

Increased myo-inositol in the posterior cingulate cortex in first-episode major depressive patients

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ABSTRACT

Major depressive disorder (MDD) is a severe, disabling pathology characterized, in addition to affective, cognitive and motor symptoms, by self-focused attention and rumination. During recursive self-focused processes and rumination, the posterior cingulate cortex (PCC) is activated. *In vivo* proton magnetic resonance spectroscopy (MRS) is a noninvasive imaging technique that can directly assess living biochemistry in localized brain regions. The aim of this study, therefore, was to use ¹H-MRS as a means of analyzing brain metabolites in the PCC of a group of first-episode, unmedicated MDD patients. PCC metabolite levels were analyzed at 3-T in a single voxel located bilaterally over the PCC in 7 patients diagnosed for the first time with MDD and with no previous pharmacological treatment, as well as in 9 control subjects. Differences in metabolite levels between groups were compared using independent t-tests. Myo-inositol was significantly higher, and NAA + NAAG/Cr significantly lower, in MDD patients than in controls. The other brain metabolites showed no statistical differences. The present results suggest that alterations in PCC metabolite levels are likely involved in MDD pathophysiology, and may help to improve our understanding of MDD and the role of the PCC in some symptoms of depression.

Keywords: Major Depressive Disorder; Posterior Cingulate Cortex; Metabolites; ¹H-MRS; Myo-Inositol; N-Acetyl-Aspartate

1. INTRODUCTION

Major depressive disorder (MDD) is a complex pathol-

ogy with cognitive and emotional symptoms; is considered one of the most prevalent and disabling of all psychiatric disorders [1]. In addition to affective symptoms such as low mood, anhedonia, poor motivation, impaired psychomotor activity and reduced energy, MDD is characterized by self-focused attention [2] and rumination; *i.e.*, recurrent obsessive thoughts on one's negative mood, guilt, death, failure or inadequacy [3], and on the possible causes and consequences of these symptoms [4]. Converging evidence from clinical, neuropathological and neuroimaging studies of depression have shown structural, metabolic and electroencephalographic alterations in specific brain regions linked to distributed networks involved in cognitive and emotional modulation. MDD has been associated with decreased activity in prefrontal areas, including the dorsolateral and ventrolateral prefrontal cortices, the parietal lobule and the dorsal anterior and posterior cingulate cortices, and with increased activation of limbic and paralimbic areas, such as the anterior subgenual cingulate, the insula, the hippocampus, the hypothalamus and the amygdala [5-7]. Some of these regions overlap two brain networks: the default-mode network [8] and the cortical midline network, both of which are involved in self-referential processes and depression [2,9]. Activation of the default-mode network has been associated with introspective states, such as processes implying reference to oneself [10], episodic memory and rumination [11], while some structures of the midline network are activated in self-related tasks [12]. Brain regions participating in the default-mode network have been found to be less deactivated in depressed patients at rest [13,14], a decreased deactivation that has been correlated with the severity of depression and feelings of hopelessness [15]. In recent years, the posterior cingulate cortex (PCC) has become a focus of

attention for two reasons: first, it has been linked to self-focus and rumination; and, second, it forms part of both of these networks. The PCC has been found to be activated in healthy subjects during information retrieval from episodic [16] and autobiographic memories [17], as well as during self-referential processing [10,18,19], and rumination [20]. Interestingly, some neuroimaging studies have found both structural and activity alterations in the PCC of MDD patients; for example, MDD patients have reduced cortical thickness [21], decreased gray matter volume [22] and lesser cortical folding and gyri-fication index over PCC [23]. MDD patients show electroencephalographic hypoactivation over the posterior cingulate while at rest [24], and decreased blood flow with sad, compared to neutral word retrieval [25]; whereas they present greater activation in the PCC than controls during rumination compared to the abstract distraction condition [20], and to sad faces compared to healthy volunteers before antidepressant treatment. This highly-activated state of the PCC decreases after effective antidepressive pharmacological treatment [5,26]. In addition to numerous abnormalities in brain morphology and neurotransmitter systems, a growing body of evidence suggests that metabolite levels in several brain regions, as assessed by *in vivo* proton magnetic resonance spectroscopy (MRS), are altered in MDD and may play an important role in the pathophysiology of depression. Magnetic resonance spectroscopy is a noninvasive imaging technique that can directly assess the most abundant metabolites in localized brain regions [27]. Changes in metabolite levels can be considered markers of the functional integrity and viability of brain tissue, and have been used successfully in the study of psychiatric disorders [28]. Most of the MRS studies in cases of depression have focused on anterior brain areas. Myo-inositol (mI), one of the metabolites analyzed by MRS, is a precursor molecule for several brain metabolites. It participates in signaling processes in the phosphatidylcholine system and is involved in the regulation of cellular osmolarity; therefore, it has been considered as a possible marker of inflammatory responses in the brain and of glial cell loss [27,29]. Levels of mI have been found to be lower in the anterior cingulate cortex [21], as has the mI/Cr (creatine) ratio in the left and right prefrontal regions [30] and in the prefrontal and anterior cingulate cortices in medicated patients after several weeks of wash-out [31]. In contrast, higher levels have been seen in the medial prefrontal cortex and pregenual cingulate cortex of medication-free, fully-recovered patients [32] and in the left dorsolateral prefrontal cortex in treatment-naïve, first-episode, female patients and after antidepressant treatment [33]. N-acetylaspartate (NAA) and choline compounds (Cho) participate in lipid biosynthesis; hence they are considered putative markers of neu-

ronal integrity [27]. First-episode and treatment-naïve patients with MDD showed significantly lower NAA/Cr ratios in the DLPFC compared to control subjects [34] and to recurrently-remitted and chronic patients, while choline compounds show increased values in chronically-depressed patients with prolonged illness duration [35]. However, most of the MRS studies of MDD have reported no differences in NAA [27,31]. Glu and GABA have been reported to be lower in dorsomedial, ventromedial and anterolateral prefrontal regions in non-medicated MDD patients [36], while the decreased levels of Glu and Gln/Cr in the pregenual region of the cingulate cortex are associated with the severity of depressive episodes [37]. However, Glu decreases in both remitted and chronic, non-remitted MDD patients compared to first-episode and control subjects [35]. These apparently discrepant results in MRS studies of depression may be explained by the variability and specific characteristics of the different patient groups studied, including different age, female *vs.* male, drug-naïve *vs.* medicated, first-episode *vs.* chronic depressives, and remitters *vs.* non-remitters, as well as to the sensitivity of the methodology utilized to assess metabolite levels. Despite the many studies reporting structural and activation alterations of the PCC and an association of the PCC with rumination and self-focus in MDD, little is yet known about the biochemical composition of the PCC in MDD. The aim of the present exploratory study, therefore, was to use ¹H-MRS at 3-T to examine metabolite levels in the PCC in first-episode, drug-naïve patients with MDD. We examined the metabolites in a voxel centered on the PCC, hypothesizing that because the PCC presents structural and activation abnormalities, metabolite levels will be altered in MDD patients compared to healthy individuals.

2. METHODS AND MATERIALS

2.1. Subjects

Eight adult male patients from 21 to 46 years of age participated in this ¹H-MRS study. To avoid possible confounding factors derived from plastic changes in brain metabolites due to long-term illness evolution, or those introduced by lifelong pharmacological use, only first-episode, unipolar-diagnosed MDD (MDDG) and naïve-treatment patients were included. Patients were recruited from the Clinical Service of Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (INPRFM) in Mexico City. A psychiatrist confirmed both the primary diagnosis of unipolar MDD and the absence of any other Axis I psychiatric disorders, according to DSM-IV criteria [38]. A control group (CG) (n = 9) within the same age range (23 to 47 years old) was recruited through announcements posted around the INPRFM. Healthy controls were free of medication and had no current symp-

toms or medical histories of psychiatric, neurological or medical disorders. They were screened through a diagnostic interview and were subjected to the same tests as the MDD patients. To confirm the absence of psychiatric disorders in CG and comorbidity in the MDDG, all participants were screened using the SCL-90R questionnaire, which gives a global severity index derived from nine subscales that explore somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoia, ideation, and psychoticism [39]. The Hamilton Depression Scale [40] and Beck Depression Inventory [41] were used to confirm diagnoses and determine the severity of MDD, as well as its absence in CG. Only patients with moderate-to-severe depression according to the Hamilton Depression Scale (score > 14) and the Beck Depression Inventory (score > 10) were included. Control subjects had to be within normal range on both scales (*i.e.*, Beck <7; Hamilton <10). None of the participants in CG met the criteria for either current or past MDD episodes. The exclusion criteria for MDD patients included: 1) other Axis I psychiatric disorders and symptoms; 2) a history of alcohol or substance abuse within the 6 months prior to entering the study; 3) the presence of neurological disorders and physical illness. The exclusion criteria for healthy controls included psychiatric illness in first-degree relatives, and current or past medical or neurological illness. Exclusion criteria for all potential participants were counter-indications for ¹H-MRS. All participants gave their informed, written consent after a full explanation of the study protocol, which was approved previously by the Ethics Committee of the INPRFM.

2.2. Procedure

Once the Clinical Service of the INPRFM had screened the MDD patients to determine those who satisfied the inclusion and exclusion criteria, those individuals were scheduled for a single session at the Cerebral Imaging Area of the INPRFM just prior to beginning antidepressant treatment. Evaluations and scanning were done in a single session that was divided into two phases. In the first, subjects were assessed by a trained psychiatrist (J.J.C.) in accordance with the Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the SCL-90R questionnaire. In the second phase, the actual ¹H-MRS scanning was conducted. Control subjects followed exactly the same procedure.

2.3. ¹H-MRS Scanning

Localized ¹H-MRS was performed in a routine clinical MR scanner Achieva Quasar Dual MRI System (Phillips Medical Systems, Eindhoven, Holland) at 3.0 Tesla. Each subject participated in a single voxel spectroscopy scan

located in the posterior cingulate cortex (PCC). As an anatomical reference of high resolution and contrast, it was included the T1 image acquisition with inverse recovery pulses (IR), (repetition time) TR = 2949 ms, (echo time) TE = 15 ms, inversion time (IT) = 400 ms. A 20 × 20 × 20 mm³ voxel was placed bilaterally on the PCC aligned tangential to the splenium of the corpus callosum in a sagittal plane, centered on the midline (**Figure 1**). Single-voxel ¹H-MRS spectroscopy was conducted using a short echo PRESS (Point Resolved Spectroscopy Sequence) (TE = 40 ms, TR = 2000 ms, NS = 64). Quantification of metabolic intensities was performed by using the LCModel [7] with water suppress peak as reference [42]. The Linear Combination of Metabolite Basis Spectra (LCModel) normalizes the metabolite spectra obtained using the water suppressed peak as reference [42].

2.4. Statistical Analysis

Statistical analysis was performed with commercial SPSS software (SPSS 17.0 for Windows). Student-T tests for independent samples were used to compare statistical differences between MDDG and CG for each of the metabolites assessed in the PCC.

3. RESULTS

One MDD patient had to be excluded due to claustrophobia, which caused the scanning sessions to be interrupted; thus 7 of the 8 MDD patients and all of the control subjects completed the study. The results obtained from the Hamilton Depression Scale (MDDG: mean = 21.11, SD = 5.32; CG: mean = 1.33, SD = 1.52; $t = 4.40$; $p < 0.0009$) and the Beck Depression Inventory (MDDG: mean = 27.44, SD = 6.54; CG: mean = 1.66, SD = 1.52; $t = 8.42$; $p < 0.00001$) showed the expected significant differences between MDDG and CG, thus confirming the diagnoses of major depressive disorder in the former and the absence of depression in the latter. Results of the SCL-90R questionnaire confirmed the absence of psychiatric disorders in CG and of comorbidities in MDDG (MDDG: mean = 1.48, SD = 0.80; CG: mean = 0.071, SD = 0.02; $t = 2.36$; $p = 0.16$). Location of the voxel and Representative spectra and LCModel fits are illustrated in **Figure 1**. The results of ¹H-MRS scanning for the metabolites assessed are shown in **Table 1** and **Figure 2**. Significantly increased levels of mI and of the mI/Cr ratio, together with a decreased NAA + NAAG/Cr ratio in the PCC were observed in the MDD group compared to healthy controls. There were no significant differences between the groups with respect to the direct measurements of Cr, Cr + PCr, Glu, Gln, GPC, GPC + PCh and NAA, or in the metabolite-to-Cr ratios of Glu/Cr, GPC + PCh/Cr, NAA/Cr.

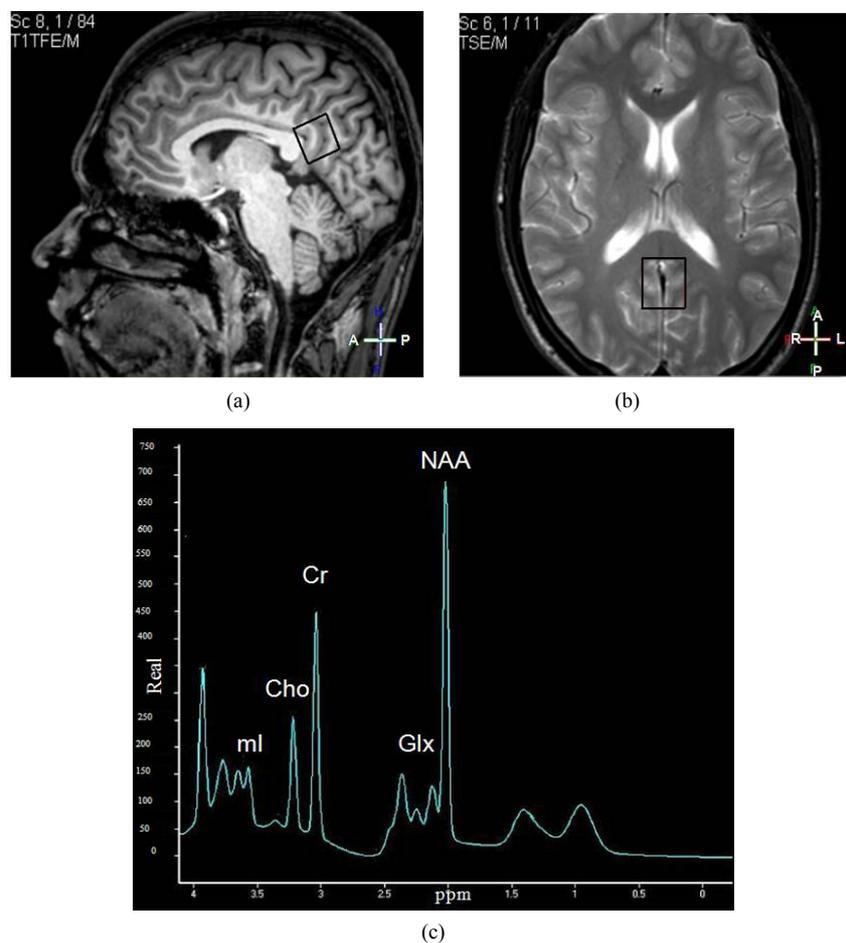


Figure 1. Schematic of voxel location over bilateral posterior cingulate cortex, sagittal view (a) and axial view (b). Representative spectra of a control subject (c).

Table 1. Absolute metabolite concentrations registered by ¹H-MRS and analyzed by LCModel for Major Depressive Disorder Group (MDDG) and Control Group (CG).

Metabolites	MDDG		CG		t	P
	Mean	SD	Mean	SD		
Creatine	4.556	1.088	3.697	0.929	1.13	0.86
Creatine + Phosphocreatine	5.481	0.557	5.120	0.545	1.30	0.85
Glutamate	10.667	2.682	11.587	2.446	0.64	0.59
Glutamate/Cr	2.046	0.533	2.384	0.651	1.23	0.43
Glutamate + Glutamine	11.531	2.938	11.933	1.995	0.30	0.40
Glycerilphosphocholine	1.109	0.184	1.098	0.108	1.49	0.26
GPC + PCh	1.109	0.184	1.064	0.143	0.55	0.58
GPC + PCh/Cr	0.203	0.031	0.210	0.040	0.39	0.9
Myo-inositol	6.136	2.01	5.1102	0.6487	1.28	0.0001
Myo-inositol/Cr	1.169	0.5111	1.035	0.1963	0.64	0.016
N-acetyl-aspartate	7.124	0.351	7.440	0.392	1.66	0.55
N-acetyl-aspartate/Cr	1.297	0.118	1.465	0.150	2.43	0.39
NAA + NAAG/Cr	7.257	0.490	7.801	0.561	0.54	0.05

SD: Standard Deviation; t: Student-t test for independent groups. GPC+PCh: glycerilphosphocholine; Cr: creatine; NAAG: N-acetyl-aspartate-glutamate; p < 0.05 in bold.

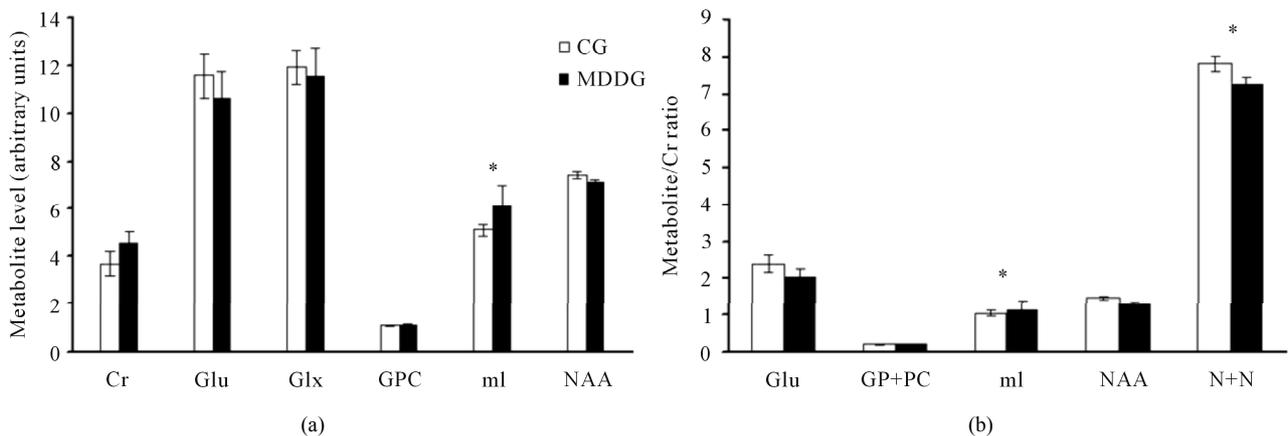


Figure 2. Mean and standard error of metabolite levels (a) and metabolite to Cr levels (b) for the control group (CG) and the major depressive disorder patients (MDDG). Asterisks above bars indicate significant differences between groups ($p < 0.05$).

4. DISCUSSION

The main finding of this exploratory study of metabolite levels in the PCC in major depression is that the mI level was significantly higher, while the NAA + NAAG/Cr ratio decreased in the PCC of first-episode, treatment-naïve male MDD patients; results that suggest the involvement of the PCC in the pathophysiology of the early stages of depression. Both the increased mI and the decreased NAA + NAAG/Cr levels indicate an alteration in PCC metabolite states that may well be associated with altered brain cell metabolism. Although the decrease observed in NAA+NAAG was only significant to the Cr ratio, Cr was not significantly different in MDD patients. NAA has been associated with neuronal integrity [27], whereas increases in mI content have been interpreted as representing either glial proliferation or an increase in glial cell size and, therefore, have been considered markers of inflammation in the brain [29]. It has also been demonstrated that high levels of mI are present in some types of neurons, where it is involved in second messenger signaling [29]. Though the present methodology is not capable of differentiating between mI level in glial or neuronal cells, or of determining whether this increase reflects compensatory changes related to other pathogenic processes (further research is needed), these results do indicate an alteration in PCC metabolite levels and thus support the involvement of the PCC in depression. Rumination and self-focused attention constitute important symptoms of depression and are considered risk factors for the onset and course of depression [2,43]. The findings of altered metabolite levels in the PCC in this study support the notion that the PCC may be involved in pathological rumination and self-focused attention in depression; however, metabolite levels in the PCC of depressed patients have not yet been assessed; thus the increase in the resonance peak of mI in the PCC cannot be directly compared with other studies. Nevertheless,

the present results of increased mI levels in the PCC in MDDG are in line with studies showing morphological alterations [21,23], lower electroencephalographic activation at rest [24], and higher metabolic activation during rumination [20] in MDD patients. The literature contains reports of functional hyper-connectivity in the PCC and the subgenual-cingulate cortex, correlated with behavioral measures of rumination and brooding in relation to the severity of depression [24]; and of the PCC with the dorsomedial prefrontal cortex, correlated with depressive symptoms in MDD [14]. The present results actually suggests an imbalance between the anterior and posterior regions of the midline system that concurs with the proposal that altered functional connectivity underlies some aspects of emotional deregulation [14]. Moreover, this agrees with studies postulating that the effects of lithium therapy in mania and depression may be a result of mI depletion [44]. Most previous studies on brain metabolites have been carried out using 1.5-Tesla scanners, but the present study used high-field imaging at 3.0 Tesla and brain water as a referencing method to provide a substantial increase in sensitivity and a better possibility of assigning resonance peaks directly, and not as a ratio to Cr. This approach makes it possible to determine whether a higher measured level of mI is due to a lower level of Cr or to a real increase of mI.

Limitations

The present data must be considered as preliminary given the small number of patients assessed and, undoubtedly, need to be corroborated in larger groups of major depression patients. Unfortunately, due to the nature of the INPRFM, the majority of patients who seek treatment have already experienced multiple depressive episodes and comorbidity with other Axis I psychiatric disorders [38], and also have long histories of drug use; thus, it was not possible to locate more than these 8

young, first-episode patients that were free of Axis I comorbidities and had not received any pharmacological treatment during at least an interval of one year. Because of the confounding effects introduced by the diversity of types of depression, illness duration, and histories of antidepressant treatment, we preferred to maintain group homogeneity rather than include a larger number of patients. Despite this shortcoming, and given the lack of studies on metabolite states in PCC in depression, we considered it important to communicate the present findings. Our MDD patients did not differ from healthy controls in the other metabolites measured. The lack of any such significant differences agrees with studies of anterior brain regions and with similar conditions as our patients in the MDDG that found no differences in other brain metabolites like Glu, Cr [31-34,37], NAA [31,33, 34] or Cho [21,31,33]; however, the possibility that these variations are due to the small number of participants cannot be discarded. In conclusion, to the best of our knowledge this is the first evidence of metabolite alterations in the PCC in moderate-to-severe depression in first-episode, medication-naïve patients. Our results suggest that alterations in PCC metabolite levels are likely involved in MDD pathophysiology and may help improve our understanding of this pathophysiology and the role of PCC in some symptoms of depression.

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