Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

Functional brain substrate of quality of life in patients with schizophrenia: A brain SPECT multidimensional analysis

Catherine Faget-Agius [a,b,f,*], Laurent Boyer [a,c,f], Raphaëlle Richieri [a,b,f], Pascal Auquier [a,c,f], Christophe Lançon [a,b,f], Eric Guedj [d,e]

[a] Aix-Marseille University, EA 3279, 13005 Marseille, France
[b] Department of Psychiatry, Conception University Hospital, 13005 Marseille, France
[c] Department of Public Health, La Timone University Hospital, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France
[d] Service Central de Biophysique et Médecine Nucléaire, La Timone University Hospital, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France
[e] Centre Européen de Recherche en Imagerie Médicale (CERIMED), Aix-Marseille University, Marseille 13005, France
[f] EA 3279-Public Health, Chronic Diseases and Quality of Life, School of Medicine, Timone University, 13005 Marseille, France

ARTICLE INFO

ABSTRACT

The aim of this study was to investigate the functional brain substrate of quality of life (QoL) in patients with schizophrenia. Participants comprised 130 right-handed patients with schizophrenia who underwent whole-brain single photon emission computed tomography (SPECT) with ^{99m}Tc-labeled ethylcysteinate dimer (^{99m}Tc-ECD) for exploring correlations of regional cerebral blood flow (rCBF) with the eight dimensions score of the Schizophrenia Quality of Life questionnaire (S-QoL 18). A significant positive correlation was found between the global index of the S-QoL 18 and rCBF in the right superior temporal sulcus and between psychological well-being dimension and rCBF in Brodmann area (BA)6, BA8, BA9, and BA10 and between self-esteem dimension and rCBF in striatum and between family relationship dimension and rCBF in BA1, BA2, BA3, BA4, BA8, BA22, BA40, BA42 and BA44 and between relationship with friends dimension and rCBF in BA44 and between physical well-being dimension and rCBF in parahippocampal gyrus, and finally between autonomy dimension and rCBF in cuneus and precuneus. A significant negative correlation was found between resilience dimension and rCBF in precuneus and between sentimental life dimension and rCBF in BA10. Our findings provide neural correlates of QoL. Brain regions involved in cognitions, emotional information processing and social cognition underlie the different QoL dimensions.

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1. Introduction

Over the last decades, quality of life (QoL) has been recognized as a key factor in the assessment and the outcome of patients with schizophrenia (Hofer et al., 2005). Measuring QoL has become of great importance to follow disease progression (Awad et al., 1997). More particularly, QoL is considered as a valid predictor of relapse in schizophrenia (Boyer et al., 2013), and of long-term symptomatic remission, functional recovery and disability (Lambert et al., 2010; Baumstarck et al., 2013). In addition, QoL measurements allow evaluating treatments and caring management effectiveness (Awad et al., 1997). As a consequence, the targets in care management are not limited to reducing the symptoms but also include the improvement of QoL (Meltzer, 1999; Zouari et al., 2012;

Boyer et al., 2013). However, QoL assessments fail to affect clinical management (Awad and Voruganti, 2012; Boyer and Auquier, 2012a). Several explanations have been put forward including the lack of agreement of a definition of QoL, and the lack of appropriate conceptual models defining the construct of QoL (Awad and Voruganti, 2012). A better understanding of the scientific foundation of the construct itself is therefore needed.

New avenues of neuroimaging have been initiated to determine the neurobiological basis of QoL in schizophrenia. In support of this view, a negative association between QoL level and the perfusion of the superior temporal sulcus has been reported suggesting an involvement of self/other awareness and metacognition neural substrate in QoL (Boyer et al., 2012). Another recent study has shown an association between QoL and the neural activity in the prefrontal cortex during a verbal fluency task (Pu et al., 2013). Finally, a morphometric study using magnetic resonance imaging (MRI) has found correlations between cortical grey matter reductions and QoL (Ubukata et al., 2013). However, despite the multidimensional aspect of QoL (Lehman, 1983), these studies have

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investigated a global index or some QoL dimensions. To our knowledge, no neuroimaging study has examined QoL with a complete multidimensional approach.

Single photon emission computed tomography (SPECT) with [99mTc]-labeled ethylcysteinate dimer (99mTc-ECD) is a valuable brain-imaging tool to study regional cerebral blood flow (rCBF) in a range of psychiatric disorders such as schizophrenia (Faget-Agius et al., 2012; Boyer et al., 2012; Boyer et al., 2014). This exploratory study investigated the neural substrate underlying QoL dimensions in a large group of patients with schizophrenia, using whole-brain 99mTc-ECD-SPECT voxel-based statistical analysis of rCBF.

2. Methods

2.1. Subjects

We retrospectively collected data for 130 patients with a diagnosis of schizophrenia (mean age=35.8 years, SD=11.1; 95 males) who had a complete clinical evaluation into a referral center for the assessment of schizophrenia in Conception University Hospital, Marseille, France. Patients had a clinical standardized assessment completed by biological and neuroimaging (including electroencephalography to eliminate a differential diagnosis of epilepsy and to control the tolerance of psychotropic drugs; brain MRI and brain SPECT) exams in order to confirm diagnosis and disease severity and to search comorbidities. The brain perfusion SPECT is of particular interest to define patient's pathological status, and exclude other conditions. The inclusion criteria were diagnosis of paranoid schizophrenia according to the DSM-IV-TR criteria (American Psychiatric Association, 2000), stable disease no need for hospitalization at inclusion, no major change in the patients' condition for 2 months before inclusion (Appelberg et al., 2004), age over 18 years, outpatient, right-handed, French native language, and informed consent to participate in the study. The exclusion criteria were psychiatric diagnosis other than paranoid schizophrenia on Axis I of DSM-IV-TR, decompensated organic disease, and mental retardation.

The data collection was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL number: 1223715). Our research was conducted in accordance with the Declaration of Helsinki and French good clinical practices (CNIL, n.d.; WMA, 2008). In particular, patients received an explanation of the study and gave written, informed consent after a standardized and structured clinical interview.

2.2. QoL measure

We assessed QoL using the Schizophrenia Quality of Life questionnaire (S-QoL 18), a self-administered, multidimensional questionnaire developed and validated for the specific assessment of QoL in schizophrenia (Boyer et al., 2010). The S-QoL 18 was constructed on the basis of patients' experiences (Auquier et al., 2003; Lançon et al., 2007) ensuring a more appropriate content than questionnaires based on experts' determination (Cramer et al., 2000). Because the QoL is a multidimensional concept (Awad et al., 1997; Awad and Voruganti, 2012), we used a scale with a multidimensional construct (Auquier et al., 2003; Lançon et al., 2007; Boyer et al., 2010). The S-QoL 18 comprises 18 items describing the following eight dimensions: psychological well-being, self-esteem, family relationships, relationships with friends, resilience, physical well-being, autonomy, and sentimental life as well as a global score (the index) (Boyer et al., 2010). Dimension and index scores range from 0, indicating the lowest QoL, to 100, the highest QoL.

2.3. Data collection

The following data were collected in patients:

1. Socio-demographic information: gender, age, and educational level (elementary school vs. high school), lifestyle ascertained during the psychiatric evaluation.
2. Clinical characteristics: duration and course of disease; substance abuse history; depression based on the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990); psychotic symptoms based on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).
3. Drug information: medication (first-generation antipsychotics—FGAs, second-generation antipsychotics—SGAs); chlorpromazine-equivalent daily dose; and drugs: antidepressants; treatment compliance assessed by the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000).

2.4. SPECT protocol and analysis

Brain SPECT was performed in all patients, with the same camera, and under the same conditions, as previously described (Richieri et al., 2011). The exam was performed after QoL measurement during the global assessment on the same day within a maximum of 2 h.

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; MATLAB User's, 1998)

Images were initially converted from the DICOM to the analyse format using MRIcro (www.mricro.com), and transferred to SPM8. SPECT analyses were limited to gray-matter areas using the AAL cortical mask (Tzourio-Mazoyer et al., 2002). Data were then standardized with the Montreal Neurological Institute (MNI) atlas, using a 12-parameter affine transformation, followed by non-linear transformations and trilinear interpolation. Dimensions of resulting voxels were $2 \times 2 \times 2$ mm. 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 control for individual variation in global brain perfusion.

Voxel based correlation was searched in the whole group of patients for each of eight QoL dimensions and for global index, using age, gender, educational level and antipsychotic treatments expressed in chlorpromazine equivalent daily dose as covariables. The SPM (T) maps were obtained at a height threshold of $p < 0.005$ (uncorrected) for the voxel, and of $p < 0.05$ for the cluster (corrected and uncorrected).

3. Results

3.1. Patient characteristics

Characteristics of the 130 patients are presented in Table 1.

Mean duration of disease was 13.2 years, SD=9.2 for the whole group of patients. Disease severity was considered as moderately with a mean total PANSS score of 72.4, SD=18.2. The mean total CDSS score was 3.6, SD=3.9. Thirty percent of the patients had a substance abuse history. Patients were adherent to treatment with a mean MARS score of 6.9, SD=1.9. Second generation antipsychotics were used to treat 115 patients.