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Chronic and treatment-resistant depression : a study using arterial spin labeling perfusion MRI at 3 tesla.

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1. Introduction

Chronicity in depressive illness is estimated at 20%, and to this day, despite the development of new antidepressant drugs, failures are observed in approximately 30% of treated cases (Thase, 2001). Treatment-resistant depression is defined as a major depressive disorder (MDD) which fails to respond to antidepressant treatment or which does not evolve favorably under the influence of this treatment (Thase et al., 2001). Treatment resistance is currently studied using a multi-dimensional approach. Several levels of resistance have been defined, on the basis of the number of antidepressant trials the class of drugs, and their administration in adequate doses and for sufficient durations (Drevets, 2000). Physical treatment by electroconvulsive therapy is also taken into account.

Recent studies using neuroimaging techniques have led to a better understanding of the depressive disease pathophysiology and have redefined the neurobiological hypothesis of depression (Brody et al., 2001a; Drevets, 2000; Tekin and Cummings, 2002). This hypothesis is based on the existence of dysfunctional cortico-subcortical circuits. The anterior cingulate cortex (ACC) has become a particular area of interest in depression research. Morphological and functional imaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) with the blood oxygen level dependent (BOLD) effect have revealed dysfunction in this region (Ballmaier et al., 2004; Drevets et al., 1997; George et al., 1997; Liotti et al., 2002; Mayberg et al., 1997). Some studies have identified the subgenual ACC (sACC) as the focus of this dysfunction. The sACC is the ventral part of the ACC, located beneath the genu of the corpus callosum, and corresponds primarily to Brodmann's area (BA) 25. This area is also called Cg 25. In addition to showing reduced

volume in depression (Botteron et al., 2002; Drevets et al., 1997; Hirayasu et al., 1999; Liotti et al., 2002), the sACC tends to display increased resting-state functional connectivity in major depression (Greicius et al., 2007). Moreover, some studies have demonstrated the consistent involvement of the subgenual cingulate in both acute sadness and antidepressant treatment effects, suggesting a critical role of this region in modulating negative mood states (Liotti et al., 2002; Mayberg et al., 1999; Seminowicz et al., 2004). A recent clinical trial suggested that deep brain stimulation (DBS) of this region might ameliorate symptoms in patients (Mayberg et al., 2005). In this study, Mayberg et al. (Mayberg et al., 2005) observed a unique pattern of high sACC blood flow among chronically depressed and treatment-resistant patients compared with healthy subjects, using PET scans with the H₂(15)O water bolus technique.

Functional neuroimaging techniques (PET, SPECT and functional MRI (fMRI)) both have their limitations. PET and SPECT studies expose subjects to radioactive tracers, thus limiting their repetition. Moreover, spatial resolution with these techniques is poor. Functional MRI overcomes these limitations, but until recently could not be readily applied to resting-state investigations. Moreover, it only studies neuronal activation indirectly and brain perfusion not at all. A recent perfusion MRI technique (Wintermark et al., 2005), arterial spin labeling (ASL) magnetically labels arterial blood water as an endogenous tracer for perfusion (Detre and Alsop, 1999). ASL can measure resting-state cerebral blood flow without the injection of contrast media. Gray matter perfusion measures using ASL correlate with measures obtained using H₂(15)O PET with humans (Ye et al., 2000). A few studies have used ASL to investigate psychiatric disorders, but only at 1.5 tesla (T) (Clark et al., 2006; Clark et al., 2001; Doraiswamy et al., 1999). As ASL is a low signal-to-noise ratio (SNR) technique, the shift from 1.5 to 3 T should be regarded as a means of increasing the SNR. The concomitant increase in the T₁ relaxation time should improve the SNR still further (Golay and Petersen, 2006).

The aim of this study was to compare the resting-state perfusion of chronically depressed and treatment-resistant patients vs. healthy controls using the ASL perfusion technique at 3T and focusing on the sACC.

2. Method

2.1. Study design:

This prospective study was approved by the ethics committee of our hospital. We recruited depressed patients from the adult psychiatry department of our hospital. Healthy subjects were recruited through the press and were remunerated. After a complete description of the study had been given to the subjects, their written informed consent was obtained.

2.2. Subjects:

All depressed patients met the DSM-IV criteria for major depressive disorder (unipolar) and were assessed by means of a structured psychiatric interview. To be included, they had to meet several criteria. First, the patients had to have experienced a chronic depressive disorder for at least two years, confirmed by the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). They all had to have undergone at least two episodes of depression prior to the current episode. All chronic and treatment-resistant patients had scores of 16 or more on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and scores of 4 or more on the first item of the Clinical Global Impression (CGI) (Guy, 1976). Patients had no cognitive impairment and scored above 130 on the Mattis scale (Mattis, 1976). The depressed patients were resistant to drug therapy: absence of response to at least three different antidepressant molecules, ineffectiveness of additional mood stabilizers (lithium, valproate, etc.), thyroid extracts and atypical antipsychotics. These treatments had been prescribed in effective doses and for a sufficient duration, in line with their recommendations (Fava, 2003; Thase and Rush, 1997). Patients had been resistant to psychotherapy (cognitive-behavioral, analytical or support) for at least two years. They were also resistant to electroconvulsive therapy (ECT). They were taking their usual medication.

Healthy subjects underwent the same psychometric assessments. They had no history (current or past) concerning a depressive disorder or any other psychiatric disorder.

All depressed and healthy subjects underwent also a structured interview using the Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID II) (Maffei et al., 1997) in order to assess the personality disorders.

Exclusion criteria included other Axis I disorders, which were explored using DIGS, and suicidal risk > 2 in item 3 of the HDRS. Using SCID II, subjects with a personality

disorder (Clusters A and B of Axis II of the DSM IV, excluding the narcissistic and histrionic traits) were excluded. Patients with severe intercurrent disease were not included. Other exclusion criteria were active substance abuse or dependence, a history of alcohol or cocaine abuse or dependence, potential safety contraindications for MRI (pacemakers, metal implants, pregnancy, lactation), neurological problems or a history of significant head injury, and significant circulatory conditions (including hypertension) that could affect cerebral circulation.

All subjects were clinically stable and their medication had not been modified for at least two weeks. **For patients, after examination, the antidepressive treatment was the same for at least 6 months.**

Subjects were six patients with chronic and treatment-resistant depression (four men and two women; mean age=52.50 years [S.D.= 8.67]) and six nondepressed healthy control subjects (three men and three women; mean age=47.17 years [S.D.= 7.41]). **Because of few subjects, we used a statistical non parametric test, the Mann-Whitney U-test, to compare these two independent samples concerning the age. We found no significant difference between the two groups (p= 0.24). We have also used a comparison between the gender. Using the Khi-deux test (X²), we don't have found a significant difference concerning the gender between the two groups (p=0.49).**

All patients had met the inclusion criteria. For the chronically depressed and treatment-resistant patients, the mean score on the 17-item HDRS was 22.5 [S.D.= 4.97]. The mean score on the first item of the CGI was 5.83 [S.D.= 0.41] and the mean score on the Mattis scale was 135.67 [S.D.= 3.44]. For the healthy subjects, the mean score on the 17-item HDRS was 0.67 [S.D.= 1.03]. The mean score on the first item of the CGI was 1 [S.D.= 0] and the mean score on the Mattis scale was 141.5 [S.D.= 2.07]. Out of six chronically depressed and treatment-resistant patients, three patients had no Axis II disorder, two patients had an obsessive compulsive personality, and one patient had a depressive personality disorder. No personality disorder was found in the six healthy controls.

2.4. Imaging protocol:

All MRI studies were performed on a Philips Achieva 3T system (Philips Medical Systems, Best, The Netherlands) using an 8-channel head coil for all imaging. An anatomical scan was performed using the following 3D-T1 weighted sequence: 182 sagittal slices, field of view $256 \times 256 \text{ mm}^2$, acquisition matrix 256×256 , voxel size $1 \times 1 \times 1 \text{ mm}^3$, TE 4.6 ms, TR 9.9 ms, flip angle 8° and acquisition time 3 min. 53 s.

Multislice PASL acquisition included 7 parallel slices with a 7-mm slice thickness. The third slice was aligned with the AC-PC plane. An interslice gap of 0.2 mm was used. The parameters were: FOV $240 \times 180 \text{ mm}^2$, acquisition matrix 64×48 , voxel size $3.75 \times 3.75 \times 7 \text{ mm}^3$. The labeling pulse was a STAR pulse (Edelman and Chen, 1998). The labeling slab was positioned at the level of the neck vessels. The time between the labeling pulse and the beginning of the readout (TI) was 1200 ms. Thirty pairs of labeled and control images were acquired in a single shot EPI sequence, with a TE as short as possible and a TR of 4000 ms. SENSE factor 2 was applied. The acquisition time was 4 min. 8 s.

2.5. Image analysis:

Images were transferred to a post-processing console in a proprietary format. For each subject, the ASL images were analyzed using Philips Medical Systems ASL processing software. A subtraction between labeled and unlabeled images for each of the 30 volumes was performed. Over-artefacted images were eliminated. For each subject, we converted the image files from the proprietary format to Analyze. The rest of the analysis was conducted using SPM2 software (www.fil.ion.ucl.ac.uk/spm/spm2). We combined both geometrical transformations (normalization and coregistration) in order to express all the ASL images of all the subjects in the same T1 template coordinate system. Finally, the individual ASL results were spatially smoothed.

2.6. Statistical analysis:

The group analysis was performed using SPM2. Several tests were carried out with different parameters, in order to establish an appropriate statistical model and to optimize the results. The comparison of the two groups was conducted by means of a two-sample t-test, in order to detect hyperperfusion. The uncorrected threshold was $p=0.001$. The coordinates of the significant areas computed using SPM2 were transformed into Talairach space using the Talairach Daemon.

3. Results

Successful multislice PASL acquisitions were obtained for all patients and healthy controls. We detected significant differences in the activity of various brain areas, between the two groups of subjects (chronically depressed and treatment-resistant patients vs. healthy controls). The statistical comparison revealed significantly ($p=0.001$) hyperperfusion in the depressed patient group compared to the healthy control group (Figure 1). These regions included the bilateral sACC (BA 25), left prefrontal dorsomedian cortex (including BA10), left ACC (BA32) and left subcortical areas: putamen, pallidum and amygdala (Table 1 and Figure 2).

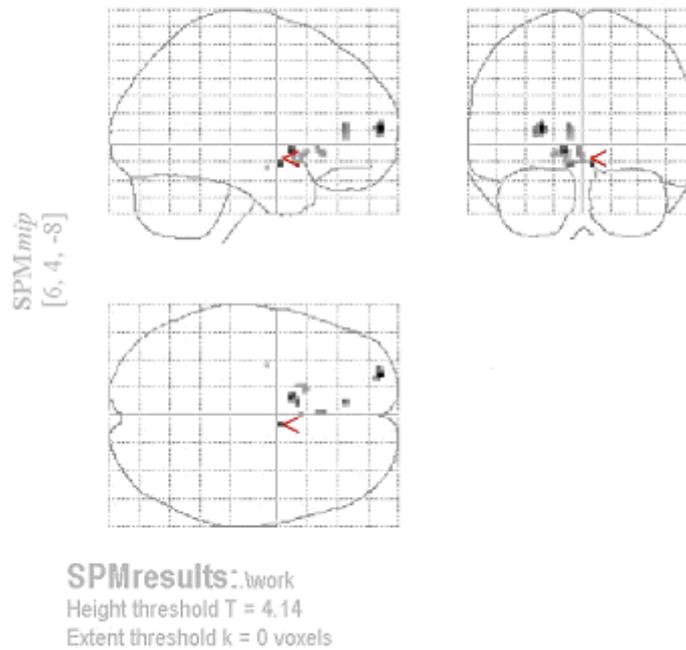


Figure 1: Statistical map of cerebral perfusion (“brain glass”) comparing treatment-resistant depressed patients (n=6) with healthy volunteers (n=6) (p value=0,001).

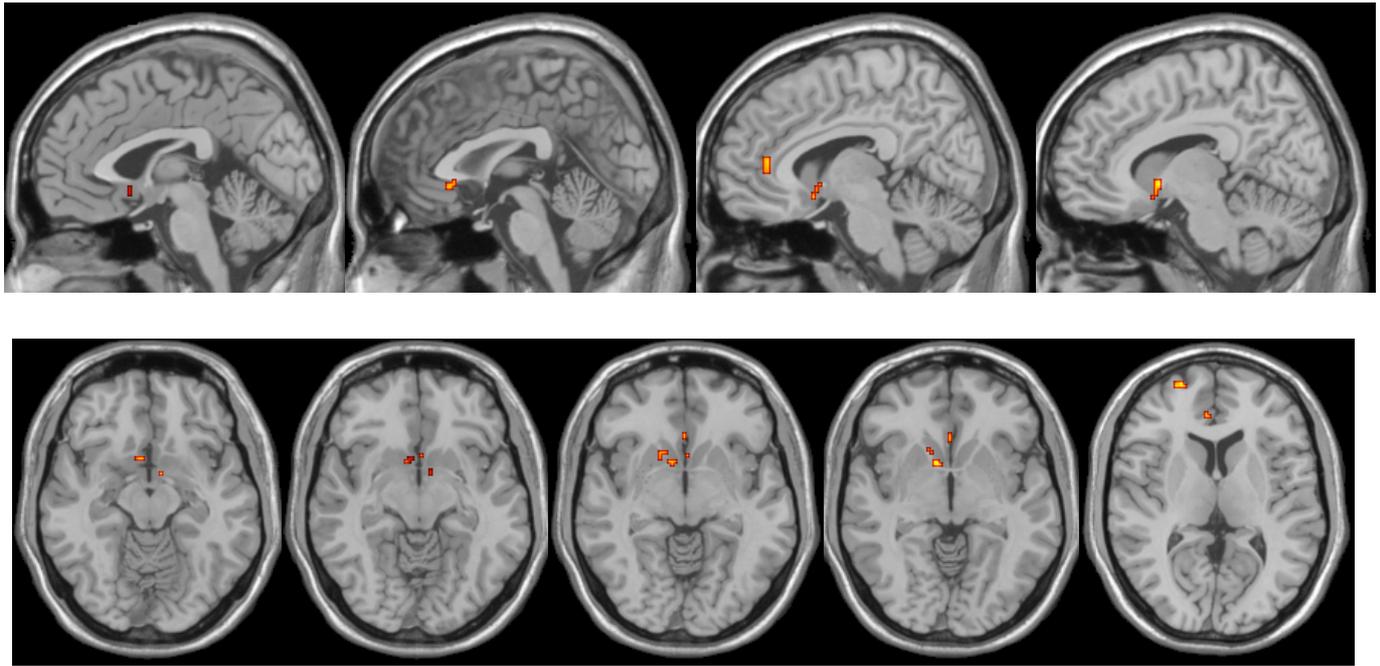


Figure 2 : Superposition of the statistical mapping areas of hyperperfusion on a normalized T1 image of a healthy subject.

Brain areas	BA	Number of voxels	X(mm)	Y(mm)	Z(mm)
Right subgenual ACC	BA25	3	6	2	-12
Left subgenual ACC	BA25	3	-1	14	-6
Corpus callosum		6	-2	28	-6
Left anterior cingulate area	BA32	14	-8	40	10
Left frontal lobe			-8	12	-12
Left lenticular nucleus		21	-10	8	-4
Left external globus pallidus					
Left putamen		7	-16	16	-6
Left lenticular nucleus					
Left prefrontal dorsomedian cortex	BA10	24	-24	62	10
Left amygdala		1	-30	-6	-14
Left parahippocampal gyrus					

Table 1: Localization in the Talairach space of the hyperperfused brain areas with statistically significant activation (p value=0.001).

4. Discussion

To our knowledge, this was the first study using the ASL perfusion MRI technique at 3T to compare populations with or without a psychiatric disorder.

Using this safe technique, hyperperfusion was observed in the bilateral sACC in the chronically depressed and treatment-resistant patients, compared with healthy controls ($p = 0.001$). These results confirm the initial hypothesis of sACC hyperactivation in patients with chronic and treatment-resistant depression, which has already been observed using other imaging techniques (including H₂(15)O PET and FDG PET) (Drevets, 2000; Mayberg et al., 1999; Seminowicz et al., 2004). The subgenual cingulate has become a particular area of interest in depression research over the last decade. An increasing number of studies have identified it as the focus of dysfunction. In support of this hypothesis, a decrease in sACC activity has been reported as part of the clinical response to different antidepressant treatments, including specific serotonin reuptake inhibitors (SSRIs) antidepressant medications, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), ablative surgery and DBS (Dougherty et al., 2003; Goldapple et al., 2004; Malizia, 1997; Mayberg et al., 2000; Mayberg et al., 2005; Mottaghy et al., 2002; Nobler et al., 2001). There have been far fewer studies of chronically depressed and treatment-resistant patients. Mayberg et al. (Mayberg et al., 2005) observed persistent metabolic hyperactivation in patients who were resistant to all the usual therapeutic treatments. However, to our knowledge, there are no specific data in the literature to show whether sACC hyperactivation is due to the chronic depression itself or whether it is related to treatment resistance. Moreover, previous studies (Drevets, 2000; Mayberg et al., 1999; Seminowicz et al., 2004) have reported significant activation of the anterior cingulate area corresponding to BA 32, without referring specifically to the Brodmann area 24a.

Recent research in functional imaging has drawn attention to a change in brain activity during the remission of depressive symptoms. Generally, patients were evaluated before and after 6 or 10 weeks of treatment. When patients responded to antidepressant drugs with remission of symptoms, studies reported a normalization of brain activity, with an increase in the activity of the cortical regions (dorsolateral prefrontal cortex, dorsal ACC) and a decrease in that of the subcortical-limbic structures (sACC, amygdala, hippocampus) (Brody et al., 2001b; Buchsbaum et al., 1997; Davies et al., 2003).

In the same context of remission of symptoms in response to treatment, the hyperactivation of the pregenual ACC (or BA24a) prior to treatment would appear to predict a positive response to treatment. (Mayberg et al., 1997)

We observed significant hyperperfusion in the prefrontal dorsomedian cortex (BA10) on the left side. Previous studies had shown a reduction in functional activity in this area for major depressive disorder but not for treatment-resistant patients (Baxter et al., 1989; Buchsbaum et al., 1997; Drevets, 2000; , 2001; Drevets et al., 2002). Therefore, the question is whether the hyperperfusion of the prefrontal dorsomedial cortex is involved in the resistance factor. Regarding the subcortical structures, our analysis revealed hyperperfusion in several basal ganglia on the left side (pallidum and putamen). There was also hyperperfusion of the left amygdala. Drevets et al. had already observed hyperactivation of the amygdala in depressed patients in several studies involving a variety of imaging techniques (Drevets, 2000; , 2001; Drevets et al., 2002; Drevets et al., 1992) and had linked it to the severity of the depressive symptoms. Therefore, it appears that the subcortical structures, and more specifically the amygdala, need to be taken into account in chronic and treatment-resistant depression.

To date, functional imaging research of the resting brain has been limited mainly to PET and SPECT studies. These techniques have some significant limitations, including poor spatial resolution and exposure to radioactive tracers, which limits the frequency with which they can be repeated. Functional MRI (fMRI) using the BOLD effect overcomes both these problems, but cannot be efficiently applied to resting-state data. Moreover it is sometimes difficult for patients with psychiatric disorders to perform the complicated cognitive tasks needed to induce activation to measure the BOLD effect in fMRI.

Arterial spin labeling (ASL) is a perfusion MRI technique in which arterial blood water is magnetically labeled as an endogenous perfusion tracer. ASL is based on the subtraction of two consecutively acquired images. The first image is usually acquired after saturation or inversion of the arterial blood magnetization upstream of the area of interest. The second image is acquired without any manipulation of the arterial magnetization, and the subtraction of both images provides information about the amount of labeled magnetization. This is an entirely non invasive technique that does not involve exposure to ionizing radiation or radioactive isotopes and thus improves patient safety. Published comparisons between normal ASL and H(2)(15)O PET subjects demonstrate a close correlation both at rest (Ye et al., 2000) and with task-related activation (Feng et al., 2004). ASL is used in studies of cerebral blood flow, particularly in the case of neurovascular (Wolf et al., 2003), neurodegenerative (Du et al., 2006) and tumor diseases (Warmuth et al., 2003). Very few studies have used ASL for

psychiatric disorders, and then only at 1.5 tesla (T) (Clark et al., 2006; Clark et al., 2001; Doraiswamy et al., 1999). As ASL is a low signal-to-noise ratio (SNR) technique, the shift from 1.5 to 3 T represents an effective means of improving ASL (Golay and Petersen, 2006). The achievable signal-to-noise ratio (SNR) increases linearly with the main magnetic field and the concomitant increase in T1 relaxation time should logically improve labeling duration. There are two major approaches in ASL: pulsed (PASL) and continuous (CASL) (Golay and Petersen, 2006), depending on the labeling scheme. Whereas the mean ratio of the SNR on the CASL versus PASL images is 1.33 at 3T (Wang et al., 2005), it not possible to use multichannel phase-array coil with parallel imaging (PI) with CASL. Because some of the most important problems at high field, in particular EPI distortion artifacts (Lupo et al., 2006), can be effectively addressed with parallel acquisition (Pruessmann, 2004), we preferred to use PASL with multichannel phase-array coil with PI.

The main limitation of this study stemmed from the difficulty of recruiting chronically depressed patients who met the strict inclusion criteria concerning resistance to treatment. The inclusion of a third group made up of depressed patients who did respond to treatment would have allowed us to validate the hypothesis that sACC hyperperfusion is specific to treatment-resistant depression.

Our study has two characteristics. First, most studies, the notion of resistance has received little or no attention. We support the hypothesis that the Cg25 area is involved in the concept of resistance and provides a better understanding of the pathophysiology of depression, demonstrating the importance of the subgenual anterior cingulate cortex. Our study also shows that ASL appears to be an appropriate technique for studying perfusion in psychiatric disorders safely. 3T MRI now represents the best means of improving this technique and, more particularly, of increasing spatial resolution without neglecting the signal-to-noise ratio.

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