correlations across subjects, and between patients and healthy subjects. In addition, correlations were looked for between these clusters in the following groups of patients: age $\geq$ and $<$ 65 years, gender (women and men), and unipolar and bipolar TRD, using Pearson's coefficients. Fisher's Z transformation was then used to compare the correlations (i.e., the functional connectivity) between these groups.

Finally, Pearson's correlation tests were used to search for relationships between clusters previously found and dimensions of Beck depression, STAI, CGI scores, illness duration and episode duration.

Statistical analyses of clinical data were carried out using SPSS 17.0 and R version 2.15.1. The statistical significance level was set at $p < 0.05$ in a two-sided test.

3. Results

3.1. Patient characteristics

Clinical characteristics of the patient group are presented in Table 1. The 127 patients were predominantly women (58.3%). Mean age was 53.4 years ($\pm$ 12.8). They presented unipolar ($n = 83$)