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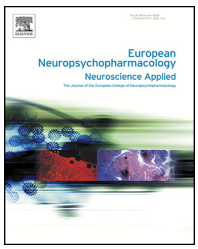

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REVIEW

Anterior cingulate cortex neurometabolites in bipolar disorder are influenced by mood state and medication: A meta-analysis of ^{1}H-MRS studies

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Abstract
The anterior cingulate cortex (ACC), a brain region that mediates affect and cognition by connecting the frontal cortex to limbic structures, has been consistently implicated in the neurobiology of Bipolar Disorder (BD). Proton magnetic resonance spectroscopy (^{1}H-MRS) studies have extensively compared *in vivo* neurometabolite levels of BD patients and healthy controls (HC) in the ACC. However, these studies have not been analyzed in a systematic review or meta-analysis and nor has the influence of mood state and medication on neurometabolites been examined in this cortical region. A systematic review and a meta-analysis of ^{1}H-MRS studies comparing ACC neurometabolite profiles of adult BD patients and HC subjects was conducted, retrieving 27 articles published between 2000 and 2018. Overall increased ACC levels of Glx [glutamine (Gln) + glutamate)/Creatine], Gln, choline (Cho) and Cho/Creatine were found in BD compared to HC. Bipolar depression was associated with higher Cho levels, while euthymia correlated with higher glutamine (Gln) and Cho. Mood stabilizers appeared to affect ACC Glu and Gln metabolites. Increased ACC Cho observed in euthymia, depression and in medication-free groups could be considered a trait marker in BD and attributed to increased cell membrane phospholipid turnover. Overall increased ACC Glx was associated with elevated Gln levels, particularly influenced by euthymia, but no abnormality in Glu was detected. Further ^{1}H-MRS stud-

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ies, on other voxels, should assess more homogeneous (mood state-specific), larger BD samples and account for medication status using more sensitive ^{1}H-MRS techniques.

1. Introduction

Bipolar disorder (BD) is a severe, chronic illness characterized by significant oscillations in mood ranging from depression to mania (Merikangas et al., 2007). Although little is known about the neurobiology of BD, recent structural and functional neuroanatomical studies have reported disintegration in fronto-subcortical circuitry (Strakowski et al., 2012; Maletic and Raison., 2014), particularly circuits mediated by the anterior cingulate cortex (ACC), a key center integrating cognitive and affective neuronal connections .

The ACC (Supplementary Material, Figure S1) is one of the most studied brain region by neuroimaging in BD. Alterations involving the ACC in BD range from abnormal morphology and brain connectivity to neurochemistry. Reduction in ACC gray matter volume has been one of the most consistent findings reported in BD (Drevets et al., 1997; Haldane and Frangou., 2004; Strakowski et al., 2012). In fact, the largest structural magnetic resonance image (MRI) study to date (Hibar et al., 2017), as well as a recent systematic review (Hanford et al., 2016) and a meta-analysis (Wise et al., 2017), have confirmed this cortical thinning. A voxel-based quantitative meta-analysis of functional MRI (fMRI) studies has also suggested a fronto-limbic dysfunction in the ACC of BD patients relative to HC subjects (Chen et al., 2011), whilst systematic reviews and meta-analyses of diffusion tensor imaging (DTI) studies in BD report alterations in white matter tracts (decreased fractional anisotropy) connecting the ACC to subcortical limbic structures (Vederine et al., 2011; Nortje et al., 2013). Additionally, ketamine, a glutamatergic receptor antagonist agent that promotes transient antidepressant effects, has been shown to increase glutamine levels in the ACC (Rowland et al., 2005) and also to modulate the functional connectivity between the ACC and pre-frontal cortex (PFC) (Lenner et al., 2017). Therefore, alterations in the morphology, connectivity and neurochemistry of the ACC appear to be implicated in BD neurobiology.

The neurochemical alterations in BD can be assessed by proton magnetic resonance spectroscopy (^{1}H-MRS), a non-invasive technique based on the signal intensity arising from protons in a given metabolite as a function of their frequency displayed in a spectrum whose peaks are proportional to the concentrations of the correspondent metabolite (Buonocore and Maddock., 2015). Thus, ^{1}H-MRS provides *in vivo* absolute or relative to creatine (/Cr) measurements of several brain neurometabolites, such as Glutamate (Glu), Glutamine (Gln), Glx (Glu + Gln), Gamma-Aminobutyric Acid (GABA), N-acetylaspartate (NAA), Choline (Cho), and Myo-inositol (mI). Precise measurements of Glu and Gln require the use of more sensitive techniques with higher field strengths ($\geq$ 3 T) and the sum of these metabolites are commonly referred as Glx (Buonocore and Maddock, 2015).

While Glu and GABA are the most common excitatory and inhibitory neurotransmitters, respectively, in the central nervous system, Gln is a "non-excitatory" form of stored Glu (Walls et al., 2015). NAA, in turn, is an amino acid synthesized in neuronal mitochondria and has been considered a marker of neuronal energy metabolism, viability and health (Stork and Renshaw., 2005). Myo-inositol (mI) is an organic osmolyte located in astrocytes and considered a glial cell marker (Brand et al., 1993), whilst Cho corresponds to phosphoryl and glycerol phosphoryl choline and is an indicator of cell membrane turnover (synthesis or breakdown) (Stork and Renshaw., 2005; Moffett et al., 2007). Creatine (Cr) has been widely used as an internal standard for ^{1}H-MRS because it is assumed that there is very little variation in the cr-phosphocreatine (P-Cr) equilibrium, resulting in a stable concentration of Cr (Buonocore and Maddock., 2015).

Previous ^{1}H-MRS studies in BD have reported increased Glx (Glutamate+Glutamine) and/or Glu in cortical frontal regions in BD (Yildiz-Yesiloglu and Ankerst., 2006; Yüksel and Öngür., 2010; Gigante et al., 2012; Chitty et al., 2013), commonly interpreted as an increased glutamatergic neurotransmission or excitatory state. Although Glx corresponds to not only a greater proportion of Glu, but also Gln, GABA and glutathione (GSH), its major contributors are Glu and Gln. Regarding NAA, previous systematic reviews and meta-analyses (Yildiz-Yesiloglu and Ankerst., 2006; Kraguljac et al., 2012) have found reduced levels in frontal regions, the hippocampus and basal ganglia, and has been interpreted as an indicator of mitochondrial dysfunction and impartment in energy production, resulting in increased lactate (Stork and Renshaw, 2005). Neuronal damage has also been suggested by previous systematic reviews that pointed to higher levels of Cho (Yildiz-Yesiloglu and Ankerst., 2006) and mI (Silverstone et al., 2005) in BD, a finding not confirmed by a meta-analysis (Kraguljac et al., 2012). In contrast, GABA has been consistently reported as unaltered in BD (Schur et al., 2016; Chiapponi et al., 2016; Romeo et al., 2018).

However, ^{1}H-MRS studies in BD are especially challenging because BD subjects can present any of at least three mood states (depression, mania and euthymia) at time of scan. Therefore, it has been hard to interpret the relationship between neurometabolite profile and clinical presentation since most studies have not taken into account the influences of both mood state and medication on neurometabolite dynamics. Indeed, very few ^{1}H-MRS systematic reviews and meta-analyses performed thus far have taken into consideration the effect of mood state or medication on metabolites levels, while none have focused specifically on a specific brain region such as the ACC. Since understanding the neurometabolic profile of the ACC in BD and how it is affected by mood states and medications is critical to elucidating the neurobiology of this disorder, the aim of this systematic review and meta-analysis was to examine, for the first time, ACC-specific cross-sectional ^{1}H-MRS studies in BD

patients compared to healthy controls, and to investigate the influence of mood state and medication on results.

2. Experimental procedures

2.1. Literature search and inclusion criteria

We conducted a search of the literature on the PubMed, EMBASE, Cochrane Library, Medline, Scopus and Google Scholar platforms following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009), as depicted in Supplementary Material, Figure S2. Using the search strings "proton magnetic resonance spectroscopy or ^{1}H-MRS" AND "bipolar disorder" AND "anterior cingulate cortex" from database inception until February 2019, a total of 53 articles published (2000 - 2018) were identified. Of the 53 manuscripts considered eligible for full-text search, only 27 cross-sectional studies met the following study inclusion criteria: articles written in English; studies performed in subjects with mean age $\geq$ 18 years; ACC as the region of interest; cross-sectional studies comparing BD and HC groups; longitudinal studies (2 studies) were included only if they provided baseline data comparing BD and HC groups; magnetic field $\geq$1.5 Tesla (except for Glx, Glu and Gln $\geq$3 Tesla); and studies using the DSM diagnostic criteria for BD and mood states (mania, depression or euthymia). Besides DSM-criteria, the use of mood-state classification by a symptoms scale was accepted.

The quality of each individual study was assessed in relation to clinical and demographic aspects (e.g., age, sex, education, illness duration and severity, exclusion of systemic diseases, neurodevelopmental disorder, history of drug or alcohol abuse), sample sizes, and ^{1}H-MRS acquisition and analysis methodology (e.g., voxel placement, use of Cramer-Rao lower bound (CRLB) or equivalent filtering for spectral quality assessment).

2.2. Meta-analytic procedure

Means and standard deviations (SD) of Glx, Glu, Gln, GABA, NAA, mI and Cho concentrations, as well as sample sizes for both BD and HC groups were extracted from each study or acquired by contacting the respective corresponding author if the data was presented as graphs or median/quartile range (e.g., Prisciandaro et al., 2017; Wise et al., 2018). In cases of overlapping samples involving two publications, only the study with the larger sample size was included in the meta-analysis. Absolute and over creatine (/Cr) concentrations were considered, but sensitivity and/or subgroup meta-analyses stratified by mood state (hypomania/mania, depression, or euthymia) and medication status (medication-free) were performed. Meanifull meta-analyses were considered if there were a minimum $\geq$3 studies available. The meta-analyses were performed using Comprehensive Meta-analysis software version 3.3 developed by Biostat (Borenstein et al., 2005). The effect size used was Hedges' g (Hedges and Olkin., 1985) using 95% confidence intervals, adopting the following classification: 0.2=small; 0.5=medium; and 0.8=large (Cohen, 1988). The p-value was set to 0.05 and heterogeneity was estimated using I^2 statistics, considering I^2 of 25%, 50% and 75% as small, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003). Random effects modeling was used because considerable clinical and methodological heterogeneity among the selected studies was assumed. Meta-regressions were performed to assess the relationship between moderators (subject age and publication year) and effect size of neurometabolites between patients and controls. Publication bias (meta-analysis $\geq$ 10 studies) was evaluated using a funnel plot and Egger's linear regression method test (Egger et al., 1997).

3. Results

3.1. Glutamatergic metabolites

Table 1 shows twelve studies published between 2007 and 2018 that compared ACC concentrations of Glx, Glu and Gln in adult BD patients relative to HC by ^{1}H-MRS at a magnetic field $\geq$ 3T.

3.1.1. Glx

Overview. A meta-analysis of four studies for which data were available involving a total of 354 subjects (197 BD, 157 HC), showed significantly overall higher ACC Glx/Cr in BD relative to HC (g:0.47, 95% CI: 0.18 to 0.75, Z: 3.22, $p=0.001$; tau^2=0.01; Q:3.51, df:3; $p=0.31$, I^2=14.5%), independently of the quantification method used (Fig. 1). Meta-regression revealed no influence of subject age [coefficient: −0.074; 95% CI: (−0.169, 0.020); $p=0.12$] or year of publication [coefficient: 0.0135; 95% CI: (−0.071, 0.058); $p=0.75$] on the results.

Mood states. There were not enough studies (n <3) to perform meaninfull meta-analyses in depressive, manic and euthymic mood states.

Medication status. There were not enough studies (n <3) to perform a meaningful meta-analysis in medication-free and medicated samples.

3.1.2. Glutamate (Glu)

Overview. Table 1 shows ten studies that measured Glu or Glu/Cr in the ACC of BD subjects as compared to HC using both conventional techniques (e.g. PRESS) with a magnetic field $\geq$ 3T or more sensitive techniques (e.g. JPRESS). The pooled meta-analysis of 9 studies (592 subjects: 303 BD; 289 HC) revealed no significant differences between groups (g: 0.08, 95% CI: −0.36 to −0.19, Z: 0.58, $p=0.55$; tau^2=0.18; Q: 32.8, df:8; p<0.0001; I^2=75.6%; Supplementary Material, **Fig. S 3A**).

Mood states. There were not enough studies (n <3) to perform meaninfull meta-analyses in depressive and manic mood states (Supplementary Material, **Fig. S 3A**). The pooled meta-analysis of 5 studies that assessed ACC Glu/Cr or Glu in euthymic mood state found also no significant differences between groups (g: 0.17, 95% CI: −0.30 to −0.65, Z: 0.7; $p=0.70$; $tau^2=0.27$;Q: 21.82, df:3 p<0.0001, I^2=86.2%; Supplementary Material, **Fig. S 3A**)

Medication status. There were not enough studies (n <3) to perform meaninfull meta-analysis in the medication-free group (Supplementary Material, **Fig. S 3B**). The meta-analysis of eight studies performed in medicated subjects revealed no differences between groups (Supplementary Material, **Fig. S 3B**). However, some studies provided evidence of lower levels of Glu/Cr in euthymic subjects taking anticonvulsants (Soeiro-de-Souza et al., 2013, 2015, 2018a).

3.1.3. Glutamine (Gln)

Overview. Four studies (Table 1) measured ACC Gln using higher magnetic fields and/or 2D MRS sequences. Three of these studies reported increased Gln/Glu or decreased Glu/Gln in BD patients relative to controls (Öngür et al., 2008; Soeiro-de-Souza et al., 2015; Kubo et al., 2017). The meta-analysis of these studies (227 subjects:115 BD; 112

Table 1 Cross-sectional ^{1}HMRS studies comparing ACC neurometabolites concentration between bipolar disorder and healthy controls subjects.

Reference	BD type	Sample Size (P/C)	Mean Age	Mood State	Medication	Field Strength (T)/ Echo Time (ms)	MRS sequence	Metabolites reported	Significant Results
Moore et al., 2000	I	9/14	37.9/36	DMS	Li, Ac,Ad	1.5/30	STEAM	Cho/Cr, mI/Cr	Cho/Cr↑
Dager et al., 2004	I, II	23/26	30.3/31	DMS, D	MF	1.5/variable	PEPSI	NAA, Cho, mI	None
Amaral et al., 2006	I	13/15	34.5/34	E	Li, Ac,Ad, Ap	1.5/144	PRESS	NAA/Cr, Cho/Cr	None
Frye et al., 2007a	I, II	23/12	35.6/32	D	MF	1.5/30	PRESS	Cho, Cho/cr	None
Frye et al., 2007b	I	16/17	37.5/32.9	M/H	Li, Ac, Ap	3/20	STEAM	Glx/Cr, NAA/Cr, Cho/Cr, mI/Cr	None
Malhi et al., 2007	I	9/9	40.7/41	H	Li, Ac, MF	1.5/30	FSPGR	NAA, Cho, mI	NAA ↓, Cho ↓
Malhi et al., 2007	I	9/9	40.7/41	E	Li, Ac, MF	1.5/30	FSPGR	NAA, Cho	None
Öngür et al., 2008	I	15/21	36.3/34.3	M	Li, Ac Ap	4/variable	J-PRESS	Glu, Gln, NAA, Cho, mI	Gln/Glu ↑
Port et al., 2008	I, II	21/21	30.8/31	DMS	MF	3/ 30	PRESSCI	Cho	None
Scherk et al., 2009	I	33/29	33/29	E	Li	1.5/30	PRESS	NAA/Cr, Cho/Cr, mI/Cr	None
Brady et al., 2012	I	14/21	37.6/35	M	Li,Ac,Ap	4/ variable	JPRESS	NAA/Cr	None
Xu et al., 2013	I, II	24/20	34/31	DMS	MF	3/30	2D MRSI	Glx/Cr, Glu/Cr,	None
Soeiro-de-Souza et al., 2013	I	40/40	29/29	E	Li,Ac,Ad,Ap	3/80	PRESS	Glx/Cr, Glu/C, NAA/Cr, Cho/Cr, mI/Cr	Glx/Cr ↑, Glu/Cr ↑, Cho/Cr ↑
Zhong et al., 2014	NM	20/13	30.5/28	D	MF	1.5/ 144	PRESS	NAA/Cr, Cho/Cr	None
Ehrlich et al., 2015	I	21/42	45.9/39.3	E	Li, Ac,Ad,Ap	3/80	PRESS	Glu/Cr, Gln/Cr, NAA/Cr, Cho/Cr	Glu/Cr ↑, Gln/Cr ↑, NAA/Cr ↓
Croarkin et al., 2015	I, II	15/9	NM	D	Li,Ac,Ad,Ap	1.5/30	L-COZY	NAA/Cr	NAA/Cr ↓
Soeiro-de-Souza et al., 2015	I	40/44	31.7/25.7	E	Li,Ac,Ad,Ap	3/variable	JPRESS	Glu, Gln	Glu↓, Gln ↑, Glu/Gln ↓
Cao et al., 2016	I	50/44	35.7/35.4	DMS	Li, Ac, Ad, MF	3/80	PRESS	Glu/Cr, NAA/Cr, Cho/Cr, mI/Cr	Cho/Cr ↑
Li et al., 2016	NM	13/20	31/31.7	D	MF	3/30	2D MRS-PRESS	Glx, NAA, Cho, mI	Glx ↑
Galińska-Skok et al., 2016	I	27/10	43/40.2	DMS	Li, Ac, Ap, Ad	1.5/35	PRESS	NAA/Cr, Cho/Cr, mI/Cr	None
Kubo et al., 2017	I, II	20/23	45.0/46.4	DMS, E	Li,Ac,Ap	3/18	STEAM	Glu, Gln, NAA, Cho	Gln ↑, Gln/Glu ↑, NAA ↑, Cho ↑
Prisciandaro et al., 2017	I, II	20/19	36.8/38.0	D	Li,Ac,Ad,Ap	3/ variable	JPRESS	Glu/Cr	None
Soeiro-de-Souza et al., 2018a	I	128/80	32.04/28.1	E	Li,Ac,Ap	3/80	PRESS	Glx/Cr, Glu/Cr	Glx/Cr ↑, Glu/Cr ↑
Soeiro-de-Souza et al., 2018b	I	129/79	32/28.4	E	Li,Ac,Ap	3/80	PRESS	NAA, Cho, mI	NAA ↑, Cho↑

(*continued on next page*)

Table 1 (*continued*)

Reference	BD type	Sample Size (P/C)	Mean Age	Mood State	Medication	Field Strength (T)/ Echo Time (ms)	MRS sequence	Metabolites reported	Significant Results
Wise et al., 2018	NM	9/20	31.44/30	D	MF	3/30	PRESS	Glu/Cr	None
Zhong et al., 2018	NM	92/42	25.4/25.	D	MF	3/ 144	PRESS	NAA/Cr, Cho/Cr, mI/Cr	None
Huber et al., 2018	I, II	19/10	18/19	D	NM	3/ variable	JPRESS	NAA	None

Abbreviations: Ac: Anticonvulsants; **Ad:** Antidepressants; **Ap:** Antipsychotics; **C**: Healthy Controls; **D:** Depression; **DMS:** Different mood states; **E:** Euthymia; **H:** Hypomania; **Li**: Lithium; **M:** Mania; **MF**: Medication-free; **MS**: Mood stabilizers; **N**: Number of subjects; **NM:** Not Mentioned; **P**: Patients.

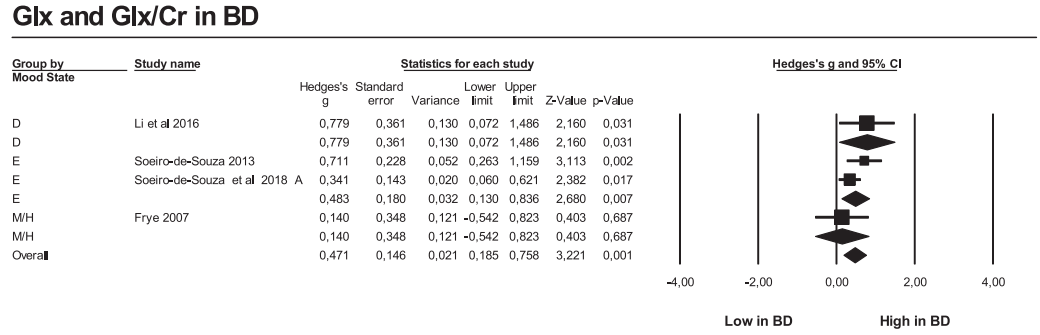


Fig. 1 Forest Plot for meta-analysis of ACC Glx/Cr in overall BD.

HC) revealed significantly increased Gln levels in BD relative to HC groups (Fig. 2): g: 0.57, 95% CI: 0.18 to 0.96, Z: 2.8, $p=0.004$; tau^2 =0.23; $Q=14.51$, df=4, $p=0.006$; I^2=72.4%. Meta-regression revealed no influence of subject age [coefficient: 0.06; 95% CI: (−0.0046, 0.12); $p=0.06$] or year of publication [coefficient: 0.048; 95% CI: (−0.11, 0.21); $p=0.21$] on the results.

Mood states. There were not enough studies (n <3) to perform meaninfull meta-analyses in depressive and manic mood states (Fig. 2). The sensitivity meta-analysis of three studies performed in euthymic state (194 subjects; 100 BD; 94 HC) revealed increased ACC Gln levels in BD (Fig. 2): g: 0.94, 95% CI: 0.12 to 1.77, Z: 2.26, $p=0.024$; tau^2 =0.44; $Q=12.68$, df=2, $p=0.002$; I^2=84.24%. Furthermore, decreased Glu/Gln (Soeiro-de-Souza et al., 2015) or increased Gln/Glu (Kubo et al., 2017) were found in euthymic BD samples.

Medication status. No study was performed in medication-free sample. In one study performed on medicated subjets, higher Gln was observed among anticonvulsant users compared to non-users (Soeiro-de-Souza et al., 2015).

3.2. N-acetylaspartate (NAA)

3.2.1. Overview

Eighteen studies provided NAA data for the ACC (Table 1). The pooled meta-analysis of the sixteen of studies that measured ACC NAA, comprising 1028 subjects (502 BD and 526 HC), revealed no significant differences between BD and HC: g: - 0.07, 95% CI: −0.31 to 0.16, Z: −0.16, $p=0.52$; tau^2=0.76; $Q=207.5$, df=19, $p<0.0001$; I^2= 90.84% (Supplementary Material, **Fig. S 4A**). Although visual inspection of the funnel plot showed some asymmetry (Supplementary Material, **Fig. S 4B**), no publication bias was detected by Egger's linear regression method [Supplementary Material, **Fig. S 4B**; Egger: bias = −1.88 (95% CI = −7.2 to 3.5) $p=0.47$].

3.2.2. Mood states

It was possible to obtain meaningful meta-analyses for the three different mood states regarding NAA (Supplementary Material, **Fig. S 4A**). A pooled meta-analysis of four studies performed in subjects under depression comprising 263 individuals (159 BD and 104 HC) revealed no significant differences in ACC NAA levels between groups: g: 0.48, 95% CI: −1.39 to −0.43, Z: −1.03, $p=0.3$; tau^2 = 0.60; $Q=26.8$, df=4, $p<0.0001$; I^2=85% (Supplementary Material, **Fig. S 4A**). Similarly, the sensitivity meta-analysis of three studies performed in manic/hypomanic states revealed also no differences between BD and HC (g: −0.07, 95% CI: −0.31 to 0.16, Z: - 0.63, $p=0.52$; tau^2=0; $Q=1.63$, df=2, $p=0.44$; I^2= 0%) and for the euthymic sub-group, a pooled meta-analysis of 7 studies revealed similar results (g: −0.16, 95% CI: −0.22 to 0.33, Z: 0.39, $p=0.69$; tau^2 =0.12; $Q=13.7$, df=5, $p=0.017$; I^2= 63.7%; Supplementary Material, **Fig. S 4A**).

3.2.3. Medication status

The meta-analysis of three studies performed in medication-free individuals totaling 207 subjects (132 BD, 75 HC) revealed no differences in ACC levels of NAA

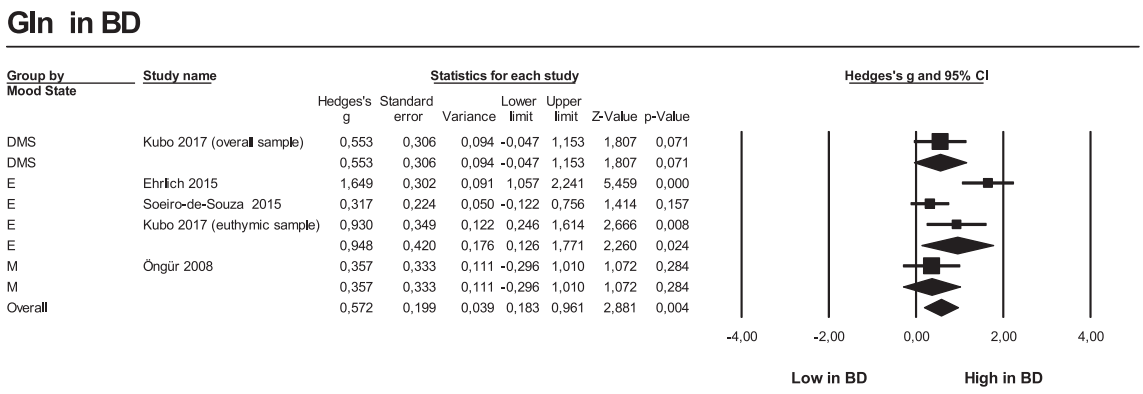


Fig. 2 Forest Plot for meta-analysis of ACC Gln-in overall BD as influenced by the mood states.
DSM: Different mood states; E: Euthymia; M: Mania/hypomania.

in BD relative to HC (g: 0.38, 95% CI: - 0.60 to −1.37, Z: 0.76, $p=0.44$; tau^2 =0.84; $Q=21.2$, df: 2, $p<0.001$; $I^2=$ 90%; Supplementary Material, **Fig. S 4C**), although all were performed in patients during a depressive state. Similalry, no between-group was recorded in the medicated sub-group regarding NAA (Supplementary Material, **Fig. S 4C**). However, some studies provided evidence of increased levels of NAA in euthymic subjects on lithium (Soeiro-de-Souza et al., 2018b) and after anticonvulsant treatment (Croarkin et al., 2015).

3.3. Choline-containing compounds (Cho)

3.3.1. Overview

Sixteen studies evaluated Cho in the ACC (Table 1), comprising 982 subjects (538 BD and 444 HC). The pooled meta-analysis of fifteen of these studies (959 subjects: 529 BD and 430 HC) showed significantly increased levels of Cho in BD compared to HC (Fig. 3A; g: 0.43, 95% CI: 0.28 to 0.58, Z: 5.8, p <0.0001; tau$^2=0.49$, $Q=113.6$, df= 16, $p<0.000$, $I^2=$ 85.9%). Meta-regression revealed no influence of subject age [coefficient:0.013; 95% CI: (− 0.05, 0.08); $p=0.7$] on Cho, but a positive influence of year of publication on these results was observed [coefficient: 0.007; 95% CI: (0.006, 0.14); $p=0.03$], as shown in Fig. 3**B**. Although visual inspection of the funnel plot showed some asymmetry (Supplementary Material, **Fig. S 5**), no publication bias was detected by Egger's linear regression method (Egger: bias = 0.8 (95% CI = 4.1 to 5.7) $p=0.73$).

3.3.2. Mood states

Sensitivity meta-analyses were performed according to the different mood states. A pooled meta-analysis of three studies (199 subjects :124 BD, 75 HC) performed in the depressive state showed significantly increased ACC Cho in the BD group (Fig. 3**A**; g: 0.40; 95% CI: 0.11 to 0.69, Z: 2.69, $p=0.007$; tau$^2=0$; $Q=1.22$, df:2, $p=0.54$; I^2=0%). Meta-regression revealed no influence of subject age [coefficient:−0.028; 95% CI: (− 0.09, 0.042); $p=0.43$] or year of publication [coefficient: 0.04; 95% CI: (−0.02, 0.1); $p=0.25$] on the results. Similarly, a pooled meta-analysis of six studies performed under euthymia, comprising 441 subjects (236 BD; 205 HC), revealed increased levels of ACC Cho in BD (Fig. 3A; g:0.48, 95% CI: 0.20 to 0.66, $Z=5.01$, $p<0.0001$; tau^2 =0, $Q=2.51$, df=6, $p=0.77$; I^2=0%). Meta-regression revealed no influence of subject age [coefficient:−0.02; 95% CI: (− 0.05, 0.014); $p=0.25$] or year of publication [coefficient: 0.02; 95% CI: (−0.01, 0.06); $p=0.22$] on the results. However, for the manic/hypomanic sub-group, a pooled meta-analysis of three studies showed no significant differences between groups (g: 0.12, 95% CI: −0.18 to 0.54, $Z=0.60$, $p=0.54$; tau^2 =0; $Q=1.33$, df=2, $p=0.5$; I^2=0%).

3.3.3. Medication status

A pooled meta-analysis of three studies performed in medication-free individuals, comprising 199 subjects (124 BD, 75 HC) revealed significantly increased Cho in BD (Fig. 3C; g: 0.40; 95% CI: 0.11 to 0.69, Z: 4.0, $p<0.001$; tau$^2=0$; $Q=1.22$, df:2, $p=0.54$; I^2=0%), although this involved the same sample as the depressive state analysis. Meta-regression demonstrated no influence of subject age or year of publication on Cho (see depressive mood state). Similalry, the meta-analysis of medicated subjects also showed increased Cho and Cho/Cr levels in medicated BD (Fig. 3**C**; g: 0.66; 95% CI: 0.25 to 1.08, Z: 3.1, $p=0.002$; tau$^2=0.49$; $Q=79$, df: 12, $p<$ 0.001 ; I^2=87%).

3.4. Myo-inositol

3.4.1. Overview

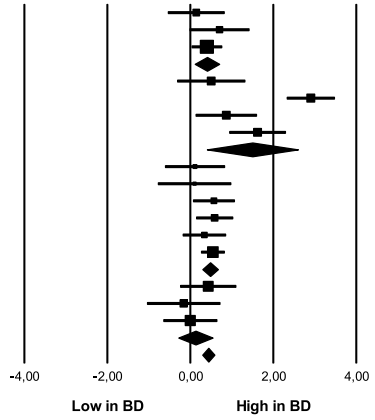
Twelve studies measured mI in the ACC (Table 1). The pooled meta-analysis of eleven of these studies assessing mI (757 subjects: 432 BD and 325 HC) found no significant difference (Supplementary Material, **Fig. S 6A**) (g: 0.04, 95% CI: −0.11 to 0.19, Z: 0.31, $p=0.60$; tau^2 =0.13 ; $Q=34.8$, df: 12, $p<0.001$; $I^2=$ 65%). Although some asymmetry was observed in the funnel plot (Supplementary Material, **Fig. S 6B**), no publication bias was detected by Egger's linear regression method [Supplementary Material, Fig. S6B; Egger: bias = −1.60 (95% CI = −5.06 to 1.85); $p=0.33$].

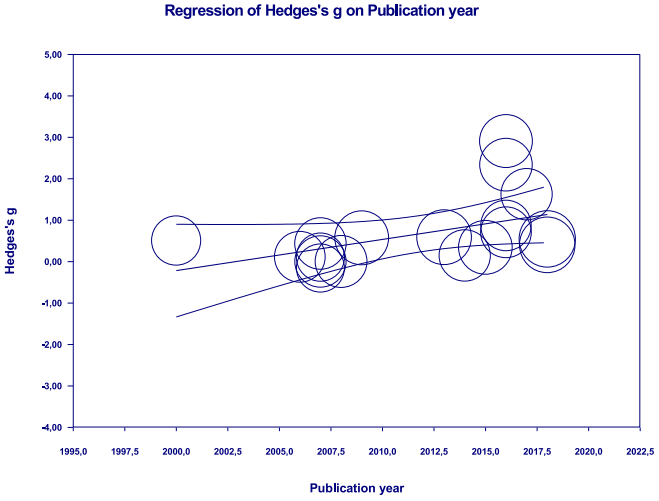
3.4.2. Mood states

Sensitivity meta-analyses were conducted considering the different mood-states (Supplementary Material, Fig. S 6A).

Cho and Cho/Cr in BD

Group by Mood State	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
D	Zhong 2014	0,145	0,348	0,121	-0,538	0,827	0,415	0,678
D	Li 2016	0,704	0,367	0,134	-0,014	1,423	1,921	0,055
D	Zhong 2018	0,401	0,187	0,035	0,035	0,767	2,145	0,032
D		0,404	0,150	0,023	0,110	0,698	2,690	0,007
DMS	Moore 2000	0,505	0,418	0,175	-0,315	1,325	1,207	0,227
DMS	Cao 2016 (overall sample)	2,905	0,295	0,087	2,327	3,483	9,854	0,000
DMS	Galiska-Skok 2016	0,869	0,376	0,141	0,132	1,606	2,310	0,021
DMS	Kubo 2017	1,623	0,347	0,121	0,942	2,303	4,671	0,000
DMS		1,498	0,560	0,313	0,401	2,595	2,677	0,007
E	Amaral 2006	0,113	0,368	0,136	-0,608	0,835	0,308	0,758
E	Malhi 2007 (euthymic sample)	0,103	0,449	0,202	-0,777	0,984	0,230	0,818
E	Scherk 2009	0,570	0,256	0,066	0,067	1,073	2,223	0,026
E	Soeiro-de-Souza 2013	0,586	0,226	0,051	0,143	1,030	2,592	0,010
E	Ehrlich 2015	0,341	0,266	0,071	-0,180	0,861	1,282	0,200
E	Soeiro-de-Souza 2018B	0,545	0,145	0,021	0,262	0,829	3,766	0,000
E		0,480	0,096	0,009	0,292	0,668	5,011	0,000
M	Frye 2007	0,432	0,344	0,118	-0,242	1,107	1,257	0,209
M	Malhi 2007 (manic sample)	-0,158	0,450	0,202	-1,040	0,723	-0,352	0,725
M	Öngür 2008	0,000	0,331	0,109	-0,648	0,648	0,000	1,000
M		0,127	0,211	0,044	-0,285	0,540	0,605	0,545
Overall		0,435	0,075	0,006	0,289	0,582	5,820	0,000





Cho and Cho/Cr in BD: medication effect

Group by Medication status	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
M	Moore 2000	0,505	0,418	0,175	-0,315	1,325	1,207	0,227
M	Amaral 2006	0,113	0,368	0,136	-0,608	0,835	0,308	0,758
M	Frye 2007	0,432	0,344	0,118	-0,242	1,107	1,257	0,209
M	Malhi 2007 (manic sample)	-0,158	0,450	0,202	-1,040	0,723	-0,352	0,725
M	Malhi 2007 (euthymic sample)	0,103	0,449	0,202	-0,777	0,984	0,230	0,818
M	Öngür 2008	0,000	0,331	0,109	-0,648	0,648	0,000	1,000
M	Scherk 2009	0,570	0,256	0,066	0,067	1,073	2,223	0,026
M	Soeiro-de-Souza 2013	0,586	0,226	0,051	0,143	1,030	2,592	0,010
M	Ehrlich 2015	0,341	0,266	0,071	-0,180	0,861	1,282	0,200
M	Cao 2016 (overall sample)	2,905	0,295	0,087	2,327	3,483	9,854	0,000
M	Galiska-Skok 2016	0,869	0,376	0,141	0,132	1,606	2,310	0,021
M	Kubo 2017	1,623	0,347	0,121	0,942	2,303	4,671	0,000
M	Soeiro-de-Souza 2018B	0,545	0,145	0,021	0,262	0,829	3,766	0,000
M		0,667	0,213	0,045	0,250	1,084	3,133	0,002
MF	Zhong 2014	0,145	0,348	0,121	-0,538	0,827	0,415	0,678
MF	Li 2016	0,704	0,367	0,134	-0,014	1,423	1,921	0,055
MF	Zhong 2018	0,401	0,187	0,035	0,035	0,767	2,145	0,032
MF		0,404	0,150	0,023	0,110	0,698	2,690	0,007
Overall		0,491	0,123	0,015	0,251	0,732	4,005	0,000

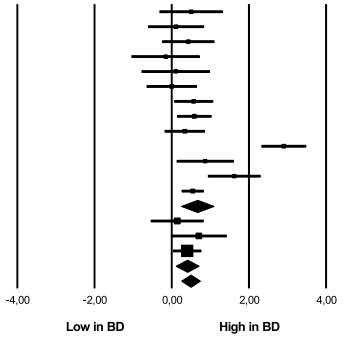


Fig. 3 A - Forest Plot for meta-analysis of ACC Cho/Cr and Cho in overall BD. **B**- Meta-regression analyses of the influences of the publication year on the effect size of studies assessing ACC Cho/Cr and Cho in overall BD. **C**- Forest Plot for meta-analysis of ACC Cho and Cho/Cr in overall BD as influenced by the medication status.

There were too few studies (n <3) to conduct a meaningful meta-analysis in the depressive mood state. A pooled meta-analysis of three studies performed in manic/hypomanic state encompassing 87 subjects (40 BD and 47 HC) found no differences in ACC mI in BD compared to controls (g: −0.05, 95% CI: −0.46 to 0.35; Z: −0.27, p = 0.78; tau^2=0, Q = 0.50, df:2, p = 0.92; I^2= 0%) and a pooled meta-analysis of four studies in the euthymic state also revealed no between-group differences (368 subjects: 211 BD; 157 HC): g: 0.11, 95% CI: −0.08 to 0.32, Z: 1.12, p = 0.26; tau^2= 0; Q = 0.36, df=3, p = 0.94; I^2= 0%.

3.4.3. Medication status

A pooled meta-analysis of three medication-free studies (Supplementary Material, **Fig. S 6C**), totaling 377 subjects (271 BD and 106 HC) revealed no differences in ACC mI between patients and controls (g: −0.21, 95% CI: -1.16 to 0.73, Z: 0.44, p = 0.65; tau^2=0.64; Q = 20.9, df=2, p<0.001, I^2=90%). Similarly, the sensitivity meta-analysis including only studies with medicated patients showed a similar result: g: −0.10, 95% CI: - 0.33 to 0.12, Z: −0.88, p = 0.37; tau^2=0.0355; Q = 13, df=9, p = 0.14, I^2=32%.

3.5. GABA

3.5.1. Overview

Four studies measured ACC GABA in the ACC involving a total of 184 subjects (103 BD; 81 HC) (**Table S1**). The pooled meta-analysis of these studies revealed no significant difference between groups: g: 0.18, 95% CI: −0.10 to 0.47, Z: 1.24, p = 0.21; tau^2=0; Q = 2.72, df=3, p = 0.23, I^2=0% (Supplementary Material, **Fig. S 7**).

3.5.2. Mood states

There were too few studies (n <3) to conduct meaningful meta-analyses for the depressive, manic and euthymic mood states (Supplementary Material, **Fig. S 7**).

3.5.3. Medication status

No studies measured GABA in a mediation-free sample. In medicated subjects, most authors found no significant differences between groups (**Table S1**).

The overall results of the meta-analyses are shown in Supplementary Material, **Table S2**.

4. Discussion

To the best of our knowledge, this is the first ACC-oriented systematic review and meta-analysis to focus on the neurometabolic profile in BD, taking into account the mood state and medication status. Meta-analyses (Supplementary Material, **Table S2**) revealed overall increased ACC levels of Glx, Gln and Cho in BD compared to HC but no significant differences for Glu, NAA, GABA or mI. While euthymia was associated with increased Cho and Gln, bipolar depression was only associated with increased Cho. No consistent data were available for mania, largely due to the small number of studies. Regarding medication effects on ACC neurometabolites, meta-analyses revealed that both medication-free and medicated BD subjects had increased ACC Cho. It was not possible to perform further meta-analyses exploring the medication effect due to the heterogeneity in medication profiles across studies or lack of detailed medication information. However, some selected studies provided evidence that anticonvulsants may impact ACC balance between Glu/Gln in BD.

The overall increased ACC Glx levels in BD patients relative to HC revealed by a meta-analysis with moderate effect size is in line with previous meta-analyses that simultaneously assessed different voxels and/or mixed adult and child/adolescent populations (Gigante et al., 2012; Chitty et al., 2013). However, there was an insufficient number of studies reporting ACC Glx in specific mood states to perform meta-analysis, precluding any conclusion as to whether increased ACC Glx is a general feature in BD or a mood state-dependent phenomenon. Since Glx represents the sum of several metabolites, predominantly Glu and Gln (Buonocore and Maddock, 2015), increased Glx has been interpreted as an indicator of glutamatergic neurotransmission (Govindaraju et al., 2000). Thus, it has been postulated that the putative increased glutamatergic neurotransmission causes supra-activation of glutamatergic receptors, increasing calcium post-synaptic influx, resulting in excitotoxicity, cell damage or even neuronal death (Berk et al., 2011; Mehta et al., 2013). Considering that Glx does not disclose whether Glu or Gln are elevated and that the latter is a non-neuroactive glutamatergic metabolite (Albrecht et al., 2007), increased Glx may not necessarily represent enhanced glutamatergic neurotransmission. Indeed, our meta-analysis failed to confirm any alteration of ACC Glu in BD, and thus did not support the notion of an increased glutamatergic state in the ACC as a general feature in BD.

Conversely, we found increased overall Gln, which was particularly influenced by the euthymic mood state. However, there were too few studies to perform meta-analyses in mania and depression, precluding any conclusion regarding the ACC Gln dynamics across mood states in BD. In the central nervous system, Gln is synthetized in ascrocytes from the extracellular Glu via the Gln synthetase pathway and serves as the precursor for neuronal Glu synthesis in the glutamatergic neurons (Walls et al., 2015). Such Glu-Gln cycling across neurons and astrocytes has been interpreted as an evolutionary acquisition to buffer glutamate-related excitotoxicity, since Gln is a “non-excitatory” form of stored Glu (Walls et al., 2015; Cooper and Jeitner, 2016). Since the increased Gln found was associated with the euthymic mood state, we may hypothetise that there might occur a shift in Glu-Gln cycle towards the latter under euthymia. Indeed, anticonvulsants medication has been reported to both decrease Glu (Friedman et al., 2004; Strawn et al., 2012) and increase Gln (Soeiro-de-Souza et al., 2015). Furthrmore, some selected studies have reported that euthymic BD subjects taking anticonvulsants had lower Glx/Cr (Soeiro-de-Souza et al., 2013) or Glu/Cr (Soeiro-de-Souza et al., 2013; 2018a), as well as increased levels of Gln (Soeiro-de Souza et al., 2015; Kubo et al., 2017). However, our results should be interpreted with caution because only 4 studies have assessed Gln and none were performed unsing a field strength higher than 4 T. Therefore, we highly recommend that further studies investigate the exact composition of increased

ACC Glx, using more sensitive techniques and higher magnetic fields that allow more precise measurement of Gln and Glu, as well as in different mood states.

The overall increases in ACC Cho in BD demonstrated by meta-analyses with larger effect sizes and lower levels of heterogeneity strongly suggest it is a potential trait marker in BD, given it was observed in euthymia, depression and medication-free subjects, but not in mania. However, this finding conflicts with a previous meta-analysis focused on Cho that mixed data from multiple voxels (Kraguljac et al., 2012), although some previous reports have correlated increased Cho to the severity of both depressive (Moore et al., 2000) and manic (Cecil et al., 2002) states. Elevated Cho has been associated mostly with increased phospholipid cycling or membrane breakdown that results in the release of membrane choline compounds, commonly observed in neurodegenerative (e.g., Alzheimer Disease) and demyelination (e.g., Multiple Sclerosis) processes (Stork and Renshaw., 2005). Given that cortical thinning in frontal areas is one of the most consistent neurobiological findings documented in BD, including in the ACC (Hibar et al., 2017), our results corroborate the notion that increased Cho could be a neurochemical trait associated with increased phospholipid turnover and possibly correlated with neuro-morphometric losses. Such a phenomenon appeared to be more influenced by the depressive than manic episodes, although there were only 3 studies performed in both these mood states. Increased Cho was also observed in the pooled meta-analysis of studies that mixed subjets under different mood states and it appeared not to be influenced by the medication status. Additionally, a positive correlation was also noted between publication year and effect size, only for the overall meta-analysis, suggesting the robustness of recent studies (e.g., Soeiro-de-Souza et al., 2018a and Zhong et al., 2018) has contributed to this positive result since these studies have assessed larger samples in a single mood state. Therefore, further studies assessing homogeneous samples in specific mood state using appropriate techniques (e.g. phosphorus magnetic resonance spectroscopy) are warranted.

Such increased Cho levels, possibly associated with ACC lower cortical volume, appear not to stem from mitochondrial dysfunction since no consistent changes in NAA were observed in overall, depressed, euthymia, manic or medication-free samples. This result contradicts previous systematic review and meta-analysis (Yildiz-Yesiloglu and Ankerst., 2006; Kraguljac et al., 2012) reporting NAA decline in frontal areas, the hippocampus and basal ganglia in BD, considered a surrogate of mitochondrial dysfunction and neuronal loss (Stork and Renshaw, 2005; Moffett et al., 2007). Therefore, our data do not corroborate the mitochondrial oxidative metabolism dysfunction theory (Stork and Renshaw., 2005) for neuroprogression in BD (Berk et al., 2011). Such a Cho-NAA discordant result suggests that the increased Cho levels might be associated with abnormalities in white matter microstructures, axonal myelination and white matter tracts disconnectivity (Öngür et al., 2010 Benedetti et al., 2011; Nortje et al., 2013) rather than neuronal damage. Alternatively, it may be related to inflammatory and neurotrophic pathways (Berk et al., 2011) instead of energetic metabolism imbalances.

No evidence of alterations in ACC GABA in BD patients compared to HC was found by the present meta-analysis. This finding is in agreement with previous investigations (Chiapponi et al., 2016; Schür et al., 2016) and may potentilay be confounded by the medication effect since medications such as anticonvulsants and benzodiazepines are known to modulate GABA (Sanacora et al., 2002). Similaly, meta-analyses showed no differences in mI between groups, contradicting findings of a previous systematic review that documented higher mI levels in frontal regions (Silverstone et al., 2005).

The main limitation of the present study was the high heterogeneity observed in some overall meta-analyses, largely as a result of the different study designs, stages of illness and absence of detailed medication information, as well as differences among studies in relation to voxel size, magnetic field strength, ^{1}H-MRS editing technique, echo-time, metabolite quantification method, tissue composition correction and software used for quantification. Of these factors, voxel size may be the most significant, since there are specific cytoarchitectural areas with different functions within the ACC (Bush et al., 2000), aside from the fact that in overly small voxels, the signal-to-noise ratio might be poor. Echo-time also varied widely among studies, a factor that has been found to influence the quality of metabolite measurements, in particular Glu (Schubert et al., 2004).· Although the high I^2 values found in the present meta-analyses were comparable to those described by previous studies (Gigante et al., 2012; Schür et al., 2016; Romeo et al., 2018), sub-analyses of some of the metabolites (e.g. Cho) revealed no heterogeneity, highlighting the need for more methodologically homogenous ^{1}H-MRS studies in BD. Additionally, no meaningful publication bias was detected in the present study.

5. Concluding remarks

The results of the present meta-analysis corroborate the relevance of ACC to understanding BD neurobiology across different mood states. Although there is still room for improvement in ACC ^{1}H-MRS literature, our results strongly support the hypothesis of increased ACC cell membrane phospholipid turnover and increased Glx in BD. However, the nature of Glx increase in the ACC, as well as the Glu-Gln balance across mood states, are still poorly understood, but there is some evidence that medications can modulate the Glu-Gln cycle within the ACC. Further ^{1}H-MRS studies, in the ACC or other voxels, should assess more homogeneous (preferentially mood-state specific), larger BD samples and account for medication status using more sensitive ^{1}H-MRS techniques.

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Author contributions

Study conception: ES-M, KU-R, MG S-S; Study design: ES-M, KU-R, MGS-S; Data search and extraction: ES-M,

MGS-S; Data analysis and interpretation: ES-M, KU-R, MG S-S; Writing of manuscript: ES-M, KU-R, MGS-S. All authors approved the final version of the manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.01.096.

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