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Glutamatergic and N-acetylaspartate metabolites in acute depressive and euthymic patients with bipolar disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies

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UNIVERSITÉ CLERMONT AUVERGNE

UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

CHABERT Jonathan Alphonse

Présentée et soutenue publiquement le 17/09/2021

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Président du jury :

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ABBREVIATIONS :

ACC : Anterior cingulate cortex / cortex cingulaire antérieur

BD : Bipolar disorder

CI : Confidence interval

Cr : Creatine

DIPFC : Dorsolateral prefrontal cortex / cortex préfrontal dorsolatéral

DSM : Diagnostic and statistical manual of mental disorders

Gln : Glutamine

Glu : Glutamate

Glx : Pool Glu + Gln

HC : Healthy controls

¹H-MRS : Proton magnetic resonance spectroscopy

ICD : International classification of disease

MPFC : Medial prefrontal cortex

MRI : Magnetic resonance imaging

MCC : Medial cingulate cortex

NAA : N-acetylaspartate

PFC : Prefrontal cortex / cortex préfrontal

PRISMA : Preferred reporting items for systematic reviews and meta-analyses

ROI : Region of interest

SMD : Standardized mean differences

TCA : Tricarboxylic acid cycle

VIPFC : Ventrolateral prefrontal cortex

WmPFC : White matter prefrontal cortex / substance blanche du cortex préfrontal

INTRODUCTION :

Bipolar disorder (BD) is a mental illness with a lifetime prevalence of approximately 2.4% in the general population (1). BD is characterized by successive mood episodes (depressive, manic/hypomanic or mixed episodes), and inter-episodic periods in which the patients were in clinical remission. This classical view, however, has been challenged since a large number of euthymic BD patients suffer from numerous persistent symptoms or cognitive problems during these periods of apparent clinical stability.

It is relatively common for BD to begin with depressive episodes, since on average a patient with BD will have 2.5 major depressive episodes compared to 1 manic or hypomanic episode (2). Under these conditions, the early diagnosis of BD may be very difficult and delayed from the onset of illness, and may result in inappropriate therapeutic management. In order to improve the management of BD patients, a better understanding of the mechanisms underlying BD still seems to be of interest.

Magnetic resonance imaging (MRI) data have identified several areas with altered structure or function in BD patients. The prefrontal regions tend to be hypo-activated, which alters the regulation of the hyperactive limbic regions and therefore leads to an increased emotional response (3,4). This cortico-limbic dysregulation could be related to connectivity problems between the prefrontal and limbic regions (5). This hypothesis seems to be supported by several arguments, notably the fact that a decrease in total white matter volume has been found in BD patients (6), and that T2 or FLAIR hyperintensities in the deep prefrontal and periventricular white matter are found in various studies (7,8). The emergence of diffusion MRI has supported the dysconnectivity model in BD. In a recent mega-analysis, BD patients showed significant damage to the corpus callosum and the cingulate, but also to many other

regions, including those allowing the association between the prefrontal and limbic regions (9). However, the hyperactivity of the limbic regions does not seem to be explained solely by poor frontal regulation, since volumetric anomalies have been identified in anatomical MRI. For instance, Ellison-Wright & al found a decrease in the volume of the rostral part of the anterior cingulate cortex (ACC) in BD patients in comparison with healthy subjects (10). This decrease has also been observed in the meta-analysis of Bora & al, who also add a decrease in the volume of the fronto-insular region (11).

At the cellular level, several abnormalities have also been observed. The hypothesis of a dysfunction in the cerebral mitochondria has been the subject of numerous publications, with Morris & al going so far as to propose a model in which the various periods with mood episodes would be related to mitochondrial energy production. Thus, manic episodes would be caused by an increase in energy production, whereas depressive episodes by a decrease production (12). Genetic studies have also highlighted the involvement of mitochondria in the pathophysiology of BD, where mutations in their DNA could be at the origin of impairments in the intracellular calcium signaling system (13). N-acetylaspartate (NAA) is the most abundant molecule in the brain after water, its concentration is quantifiable by proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) and may be considered a marker of the integrity of mitochondrial energy metabolism, as it closely correlates with the concentration of ATP produced in the mitochondria (14-16). Its involvement in the pathophysiology of BD has been explored by many authors, and was further evaluated in the meta-analysis of $^1\text{H-MRS}$ studies who found a significantly lowered NAA levels in BD patients in the basal ganglia and hippocampi (17). However, due to a lack of data, Kraguljac & al could not analyze the level of NAA according to the mood state of the patients. The present meta-analysis aims to determine whether compared to healthy controls BD patients have alterations in their NAA

levels in different regions of the prefrontal cortex (dorsolateral prefrontal cortex -dlPFC-, ventrolateral prefrontal cortex -vlPFC-, medial prefrontal cortex -mPFC-, white matter prefrontal cortex -wmPFC-), the ACC, and the hippocampi. We focus only on the depressive and euthymic periods for two main reasons. First of all, it is difficult to carry out ^1H -MRS studies during manic or hypomanic episodes without administering sedative treatment, and the impact of these treatments on ^1H -MRS data has not really been studied. Moreover, in a meta-analysis, Yildiz-Yesiloglu & al did not find any modification of the NAA levels in patients suffering from a major depressive disorder, so that modifications during the depressive or euthymic phases of BD patients could help in the diagnostic process (18).

The glutamatergic system has an important role in brain plasticity, neurotransmission, energy metabolism, etc... (19). It is directly linked to NAA through the tricarboxylic acid cycle (TCA cycle), the synthesis of NAA requiring the transamination of glutamate to aspartate (15). Clark & al also propose that the NAA could in certain circumstances serve as a reservoir for glutamate (20). A growing body of evidence seems to underline its involvement in the pathophysiology of BD (21-24). In our meta-analysis we will also compare, within the different regions mentioned above, glutamate (Glu), glutamine (Gln) and Glx levels (essentially corresponding to the sum of Glu and Gln levels) between BD patients and healthy subjects.

Therefore, the objective of our meta-analysis was to evaluate if there were differences in NAA, Glutamate, Glutamine and Glx levels between BD patients and healthy controls.

METHODS :

Protocol registration:

This study was carried out by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement

The full protocol was uploaded to the International Prospective Register of Systematic Reviews (CRD42020182638).

Study search:

The search was performed with Medline, Embase, Psycinfo. All studies published before January 20, 2021 have been included.

The following search equation was used in All Fields mode: Bipolar AND (MRS OR « Magnetic Resonance Spectroscopy » OR « Magnetic Resonance Spectroscopies »). Search was supplemented with bibliographic and textbook cross-referencing, and by reviewing previous meta-analyses and systematic reviews to avoid missing potential studies.

Study selection:

Publication type:

The selected studies had to be written in English, they had to be complete articles in the form of cross-sectional studies or randomized controlled trials. The selected studies had to have a group of BD patients and a group of healthy controls (HC).

Inclusion and exclusion criteria:

Studies were included if:

- (1) patients met the Diagnostic and Statistical Manual of Mental Disorders (DSM), 3rd, 4th, or 5th edition criteria for BD, or the International Classification of Disease diagnostic (ICD) criteria for BD. The control subjects did not have any mental illness according to these same references.
- (2) BD patients had to meet criteria for a major depressive episode or be in clinical remission.
- (3) BD patients and HC had to be between 18 and 65 years of age
- (4) BD patients and HC were not required to have psychiatric, neurological, head injury or addictive co-morbidities (except for smoking)
- (5) A proton magnetic resonance spectroscopy technique was to be used, and the following metabolites were to be quantified: NAA, Glu, Glx, Gln
- (6) Regions of interest (ROI) were to target: mPFC, dIPFC, vIPFC or wmPFC, ACC, hippocampi.

Data extraction :

Two authors (JC and EA) determined the keywords together, screened abstracts and titles according to inclusion and exclusion criteria, then evaluated the full texts independently in order to determine eligible studies. Any study exclusions were justified in accordance with PRISMA criteria. Any disagreements between authors on whether or not to include a study were resolved through discussion. Data were extracted by JC, stored in an Excell spreadsheet, then verified by EA. If different publications reported data from the same population, we included data from the publication with the larger sample size. If data or

necessary informations was missing from published articles, the authors of the studies were contacted to retrieve it.

Quality assessment:

The quality of the original studies was assessed using the Newcastle-Ottawa Quality Assessment Scale after arranging it for a cross-sectional study design, similar to the meta-analysis conducted by Moriguchi & al (25).

Statistical analyses:

Statistical analyses were performed with Stata software (version 15, StataCorp, College Station, TX). The meta-analysis took into account of between- and within-study variability. To address the non-independence of data due to study effect, random-effects models (26) were preferred to the usual statistical tests to assess standardized mean differences (SMD) and their 95% confidence intervals. Means and standard-deviations were compiled when available, or estimated. SMD were interpreted according to Cohen such as: <0.2 as trivial, 0.2–0.3 as small, 0.5-0.8 as moderate, and >0.8 as large (27,28).

At the lateral ROIs (wmPFC, dlPFC, vlPFC or hippocampi) the calculation of SMD was performed in both the right and left hemispheres. At the level of medial ROIs (ACC, mPFC) many, but not all, studies used a single voxel spanning both hemispheres, preventing separate results per hemisphere. Thus similar to Moriguchi & al, at the levels of medial ROIs when data from bilateral lobes were reported separately, the left lobe was used because the left lobe was examined in most studies (25).

For stratified analyses, same statistical approach was adapted. Heterogeneity in the study results was assessed by forest plots and the I^2 statistic, typically considered low for 25%, modest for 25% to 50%, and high for 50% (29). Publication bias was assessed by funnel plots and confidence intervals for each assessment method one at a time owing to their great effect on heterogeneity. To check the robustness of the results, sensitivity analyses were performed which excluded studies that would be not evenly distributed around the base of the funnel.

Finally, we performed subgroup analyses: first, we divided the ACC studies into perigenual ACC (composed of pre- and subgenual regions) and dorsal ACC (sometimes also called the MCC); second, we performed comparisons for each region according to the method used to quantify the metabolites (absolute vs. relative).

RESULTS :

Characteristics of included studies:

The search identified 32 studies (30-61) (Fig 1), which included a total of 772 healthy controls and 845 BD patients. Among these 32 studies, 10 studies included patients in a major depressive episode (210 patients), 21 studies included BD patients in clinical remission (603 patients), and 1 study combined BD patients in a major depressive episode and in clinical remission (22 patients in each group). The characteristics of these studies are described in Tables 1 and 2.

In depressed patients, 9 studies examined NAA (82%): 4 in wmPFC, 2 in dlPFC, 1 in mPFC, 7 in ACC, 3 in hippocampi; 3 studies examined Glu (27%): 2 in ACC, 1 in hippocampi; 4 studies examined Glx (36%): 2 in dlPFC, 1 in mPFC, 3 in ACC.

In remitted patients, 19 studies examined NAA (86%): 4 in wmPFC, 2 in dlPFC, 1 in mPFC, 1 unspecified in PFC, 7 in ACC, 3 in hippocampi; 7 studies examined Glu (32%): 4 in wmPFC, 2 in dlPFC, 1 in mPFC, 1 unspecified in PFC, 7 in ACC, 3 in hippocampi; 2 studies examined Glx (9%): 4 in wmPFC, 2 in dlPFC, 1 in mPFC, 1 unspecified in PFC, 7 in ACC, 3 in hippocampi; 3 studies examined Gln (14%): 3 in ACC.

The studies using a magnetic field of 1.5 Tesla are 5 in depressed patients (42%) and 9 in remitted patients (41%). Those using a magnetic field of 3 Tesla are 6 in depressed patients (50%) and 9 in remitted patients (41%). Those using a 4 Tesla magnetic field numbered 1 in depressed patients (8%) and 2 in remitted patients (9%). Two studies involving patients in remission did not give the intensity of the magnetic field used (see Table 1).

The Newcastle-Ottawa Scale score ranged from 3 to 6 and the average was 4.44, which suggests that the quality of the included studies was good on average (see Annexe II)

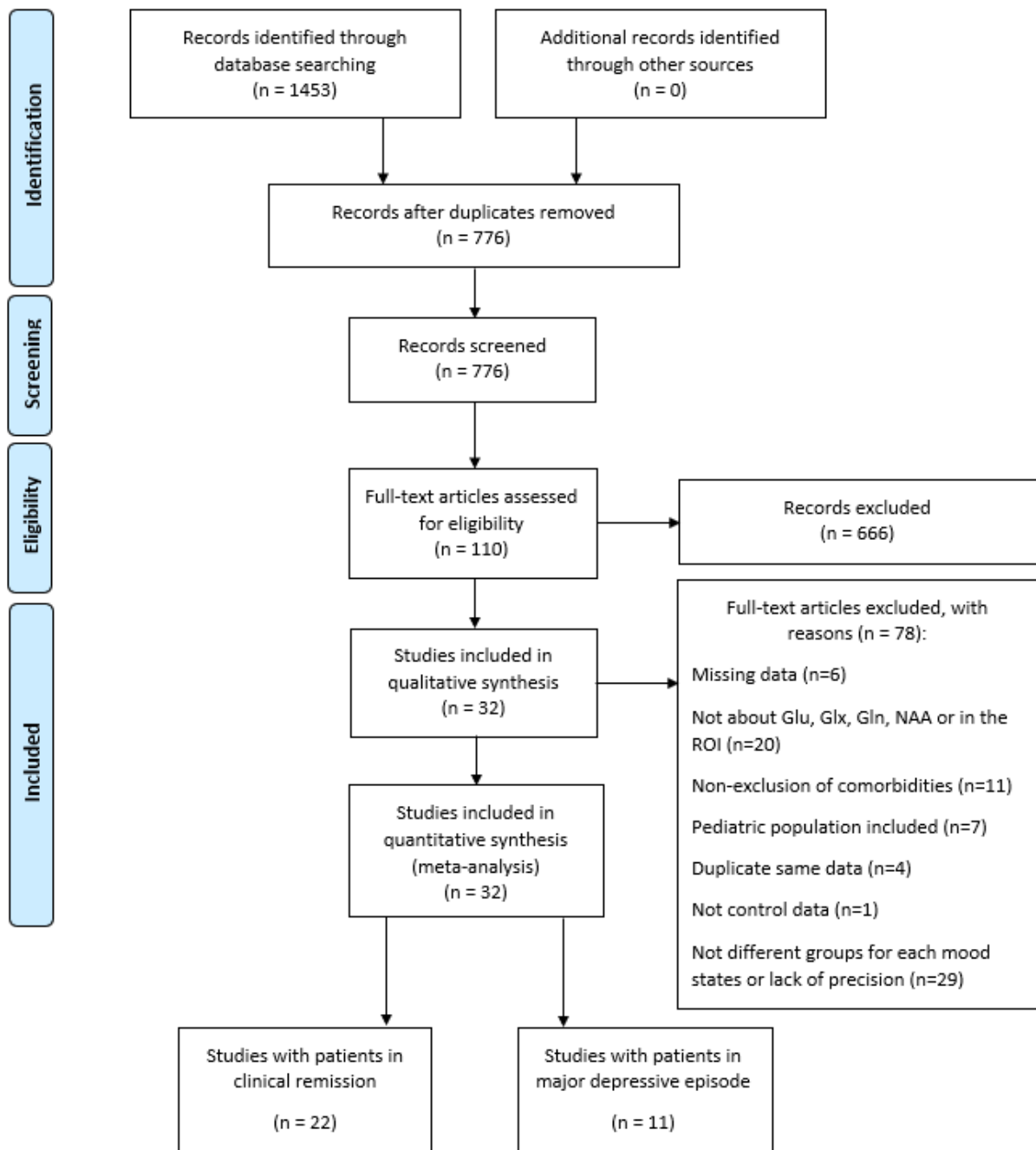


Fig 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram for study search

Meta-analysis:

BD patients in major depressive episode:

NAA levels in the wmPFC were measured in 124 BD patients and 118 healthy controls. In the left hemisphere, there were significantly lower levels of NAA in BD patients compared to

controls (SMD = -0.92 ; 95% CI, -1.30 to -0.53 ; $I^2 = 48.1%$; $p = 0.123$) (Fig. 2 and Fig. 3). In the right hemisphere, there were no significant difference (SMD = -0.52 ; 95% CI, -1.16 to 0.11 ; $I^2 = 82.1%$; $p = 0.001$) (Fig. 2 and Fig. 3).

NAA levels in the dlPFC were measured in 22 BD patients and 27 healthy controls. In the left hemisphere, there were significantly higher levels of NAA in BD patients compared to controls (SMD = 0.79 ; 95% CI, 0.20 to 1.38 ; $I^2 = 0.0%$; $p = 0.336$). There were no included studies measuring the levels of NAA in the dlPFC in the right hemisphere.

NAA levels in the other regions, as well as Glu, Glx and Gln levels in all regions showed no significant difference between BD patients and healthy controls.

BD patients in clinical remission:

NAA levels in the wmPFC were measured in 31 BD patients and 33 healthy controls. In the left hemisphere, there were significantly lower levels of NAA in BD patients compared to controls (SMD = -0.59 ; 95% CI, -1.10 to -0.07 ; $I^2 = 0.0%$; $p = 0.933$). Only the study by Liu & al measured NAA in the right wmPFC and did not find a significant difference.

Gln levels in ACC were measured in 85 BD patients and 103 healthy controls. There were significantly higher levels of Gln in BD patients compared to controls (SMD = 0.83 ; 95% CI, 0.16 to 1.50 ; $I^2 = 66.6%$; $p = 0.050$).

NAA levels in the other regions, as well as Glu and Glx levels in all regions showed no significant difference between BD patients and healthy controls.

Table 1: Characteristics of studies included with BD patients in clinical remission

Study (year)	Field Strength (Tesla)	TE (ms)	TR (ms)	Acquisition Sequence	CRLB threshold	Creatine Scaling	Patients (n)	Controls (n)	Age	Metabolite	ROI
Rocha (2015)	1.5	30	1500	PRESS			21	22	42.00	NAA	mOFC
Winberg (2000)	1.5	35	2000	PRESS		Cr-scaling	20	20	37.90	NAA	dIPFC
Senaratne (2009)	X	35	2000	PRESS	<20%		12	12	42.10	NAA, Glx	Hipp, mPFC
Scherk (2009)	1.5	30	1500	PRESS		Cr-scaling	33	29	43.86	NAA	dACC, dIPFC
Molina (2007)	1.5	136	1500	PRESS		Cr-scaling	13	10	37.80	NAA	dIPFC
Kalayci (2012)	1.5	35 and 144	3000	PRESS			15	15	38.87	NAA	dIPFC
Cumurcu (2008)	X	136	2000	PRESS		Cr-scaling	10	10	33.10	NAA	Hipp, dIPFC
Corcoran (2020)	3	80	3000	PRESS	<15%		17	41	44.64	Glu	dACC, dIPFC
Mahli (2007)	1.5	80	1500	STEAM			9	9	40.78	NAA	pACC, wmPFC
Ehrlich (2015)	3	80	3000	PRESS	<20%		21	42	45.90	NAA, Glu, Gln	Hipp, dACC
Soiero-De Souza (2015)	3	31-231	1600	JPRESS	<20%	Cr-scaling	50	38	31.70	Glu, Gln	dACC
Soiero-De Souza (2018 [1])	3	80	1500	PRESS	<20%		129	79	32.00	NAA	pACC
Soeiro-De-Souza 20(18 [2])	3	80	1500	PRESS	<20%	Cr-scaling	128	80	32.04	Glu, Glx	pACC
Amaral (2006)	1.5	144	1500	PRESS		Cr-scaling	13	15	34.54	NAA	pACC
Brady (2012)	4	30-500	2000	JPRESS	<25%	Cr-scaling	7	6	39.70	NAA, Glu	pACC
Kubo (2016)	3	18	5000	STEAM			14	23	45.00	NAA, Glu, Gln	dACC
Iosifescu (2009)	4	30	2000	PRESS	<15%		20	10	40.70	NAA	Hipp
Colla (2009)	3	80	3000	PRESS			21	19	54.20	NAA, Glu	Hipp
Haarman (2016)	3	144	2000	PRESS	<20%		22	24	44.50	NAA	Hipp
Scherk (2008)	1.5	30	1500	PRESS		Cr-scaling	13	13	31.45	NAA	Hipp
Deicken (2003)	1.5	135	1800				15	20	39.30	NAA	Hipp
Liu (2017)	3	144	1000	PRESS		Cr-scaling	22	24	26.82	NAA	wmPFC

BD = bipolar disorder; TE= time to echo; TR = repetition time; CRLB= Cramer-Rao lower bound; ROI = region of interest; NAA = N-acetylaspartate; Glu = glutamate; Gln = glutamine; mOFC = medial orbitofrontal cortex; dIPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; wmPFC = white matter PFC; pACC = perigenual anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; Hipp = hippocampus

Table 2 : Characteristics of studies included with BD patients in a major depressive episode

Study (year)	Field Strength (Tesla)	TE (ms)	TR (ms)	Acquisition Sequence	CRLB threshold	Creatine Scaling	Patients (n)	Controls (n)	Age	Metabolite	ROI
Michael (2009)	1.5	20	2500	STEAM	<20%		6	6	51.60	NAA, Glx	dIPFC
Li (2016)	3	30	1500	PRESS	<20%		13	20	31.00	NAA, Glx	dACC, mPFC
Smaragdi (2019)	3	35	1500	PRESS			16	21	37.00	NAA, Glx	dACC, dIPFC
Zhong (2014)	1.5	144	1000	PRESS		Cr-scaling	20	13	30.55	NAA	Hipp, pACC, wmPFC
Liu (2017)	3	144	1000	PRESS		Cr-scaling	22	22	24.36	NAA	wmPFC
Zhong (2018)	3	144	1000	PRESS		Cr-scaling	42	43	26.62	NAA	dACC, wmPFC
Lai (2019)	3	144	1000	PRESS		Cr-scaling	40	40	24.88	NAA	dACC, wmPFC
Croarkin (2015)	1.5	30	2000	L-COSY		Cr-scaling	15	9		Glu, Glx, NAA	ACC
Mellen (2019)	4	30-500	2000	JPRESS		Cr-scaling	23	14	62.00	NAA, Glu	pACC
Zanetti (2014)	3	35	1500	PRESS	<20%		19	17	28.70	NAA, Glu	Hipp
Atmaca (2012)	1.5					Cr-scaling	16	16	28.10	NAA	Hipp

BD = bipolar disorder; TE= time to echo; TR = repetition time; CRLB= Cramer-Rao lower bound; ROI = region of interest; NAA = N-acetylaspartate; Glu = glutamate; Gln = glutamine; dIPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; wmPFC = white matter PFC; pACC = perigenual anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; Hipp = hippocampus

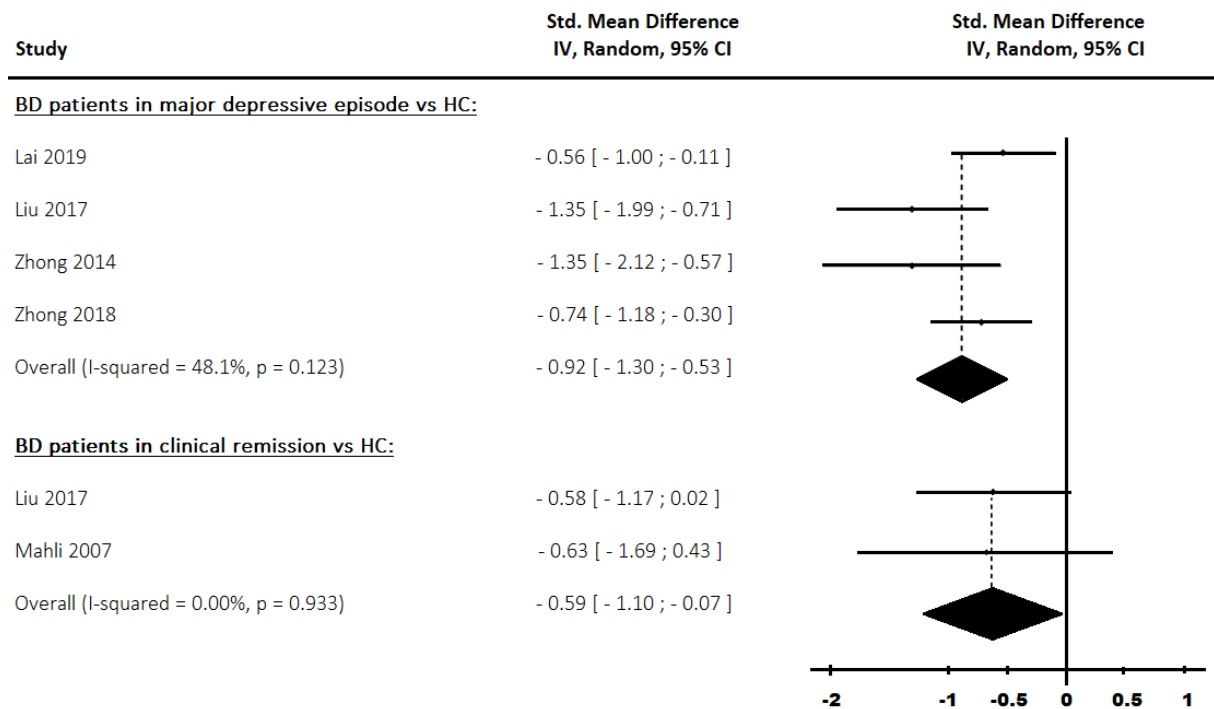


Fig 2: Studies Standardized Mean Difference (SMD) of N-acetylaspartate differences between bipolar disorder patients and controls in the left white matter prefrontal cortex

Subgroup analysis :

Our results obtained in the ACC have been further analysed by dividing for each mood state our studies into two groups: those whose the ROI was the perigenual part of the ACC, and those whose the ROI was the dorsal part of the ACC. Only the study by Croarkin & al could not be classified because it did not provide the exact positioning of the ROI (35), and no clarification was obtained from the authors. In neither subgroup was there a significant difference for any metabolite between BD patients (remitted or depressed) and healthy controls.

Other subgroup analyses have also been conducted on every metabolite in every region for varying reference methods when it was possible (absolute quantification vs relative quantification). No significant difference was found.

DISCUSSION :

Our meta-analysis aimed to determine whether quantification of NAA, Glu, Gln, Glx in the brain of BD patients without comorbidities could be useful to better understand the neurobiological mechanisms of BD. Our results showed that NAA levels in BD patients were significantly decreased in the left wmPFC during depressive and euthymic periods, significantly increased in the left dlPFC during depressive periods, and that Gln levels in BD patients were significantly increased in the ACC during euthymic periods in comparison with HC. The NAA and Gln, the Glu and the Glx levels were not statistically different between BD patients and HC in other regions.

The decrease in NAA levels in wmPFC in BD patients is probably one of the most interesting findings. NAA is produced in neural mitochondria from L-aspartate and acetyl coenzyme A. Studies have shown that its production is closely correlated with that of ATP and mitochondrial oxygen consumption (62-64), suggesting that its levels may reflect the integrity of mitochondrial energy metabolism^{15,16}. Through energy production, but also through many other mechanisms, mitochondria are involved in neuroplasticity processes, development and axonal regeneration (65,66). The decrease in NAA localized within the white matter of the prefrontal cortex is therefore consistent with the alterations in neuroplasticity and synaptic plasticity found in BD patients (67). NAA plays a unique role in the lipid synthesis of myelin sheaths, since it allows the transfer of acetate groups from the neuron to the oligodendrocytes (15,16). Thus, in addition to the abnormalities of energy production, neuroplasticity and synaptic plasticity indirectly may be impaired within the wmPFC by the decrease in NAA levels in BD patients. This decrease could also generate direct impairments of synaptic transmission and explain the T2 and FLAIR hypersignals found

on MRI (8), especially since it is possible to observe that the voxels of the included studies in our meta-analysis seem located in the same region as the hypersignals (deep white matter of PFC). Unfortunately, due to the location of the voxels where numerous nerve fibers with different destinations pass, it is difficult to link our outcome with functional abnormalities known in BD. Since the decrease in NAA was observed during both a depressive period and clinical remission, it could therefore constitute a "trait marker" of BD. It would be necessary to test whether it is also present during the manic episodes, and whether the NAA levels vary according to the duration of clinical remission.

NAA levels were also significantly increased in depressed BD patients in the left dlPFC in comparison with HC. Although this increase was also found by Kraguljac & al in their previous meta-analysis (17), the functional and anatomical MRI data do not specifically find abnormalities in this region during depressive episodes (68,69). One of the explanatory hypotheses could be related to the effects of lithium or valproate medication of the BD patients included (48). Indeed, these treatments lead to an increase in the Bcl-2 protein in the frontal cortex, a protein located in the mitochondrial membrane and involved in mitochondrial oxidation-reduction processes, but also in neuroprotection (70,71). However, it is also possible that ¹H-MRS can reveal anomalies not found in other MRI techniques. If this result is not explained by the medications effects, it will be relevant to investigate more precisely this region based on the hypothesis that it could overfunction in bipolar depression.

For Glu and Gln metabolites, very few studies met our inclusion criteria in the PFC, with a meta-analysis that could be performed only for Glx in dlPFC and that did not find any significant difference between depressed BD patients and healthy controls. It would be interesting to be able to rely on more studies on various regions of the PFC.

In the two hippocampi there were any significant difference between BD patients and healthy controls for any of the investigated metabolites. The hippocampal formation is a very plastic and vulnerable brain region, and there are anomalies in the size of the neurons and a reduction in the number of glial cells in BD patients (72,73). Therefore, it could have been expected a decrease of NAA levels in BD patients, knowing that post-mortem studies had found mitochondrial dysfunction in the hippocampi of these patients, with decreased expression of nuclear mRNA encoding mitochondrial proteins (74). Alterations of proteins involved in glycogenogenesis, glycogenolysis, and mitochondrial energy functions were also indentified (75). Our findings are different with those of Kraguljac & al who found a significant decrease of NAA/Cr in the hippocampi (17), even if, as explained previously, this meta-analysis mixed patients of various mood states. Conversely, an increase in Glu levels would have been expected since stress and glucocorticoids, which are very present in BD patients, would increase the concentrations of extra-cellular Glu in the hippocampi (76), and that there is a high level of expression of the GCP II enzyme in the hippocampi of BD patients which hydrolyzes NAAG into Glu in the glial cells (77). However, ¹H-MRS techniques do not measure glutamatergic transmission but total brain Glu, which is used in many brain functions other than neurotransmission (19). That could explain the absence of significant increase in glutamatergic metabolites in the hippocampi of BD patients.

In the ACC, whatever the metabolite studied we found no significant difference between BD patients and healthy controls. Scotti-Muzzi & al also conducted a meta-analysis comparing several neurometabolites between BD patients and HC, but specifically targeting ACC's region. Although our meta-analysis included several studies which could not be included in the analyses of Scotti-Muzzi & al due to their too recent publication, our results for NAA, Glu and Gln levels are consistent with those of Scotti-Muzzi & al (78). For the Glx levels our

results were only available for BD patients in depressive episode and they are different from those of Scotti-Muzzi & al (78). It is however important to specify that the outcomes of Scotti-Muzzi & al, could not be evaluated according to the mood state due to a number of studies lower than 3. This increase in Glx levels could therefore be due to the non-depressive periods of the disease, and could be caused in particular by the significant increase in Gln levels found in BD patients in the euthymic period. In their meta-analysis Taylor & al compared also Glx levels in the ACC of BD patients in major depressive episode and HC (79). Although they included studies that did not fully meet our inclusion criteria (one with adolescent BD patients, one with some patients in mixed episode, one whose the ROI encompasses a part of the mPFC), they also did not find significant difference. The ACC is a complex region with different sub-regions with specific connectivity and functions, the limits of which are mainly derived from the Brodmann classification (80,81). Brain imaging studies, usually divides the ACC into two main parts: the peri-genu ACC and the dorsal ACC (also commonly called MCC). In our study, we performed a subgroup analysis to see if there was a variation in results according to the parts of the ACC concerned, but we did not find any significant difference.

This meta-analysis has some limitations. First, although the meta-analysis analysed data region by region, and even by subregion in the ACC, voxel sizes and ROIs were not similar among the included studies. These differences might skew the results of ROI analyses. Second, magnetic field strength, ¹H-MRS editing technique, echo-time were also different. Third, because many studies did not detail patients' treatments, we could not perform meta-regression by treatment and assess their influence. Some studies showed that treatments can partially modify the concentrations of certain metabolites in certain regions (78). However, it remains important to note that for our primary outcome of decreased NAA in

the left wmPFC in depressed patients, BD patients were not medicated in 3 of 4 studies, with heterogeneity described as modest. Fourth, because of the lack of data or inconsistency in the scales used, we could not verify whether metabolite concentrations were dependent on the intensity of depression. Likewise, we could not verify whether metabolite concentrations were dependent on the age of onset or number of mood episodes. These factors could also possibly influence our results.

CONCLUSION :

Le trouble bipolaire est une maladie fréquente mais dont la neurobiologie reste mal connue. La ¹H-MRS est une technique de neuro-imagerie permettant de quantifier des métabolites cérébraux. De nombreuses études ont été publiées ces dernières années, mais les résultats retrouvés restent hétérogènes. Une des explications possibles pourrait être la faible taille des échantillons utilisée dans chacune des études. Nous avons donc décidé de réaliser une revue systématique de littérature et une méta-analyse afin de déterminer s'il existe des différences de concentration cérébrale de NAA, Glu, Gln et Glx entre les patients bipolaires et les sujets sains.

Nos résultats ont montré que les niveaux de NAA des patients bipolaires étaient significativement diminués dans la substance blanche du cortex préfrontal (wmPFC) gauche des patients bipolaires en phase dépressive ou euthymique, significativement augmentés dans le cortex préfrontal dorsolatéral (dlPFC) gauche chez les patients bipolaires en phase dépressive, et que les niveaux de Gln étaient significativement augmentés dans le cortex cingulaire antérieur (ACC) des patients bipolaires en rémission, en comparaison avec les sujets sains. Les niveaux de NAA, Gln, Glu, Glx n'étaient pas significativement différents entre les patients bipolaires et les sujets sains au niveau des autres régions. La diminution des niveaux de NAA dans la wmPFC des patients bipolaires en phase dépressive et de rémission met en évidence l'importance de l'énergie produite par le métabolisme mitochondrial dans la physiopathologie du trouble bipolaire, notamment via ses répercussions sur la neuroplasticité et la plasticité synaptique. Ceci pourrait expliquer certaines anomalies structurelles retrouvées en IRM. Cependant notre revue systématique de littérature a

montré que seules quelques études avaient été publiées dans les différentes sous-régions du cortex préfrontal, il serait donc intéressant de mieux les explorer dans de futurs travaux.

Le Doyen de l'UFR de Médecine,

Paul CLAVELOU



Le Président du Jury,

Pierre Michel LÉORCA

A large, dark, handwritten signature in black ink, which appears to be 'Pierre Michel LÉORCA', written over the printed name.

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ANNEXES :

Annexe I : Excluded studies :

Name of the study	First autor	Reason for exclusion
Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects?	Moore	Missing data
Chronic treatment with both lithium and sodium valproate may normalize phosphoinositol cycle activity in bipolar patients.	Silverstone	Not about Glu, Glx, Gln, NAA (on myo-I)
Brain choline concentrations may not be altered in euthymic bipolar disorder patients chronically treated with either lithium or sodium valproate.	Wu	Not about Glu, Glx, Gln, NAA (on Cho)
Brain metabolic alterations in medication-free patients with bipolar disorder.	Dager	Not different groups for each mood states or lack of precision
Lithium and valproic acid treatment effects on brain chemistry in bipolar disorder.	Friedman	Not different groups for each mood states or lack of precision
¹ H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients.	Brambilla	Not different groups for each mood states or lack of precision
Metabolic alterations in medication-free patients with bipolar disorder: a ³ T CSF-corrected magnetic resonance spectroscopic imaging study.	Port	Not different groups for each mood states or lack of precision
Brain GABA levels in patients with bipolar disorder.	Kaufman	Not different groups for each mood states or lack of precision
Bipolar disorder comorbid with alcoholism: a ¹ H magnetic resonance spectroscopy study.	Nery	Not different groups for each mood states or lack of precision
T2 relaxation time abnormalities in bipolar disorder and schizophrenia.	Ongur	Not different groups for each mood states or lack of precision
Brain-derived neurotrophic factor val66met polymorphism affects prefrontal energy metabolism in bipolar disorder.	Frey	Not different groups for each mood states or lack of precision
1) Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an in vivo ¹ H MRS study. 2) Corrected values of brain metabolites for the article: 'Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an in vivo ¹ H MRS study'.	Frey	Not different groups for each mood states or lack of precision
In vivo glutathione levels in young persons with bipolar disorder: a magnetic resonance spectroscopy study.	Lagopoulos	Not about Glu, Glx, Gln, NAA (on GSH)
Investigating the role of glutathione in mismatch negativity: An insight into NMDA receptor disturbances in bipolar disorder.	Chitty	Not about Glu, Glx, Gln, NAA (on GSH)
Perisylvian GABA levels in schizophrenia and bipolar disorder.	Atagun	Not about Glu, Glx, Gln, NAA (on GABA)
Increased Brain Lactate During Depressive Episodes and Reversal Effects by Lithium Monotherapy in Drug-Naive Bipolar Disorder: A ³ -T ¹ H-MRS Study.	Machado-Vieira	Not about Glu, Glx, Gln, NAA (on Lactate)
Neurochemical metabolites in the medial prefrontal cortex in bipolar disorder: A proton magnetic resonance spectroscopy study.	Ozdel	Non-exclusion of comorbidities

Hippocampal neurochemical markers in bipolar disorder patients following the first-manic episode: A prospective 12-month proton magnetic resonance spectroscopy study.	Silveira	Pediatric population included
Evidence of altered membrane phospholipid metabolism in the anterior cingulate cortex and striatum of patients with bipolar disorder I: A multi-voxel (1)H MRS study.	Cao	Not different groups for each mood states or lack of precision
Trait-related alterations of N-acetylaspartate in euthymic bipolar patients: A longitudinal proton magnetic resonance spectroscopy study.	Aydin	Non-exclusion of comorbidities
Neurochemical alterations in anterior cingulate cortex in bipolar disorder: a proton magnetic resonance spectroscopy study (1H-MRS).	Galinska	Not different groups for each mood states or lack of precision
Elevated Choline-Containing Compound Levels in Rapid Cycling Bipolar Disorder.	Cao	Not different groups for each mood states or lack of precision
Diagnosis and body mass index effects on hippocampal volumes and neurochemistry in bipolar disorder.	Bond	Pediatric population included
Unique prefrontal GABA and glutamate disturbances in co-occurring bipolar disorder and alcohol dependence.	Prisciandaro	Not different groups for each mood states or lack of precision
In Vivo Brain Glycine and Glutamate Concentrations in Patients With First-Episode Psychosis Measured by Echo Time-Averaged Proton Magnetic Resonance Spectroscopy at 4T.	Kim	Non-exclusion of comorbidities
Choline Compounds of the Frontal Lobe and Temporal Glutamatergic System in Bipolar and Schizophrenia Proton Magnetic Resonance Spectroscopy Study.	Galinska	Not different groups for each mood states or lack of precision
In vivo imaging of oxidative stress and fronto- limbic white matter integrity in young adults with mood disorders.	Hermens	Not about Glu, Glx, Gln, NAA (on GSH)
Type 2 diabetes mellitus: a potentially modifiable risk factor for neurochemical brain changes in bipolar disorders.	Hajek	Not different groups for each mood states or lack of precision
Inflammation, Glutamate, and Cognition in Bipolar Disorder Type II: A Proof of Concept Study.	King	Not different groups for each mood states or lack of precision
Proton magnetic resonance spectroscopic imaging of gray and white matter in bipolar-I and schizophrenia.	Bustillo	Not different groups for each mood states or lack of precision
Proton magnetic resonance spectroscopy of the brain in schizophrenic and affective patients.	Sharma	Not different groups for each mood states or lack of precision
The human brain resonance of choline-containing compounds is similar in patients receiving lithium treatment and controls: an in vivo proton magnetic resonance spectroscopy study.	Stoll	Non-exclusion of comorbidities
Choline, myo-inositol and mood in bipolar disorder: a proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex.	Moore	Not different groups for each mood states or lack of precision
Neuronal pathology in the hippocampal area of patients with bipolar disorder: a study with proton magnetic resonance spectroscopic imaging.	Bertolino	Not different groups for each mood states or lack of precision
Chronic treatment with lithium, but not sodium valproate, increases cortical N-acetyl-aspartate concentrations in euthymic bipolar patients.	Silverstone	Non-exclusion of comorbidities
Lithium and valproate protect against dextro-	Silverstone	Non-exclusion of comorbidities

amphetamine induced brain choline concentration changes in bipolar disorder patients.		
Hippocampal neurochemical pathology in patients at first episode of affective psychosis: a proton magnetic resonance spectroscopic imaging study.	Blasi	Pediatric population included
Magnetic resonance spectroscopic measurement of cerebral gamma-aminobutyric acid concentrations in patients with bipolar disorders.	Wang	Not different groups for each mood states or lack of precision
Dopamine transporter genotype influences N-acetyl-aspartate in the left putamen.	Scherk	Non-exclusion of comorbidities
Reduction in occipital cortex gamma-aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects.	Bhagwagar	Not in the regions of interest
Brain gamma-aminobutyric acid (GABA) abnormalities in bipolar disorder.	Brady	Not about Glu, Glx, Gln, NAA (on GABA)
Cortical glutathione levels in young people with bipolar disorder: a pilot study using magnetic resonance spectroscopy.	Godlewska	Non-exclusion of comorbidities
Cluster analysis reveals abnormal hippocampal neurometabolic profiles in young people with mood disorders.	Hermens	Not different groups for each mood states
Individual prediction of symptomatic converters in youth offspring of bipolar parents using proton magnetic resonance spectroscopy.	Zhang	Pediatric population included
Functional magnetic resonance spectroscopy in patients with schizophrenia and bipolar affective disorder: Glutamate dynamics in the anterior cingulate cortex during a working memory task.	Jelen	Not different groups for each mood states or lack of precision
Hippocampal 1H MRS in patients with bipolar disorder taking valproate versus valproate plus quetiapine.	Atmaca	Not different groups for each mood states or lack of precision
SNAP-25 genotype influences NAA/Cho in left hippocampus.	Scherk	Non-exclusion of comorbidities
Association of the brain-derived neurotrophic factor val66met polymorphism with magnetic resonance spectroscopic markers in the human hippocampus: in vivo evidence for effects on the glutamate system.	Gruber	Non-exclusion of comorbidities
Neurochemical alteration in the caudate: implications for the pathophysiology of bipolar disorder.	Shahana	Pediatric population included
Increased thalamic phospholipid concentration evident in bipolar I disorder.	Howells	Non-exclusion of comorbidities
Magnetic resonance spectroscopy imaging of lactate in patients with bipolar disorder.	Chu	Not different groups for each mood states or lack of precision
Hippocampal glutamatergic/NMDA receptor functioning in bipolar disorder: A study combining mismatch negativity and proton magnetic resonance spectroscopy.	Chitty	Not different groups for each mood states or lack of precision
Dorsal Anterior Cingulate Lactate and Glutathione Levels in Euthymic Bipolar I Disorder: 1H-MRS Study.	Soeiro-De-Souza	Not about Glu, Glx, Gln, NAA (on GSH and Lactate)
ACC Glu/GABA ratio is decreased in euthymic bipolar disorder I patients: possible in vivo neurometabolite explanation for mood stabilization.	Scotti-Muzzi	Duplicate same data
Neurochemical effects of quetiapine in patients	Adler	Missing data

with bipolar mania: a proton magnetic resonance spectroscopy study.		
(1)H-MRS of hippocampus in patients after first manic episode.	Gigante	Pediatric population included
Bcl-2 rs956572 polymorphism is associated with increased anterior cingulate cortical glutamate in euthymic bipolar I disorder.	Soeiro-De-Souza	Duplicate same data
Investigation of Heschl's gyrus and planum temporale in patients with schizophrenia and bipolar disorder: a proton magnetic resonance spectroscopy study.	Atagun	Not in the regions of interest
Neurochemical differences between bipolar disorder type I and II in superior temporal cortices: A proton magnetic resonance spectroscopy study.	Atagun	Not in the regions of interest
Increased thalamic N-acetylaspartate in male patients with familial bipolar I disorder.	Deicken	Not in the regions of interest
Genetic variant in SLC1A2 is associated with elevated anterior cingulate cortex glutamate and lifetime history of rapid cycling.	Veldic	Not control data
Large positive effect of lithium on prefrontal cortex N-acetylaspartate in patients with bipolar disorder: 2-centre study.	Hajek	Missing data
Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression.	Frye	Not in the regions of interest (PFC and ACC in a unique ROI)
A proton magnetic resonance spectroscopy study in schizoaffective disorder: comparison of bipolar disorder and schizophrenia.	Kalayci	Missing data
Neurochemical abnormalities in unmedicated bipolar depression and mania: a 2D 1H MRS investigation.	Xu	Missing data
Biochemical changes in the cingulum in patients with schizophrenia and chronic bipolar disorder.	Sarramea	Not in the regions of interest (ACC and PFC in a unique ROI)
A Longitudinal (6-week) 3T (1)H-MRS Study on the Effects of Lithium Treatment on Anterior Cingulate Cortex Metabolites in Bipolar Depression.	Machado-Vieira	Duplicate same data
Are working memory and glutamate concentrations involved in early-life stress and severity of psychosis?	Corcoran	Not different groups for each mood states or lack of precision
Association of altered thyroid hormones and neurometabolism to cognitive dysfunction in unmedicated bipolar II depression	Lai	Pediatric population included
Altered brain creatine cycle metabolites in bipolar I disorder with childhood abuse: A 1 H magnetic resonance spectroscopy study	Soares Bio	Duplicate same data
Choline-containing compounds detected by proton magnetic resonance spectroscopy in the basal ganglia in bipolar disorder.	Kato	Not in the regions of interest
Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders	Hamakawa	Not in the regions of interest
Proton magnetic resonance spectroscopy of the lenticular nuclei in bipolar I affective disorder.	Ohara	Not in the regions of interest
Biochemical abnormalities in basal ganglia and executive dysfunction in acute- and euthymic-episode patients with bipolar disorder: A proton magnetic resonance spectroscopy study.	Lai	Not in the regions of interest

The characteristic of cognitive impairments in patients with bipolar II depression and its association with N-acetyl aspartate of the prefrontal white matter	Zhong	Missing data
Proinflammatory Cytokines Predict Brain Metabolite Concentrations in the Anterior Cingulate Cortex of Patients With Bipolar Disorder	Poletti	Not different groups for each mood states or lack of precision
Quantitative proton magnetic resonance spectroscopy of the bilateral frontal lobes in patients with bipolar disorder.	Hamakawa	Not in the regions of interest (lack of precision of the ROI in the PFC)

Annexe II : Newcastle-Ottawa Scale :

Study and year:	Selection: Case definition:	Representativeness:	Selection of control:	Definition of control:	Comparability: Age:	Other factor:	Total:
Rocha (2015)	1	0	1	1	0	0	3
Winberg (2000)	1	1	1	1	0	1	5
Senaratne (2009)	1	1	1	1	1	1	6
Scherk (2009)	1	0	1	1	0	0	3
Molina (2007)	1	1	1	1	0	0	4
Kalayci (2012)	1	0	1	1	1	1	5
Cumurcu (2008)	1	0	1	1	0	0	3
Corcoran (2020)	1	1	1	1	0	0	4
Mahlj (2007)	1	0	1	1	1	1	5
Ehrlich (2015)	1	0	1	1	1	1	5
Sojero-De Souza (2015)	1	0	1	1	0	0	3
Sojero-De Souza (2018 [1])	1	1	1	1	0	0	4
Soeiro-De-Souza 20(18 [2])	1	1	1	1	0	0	4
Amaral (2006)	1	0	1	1	0	1	4
Brady (2012)	1	0	1	1	0	1	4
Kubo (2016)	1	1	1	1	1	1	6
Iosifescu (2009)	1	0	1	1	1	1	5
Colla (2009)	1	1	1	1	1	1	6
Haarman (2016)	1	1	1	1	1	1	6
Scherk (2008)	1	0	1	1	1	1	5
Deicken (2003)	1	0	1	1	0	1	4
Liu (2017)	1	0	1	1	1	1	5
Michael (2009)	1	0	1	1	1	1	5
Li (2016)	1	0	1	1	1	1	5
Smaragdi (2019)	1	1	1	1	0	0	4
Zhong (2014)	1	0	1	1	1	1	5
Zhong (2018)	1	0	1	1	1	1	5
Lai (2019)	1	0	1	1	1	1	5
Croarkin (2015)	1	1	1	1	0	0	4
Mellen (2019)	1	1	1	1	0	0	4
Zanetti (2014)	1	0	1	1	0	0	3
Armaca (2012)	1	0	1	1	0	0	3

SERMENT D'HIPPOCRATE :

Conseil national de l'Ordre des médecins :

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Nom, Prénom :

Signature :

SERMENT D'HIPPOCRATE :

Faculté de médecine de Clermont-Ferrand :

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Nom, Prénom

Signature

Glutamatergic and N-acetylaspartate metabolites in acute depressive and euthymic patients with bipolar disorder : a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies

RESUME :

Introduction : La physiopathologie du trouble bipolaire demeure inconnue. La spectroscopie par résonance magnétique (^1H -MRS) permet de quantifier les métabolites glutamatergiques tel le Glutamate (Glu), la Glutamine (Gln), le Glx, ainsi que le N-acetylaspartate (NAA) dans le cerveau. Nous avons conduit une méta-analyse afin de comparer les niveaux de NAA, Glu, Gln, pool Glu + Gln (Glx) entre des patients bipolaires et des sujets sains.

Méthode : La recherche a été réalisée sur Medline, Embase, Psycinfo, jusqu'au 20 janvier 2021. Les principaux critères d'inclusion étaient des études de ^1H -MRS comparant les niveaux de Glu, Gln, Glx, NAA dans les cortex préfrontaux, les cortex cingulaires antérieurs, et les hippocampes entre des patients bipolaires, en phase dépressive ou de rémission, et des sujets sains. Des « Standardized Mean Differences (SMD) » ont été calculées pour évaluer les différences.

Résultats : Parmi les 32 études identifiées, 10 ciblaient des patients bipolaires en épisode dépressif caractérisé, 21 ciblaient des patients bipolaires en rémission, et une incluait des patients bipolaires en phase dépressive et de rémission. Les niveaux de NAA étaient significativement abaissés dans la substance blanche du cortex préfrontal des patients bipolaires dépressifs et euthymiques comparativement aux sujets sains, significativement augmentés dans le cortex préfrontal dorsolatéral des patients bipolaires dépressifs comparativement aux sujets sains. Les niveaux de Gln étaient significativement augmentés dans le cortex cingulaire antérieur des patients bipolaires en rémission comparativement aux sujets sains.

Conclusion : La diminution des niveaux de NAA dans la substance blanche du cortex préfrontal des patients bipolaires pourrait être lié aux altérations de la neuroplasticité et de la plasticité synaptique retrouvés chez les patients bipolaires, mais aussi expliquer les hyperintensités profondes dans la substance blanche fréquemment retrouvées chez les patients bipolaires.

MOTS-CLES :

- | | |
|---------------------|-----------------------------------|
| - N-acetylaspartate | - Bipolar disorder |
| - Glutamate | - Magnetic resonance spectroscopy |
| - Glutamine | - Neuroimaging |