ARTICLE

Brain lactate and pH in schizophrenia and bipolar disorder: a systematic review of findings from magnetic resonance studies

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Converging evidence from molecular to neuroimaging studies suggests brain energy metabolism abnormalities in both schizophrenia and bipolar disorder. One emerging hypothesis is: decreased oxidative phosphorylation leading to accumulation of lactic acid from glycolysis and subsequent acidification of tissue. In this regard, integrating lactate and pH data from magnetic resonance spectroscopy (MRS) studies in both diseases may help us understand underlying neurobiological mechanisms. In order to achieve this goal, we performed a systematic search of case–control studies examining brain lactate or pH among schizophrenia and/or bipolar patients by using MRS. Medline/Pubmed and EBSCO databases were searched separately for both diseases and outcomes. Our search yielded 33 studies in total composed of 7 lactate and 26 pH studies. In bipolar disorder, 5 out of 6 studies have found elevated lactate levels especially in the cingulate cortex and 4 out of 13 studies reported reduced pH in the frontal lobe. In contrast, in schizophrenia a single study has examined lactate and reported elevation, while only 2 out of 13 studies examining pH have reported reduction in this measure. There were no consistent patterns for the relationship between lactate or pH levels and medication use, disease type, mood state, and other clinical variables. We highlight the need for future studies combining ^{1}H-MRS and ^{31}P-MRS approaches, using longitudinal designs to examine lactate and pH in disease progression across both schizophrenia and bipolar disorders.

INTRODUCTION

Schizophrenia and bipolar disorder (BD) are common and severe psychiatric disorders, affecting more than 80 million people worldwide [1], characterized by overlapping genetic background, brain abnormalities, and clinical presentations. Despite progress, neurobiological abnormalities underlying these disorders are not well understood, and available treatments have limited effectiveness in improving the symptoms and functional outcomes [2, 3]. Growing evidence, from molecular to neuroimaging, has recently implicated impaired brain energy metabolism, evidenced by brain glucose utilization abnormalities, mitochondrial dysfunction, and high-energy phosphate (HEP) molecule depletion in their pathophysiology [4]. Although this converging evidence suggests a relationship of brain energy metabolism to pathophysiology in psychotic disorders, the underlying mechanisms remain to be elucidated.

Our understanding of the potential role of lactate in energy metabolism during brain activation has changed radically over the past three decades, shifting from waste product to supplemental fuel and signaling molecule [5]. Schurr et al. [6] were the first to suggest that cerebral energy metabolism can be fueled by lactate under certain conditions like hypoglycemia or ischemia. There is ongoing debate regarding the preference of lactate utilization for energy production by neurons. It has been speculated that lactate is preferred as a substrate when neurons are firing at high frequencies [7]. On the other hand, it may be an "opportunistic" glucose-sparing substrate when it is abundant. Despite growing recognition of the importance of lactate in energy metabolism, it

is clear that glucose is the major energy source in normal brain at rest and during activation [5].

Elevated brain lactate concentrations can occur as a result of either increased production by mitochondrial shifts in redox state or decreased clearance by cerebral blood flow alterations and lactate metabolism. Steady-state pH_i is dependent on the balance between rates of acid extrusion and loading, which in turn depends on the activities of acid–base transporting proteins [8]. Although intracellular pH regulation is a complex process and not solely regulated by lactate concentration, an important recent meta-analysis [9] confirmed the negative correlation between brain lactate and pH levels. This study, included 10 postmortem brain studies of schizophrenia and bipolar patients, showed lower brain pH levels among patients compared to controls. They also analyzed five neurodevelopmental mouse models of psychiatric disorders (schizophrenia, BD, and autism spectrum disorder), which showed lower pH and higher lactate levels in the brains of model mice together with a significant negative correlation between them.

Among the techniques available for in vivo investigation of human brain, magnetic resonance spectroscopy (MRS) is of special relevance to this field as it can be used to obtain neurochemical information [10]. The proton (^{1}H) nucleus is the most commonly probed due to its high gyromagnetic ratio and widespread development of relevant hardware and techniques. Depending on the specific sequences used, ^{1}H-MRS allows for the quantification of *N*-acetyl-aspartate, creatine/phosphocreatine (PCr), choline compounds, myoinositol, glutamine/glutamate/GABA as well as

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Lactate & pH in schizophrenia and bipolar-systematic review…
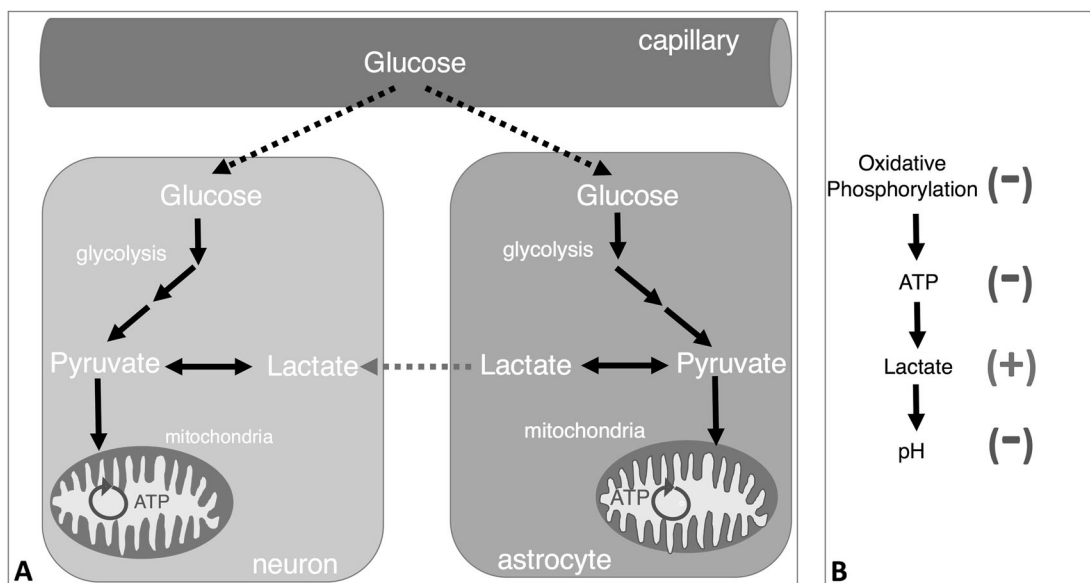AE Dogan et al.

1682

Fig. 1 Schematic view of astrocyte and neuron glucose metabolism and consequences of reduced oxidative phosphorylation. **a** Schematic representation of astrocyte and neuron glucose metabolism. Neurons and astrocytes can take up glucose from the circulation. This glucose enters glycolysis pathway and produces pyruvate, which is subsequently converted to either lactate or water and CO_2 together with 38 ATP by oxidative phosphorylation within the mitochondria. The lactate produced within astrocytes can also shuttle to neurons through transporters and can be used as an energy substrate following its conversion to pyruvate within the cytoplasm of neurons. This pyruvate is a substrate for oxidative phosphorylation taking part within mitochondria. **b** The relationship between reduced oxidative phosphorylation and lactate production, pH decrease. Reduced oxidative phosphorylation leads to a shift into glycolysis. Glycolysis results in increased production of lactate, which causes acidification of tissue and decrease in intracellular pH

lactate. Compared to ^{1}H-MRS, phosphorus (^{31}P)-MRS has lower sensitivity because of the greater mass and lower gyromagnetic ratio of the ^{31}P nucleus. ^{31}P-MRS does not suffer from problems of water and lipid contamination but its utility is limited due to poor spatial resolution, large voxel sizes, long acquisition times, and the need for dedicated hardware. PCr, inorganic phosphate (Pi), three isotopomers of adenosine triphosphate (α-, β-, and γ-ATP), phosphomonoesters and phosphodiesters, intracellular magnesium, and intracellular pH (obtained by using the chemical shift difference between Pi and PCr resonances) can be quantified by ^{31}P-MRS [11]. The combination of these two MRS approaches together with data from molecular, structural, and functional neuroimaging studies may enable us to clarify some of the underlying neurobiological mechanisms of disease in schizophrenia and BD [12].

One emerging hypothesis of metabolic dysfunction in psychotic disorders suggests that impaired oxidative phosphorylation leads to an accumulation of lactate from glycolysis and acidification of tissue (reducing pH), as well as reducing the availability of HEPs [4] (Fig. 1). Integrating such disparate MRS findings as lactate and pH abnormalities in bipolar and schizophrenia patients into a single theory of mitochondrial dysfunction has enormous potential for advancing the study of these disorders, and for developing novel treatment approaches. However, to our knowledge, there has been no systematic review of ^{31}P and ^{1}H-MRS studies of lactate or pH levels in schizophrenia and BD to date. We thus sought to systematically review all controlled studies of lactate and pH levels measured by MRS to (1) estimate the extent to which lactate and pH are altered in schizophrenia and BD, and (2) to investigate the consistency of lactate and pH findings in both schizophrenia and BD.

METHODS
Methodological strategies that are used during systematic review procedure were specified in advance and documented in a protocol (https://www.crd.york.ac.uk/PROSPERO/) with a

registration number CRD42017082064. We performed a systematic search of case–control studies examining brain lactate or pH in schizophrenia and/or BD patients. Studies were identified by searching electronic databases, scanning reference lists of articles, and consultation with experts in the field. The search was conducted using Medline/Pubmed and EBSCO databases. The last search was done on 26 April 2017. No language, publication date, nor publication status restrictions were imposed. Abstracts of the studies were reviewed and subsequently full texts were obtained. The search was run separately for four different subcategories and the results were merged. The terms used in the search were grouped as follows to capture diagnosis (schizophrenia and BD) and MRS findings (lactate and pH):

(a) Schizophrenia/lactate: ("lactic acid"[MeSH Terms] OR ("lactic"[All Fields] AND "acid"[All Fields]) OR "lactic acid"[All Fields] OR "lactate"[All Fields] OR "lactates"[MeSH Terms] OR "lactates"[All Fields]) AND ("schizophrenia"[All Fields] OR "psychotic"[All Fields] OR "psychosis"[All Fields]) AND ("magnetic resonance spectroscopy"[All Fields] OR "MRS"[All Fields]); (b) Bipolar disorder/lactate: ("lactic acid"[MeSH Terms] OR ("lactic"[All Fields] AND "acid"[All Fields]) OR "lactic acid"[All Fields] OR "lactate"[All Fields] OR "lactates"[MeSH Terms] OR "lactates"[All Fields]) AND ("bipolar"[All Fields] OR "mood disorder"[All Fields]) AND ("magnetic resonance spectroscopy"[All Fields] OR "MRS"[All Fields]); (c) Schizophrenia// pH: ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "psychosis"[All Fields] OR "psychotic"[All Fields]) AND "pH"[All Fields] AND ("magnetic resonance spectroscopy"[All Fields] OR "MRS"[All Fields]); d) Bipolar disorder/pH: ("bipolar"[All Fields] OR "mood disorder"[All Fields]) AND "pH"[All Fields] AND ("magnetic resonance spectroscopy"[All Fields] OR "MRS"[All Fields]).

Studies were included if they met all the following criteria: (1) studies included first-episode or chronic adult patients who were diagnosed with schizophrenia and/or schizoaffective and/or BD according to Diagnostic and Statistical Manual of Mental Disorders (Third or Fourth edition); (2) original in vivo ^{1}H-MRS and ^{31}P-MRS studies that measured brain lactate and/or pH levels; and (3) studies included healthy control group for comparison. Figure 2

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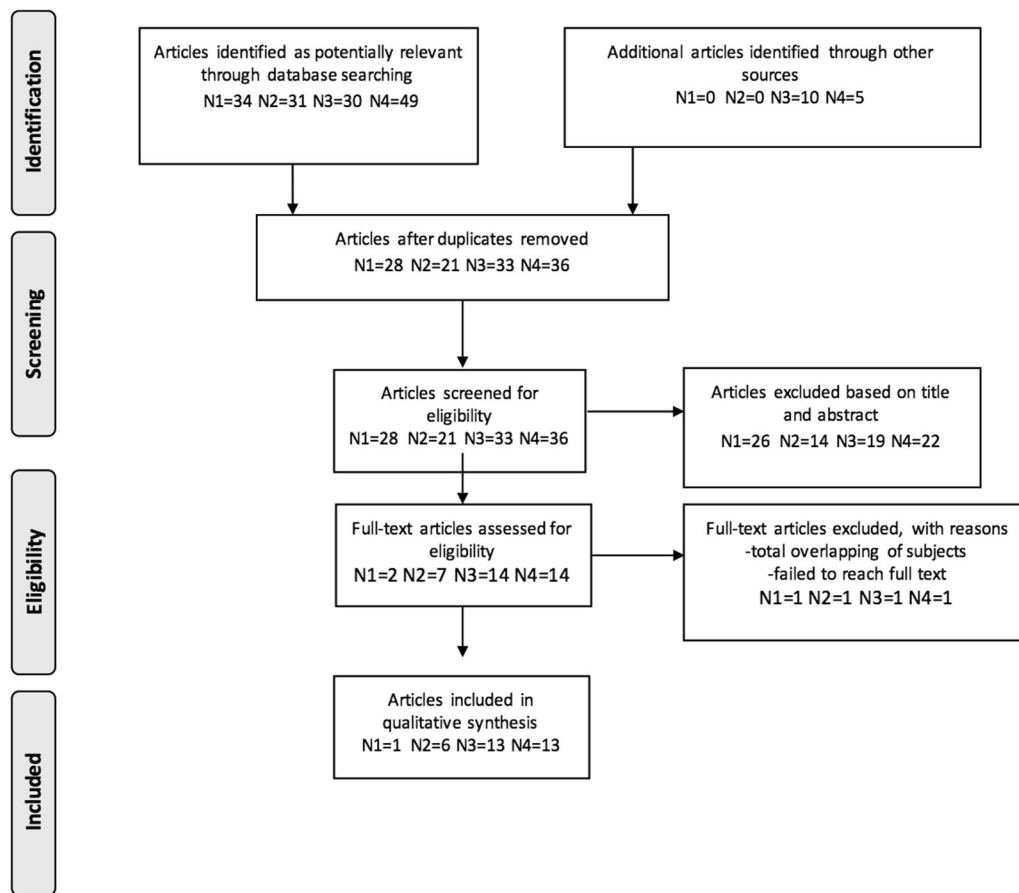AE Dogan et al.

1683

Fig. 2 PRISMA flow chart showing study selection process. This flow chart shows study selection process including identification, screening, eligibility, and inclusion steps

presents the PRISMA flow diagram showing the study selection process. We extracted results for the following data items: population; disease type; disease state; illness duration; symptom severity; medication use; magnetic field strength; data acquisition and quantitation methods; region of interest; pH; and lactate findings.

Note that we provided technical details of MRS data acquisition and analysis in the Tables as much as is available in the original manuscripts. Since the level of detail varies between papers, we were not able to provide complete information in each case.

RESULTS

Our systematic search yielded 33 studies in total composed of 7 lactate and 26 pH studies. Lactate studies were published between 2004 and 2017, whereas pH studies were published from 1991 to 2017. The study sample size ranged from 17 to 100 patients. Magnetic field strengths of the studies were between 1.5 and 7 T. Recent studies had higher field strength as expected. Because the study designs, technical details, participants, medication status, and disease state varied markedly, we focused on a qualitative synthesis rather than conducting a meta-analysis.

Lactate

Schizophrenia. Only one recent study [13] examined lactate levels in schizophrenia (Table 1) using ^{1}H-MRS. Data were collected from the anterior cingulate cortex (ACC) of 27 schizophrenia patients (mean illness duration 13.1 years) at 7 T. All but five of the patients were using antipsychotic drugs. Lactate concentrations were elevated in schizophrenia patients and were negatively correlated with general cognitive function and functional capacity. There were no significant relationships between lactate levels and positive/negative symptom severity or chlorpromazine equivalent units.

Bipolar disorder. One study [14] was excluded because of the overlap of subjects with another study [15], which included the same patients, as well as others. Five of the six studies we included reported elevated lactate levels in bipolar patients compared to healthy controls, indicating a distinct pattern (Table 2). The only study [16] that showed a contrary result found no difference during mania but reported a significantly decreased brain lactate levels during euthymia compared to healthy controls. This study was a follow-up study that included only manic bipolar I patients who were all taking medications and were re-examined when they became euthymic.

Disease type: Two studies included only BD I patients [16, 17], three studies included both BD I and BD-II [15, 18, 19], and in one study [20] illness type was not mentioned. The only study that showed reduced lactate levels included only BD I patients. Only a single study [15] compared metabolite levels between BD I and BD-II patients, and found elevated lactate in BD I patients but not in BD II. However, BD I patients had significantly higher scores both in depression and mania scales compared to BD II patients.

Mood state: Three of six studies were uniform in nature regarding mood state [16–18], whereas the other three studies [15, 19, 20] were mixed. Studies that were conducted with a single mood state included either depressive [18], manic [16], or

Lactate & pH in schizophrenia and bipolar-systematic review...
AE Dogan et al.

1684

Table 1. Schizophrenia and lactate study

Study	Subjects	Medication	FE/chronic	FS	Method	Region	Lactate
Rowland et al. [13]	27 SZ or SAD 29 NC	5 MF 22 Med (AP)	Not mentioned	7 T	Single-voxel spectroscopy STEAM sequence TE = 14 ms, TR = 3000 ms Voxel size: $30 \times 20 \times 20$ mm^3 Quantification: LCModel	ACC	↑

FE first episode, *FS* field strength, *SZ* schizophrenia, *SAD* schizoaffective disorder, *NC* normal control, *MF* medication-free, *Med* Medicated, *AP* antipsychotic, *STEAM* stimulated echo acquisition mode, *TE* echo time, *TR* reaction time, *LCModel* Linear Combination of Model Spectra, *ACC* anterior cingulate cortex

euthymic [17] patients. Among the studies that included patients in different mood states, two [19, 20] mentioned a subgroup analysis for mood state and neither found a correlation between lactate levels and mood state. A follow-up study by Brady et al. [16] compared lactate levels during manic and euthymic periods of patients. During mania, bipolar patients had lactate levels comparable to healthy subjects but during euthymia these levels were significantly reduced.

Medication use: Three studies included only medication-free patients [15, 18, 19] and only one of these [18] included drug-naive patients. The medication-free period ranged between 2 weeks and 6 months in different studies. Studies that did an additional analysis of medication use did not report any difference in lactate levels between drug-free and drug-naive patients, and medication-free and medicated patients. Studies involving medicated patients found no correlation between medication type (mood stabilizer/antipsychotic/antidepressant) and lactate levels. A follow-up study by Machado-Vieira et al. [18] compared baseline and post-treatment (6 weeks of lithium) lactate levels. After lithium treatment, lactate levels were reduced. And this reduction was independent from plasma lithium levels and clinical improvement. One study [14] was excluded because of overlapping of subjects with the study by Dager et al. [15]. Excluded study rescanned 21 bipolar patients after either lithium ($n = 12$) or valproate ($n = 9$) treatment and found no significant difference in lactate levels after treatment [14].

Symptom severity: Studies that did an additional analysis [15, 16, 18, 19] showed no correlation between symptom severity and brain lactate levels.

Brain region: The ACC with or without posterior cingulate cortex was the main region of interest in most of the studies. A study [15] with a relatively low field strength investigated a broader area, including the frontal lobe, caudate, putamen, insula, thalamus, parietal, and occipital lobes also showed elevated lactate levels.

pH
Schizophrenia. We excluded a study [21] because 11 of 26 patients were overlapping with the study by Kato et al. [22], which included 27 patients. We identified 13 studies examining pH in schizophrenia and 11 of them reported no difference of brain pH in schizophrenia patients compared to healthy controls (Table 3). A recent study [23] with a relatively higher field strength (4 T) found decreased pH in the frontal lobe of chronically ill patients. This study included patients taking medication and did not show any correlation between antipsychotic dosage and pH levels but they reported a negative correlation between intracellular pH and body mass index (BMI). Another study [24] examined multiple study groups. In the first analysis, clozapine-using patients showed reduced pH levels compared to haloperidol-using patients and healthy controls. In the second analysis, pH did not change when medication-free patients were treated with typical or atypical antipsychotics for 2 weeks. No clear patterns were detected in

relation to illness duration, symptomatic status, or brain region in studies of pH in schizophrenia.

Bipolar disorder. We excluded a study by Kato et al. [25] because 9 of the 10 subjects in that report overlapped with another study by the same group. We also excluded the euthymic patients from a study by Kato et al. [26] in order to avoid duplication because those data were used also in another study by Kato et al. [27]. Four [27–30] of 13 studies reported decreased brain pH in bipolar patients compared to healthy controls (Table 4).

Disease type: Three [27, 29, 30] out of four studies that reported decreased brain pH were conducted with both bipolar I and II patients, whereas one study [28] did not mention disease subtype. A positive study [27] performed a further analysis and did not find any difference in pH between type I and II patients. There was only a single study [30] that included both types of bipolar disease and reported decreased pH in bipolar I patients but not in bipolar II patients.

Mood state: Seven [26, 27, 29, 31–33] of the studies were uniform in nature regarding mood state, whereas the rest were either mixed or unspecified. Most of the uniform studies were conducted with euthymic patients. All of the four studies with positive results included euthymic patients. Not all the euthymic patients had decreased pH but all the patients who had decreased pH were euthymic. A follow-up study [26] examined patients during a manic episode and re-examined when they became euthymic. Brain pH of manic patients was similar to that of the control group, whereas pH during euthymia decreased compared to both pH of the control group and pH during manic episode. Another follow-up study [30] examined bipolar I patients when they were depressed and euthymic, and found decreased pH while they were euthymic but not depressed.

Medication use: Studies that reported decreased brain pH included patients who were either medication-free, medicated, or both. There was only a single study [30] comparing brain pH of medicated and non-medicated patients. This report concluded that pH was lower in medicated patients than in drug-free patients. Another positive study [27] found no pH difference between patients using antipsychotics or antidepressants and those who were not, however they found a positive correlation between pH and duration of lithium treatment. When the same team investigated the correlation between plasma lithium concentration and brain pH in another study [26] they did not find any correlation. The only study examining lithium effect before and after treatment among six manic patients [26] came up with no significant changes in pH after treatment.

Symptom severity: Most of the studies did not mention performing a subgroup analysis of symptom severity and pH level, and the only three studies that explored manic or depressive symptoms found no correlation to pH.

Lactate & pH in schizophrenia and bipolar-systematic review...
AE Dogan et al.

1685

Table 2. Bipolar disorder and lactate studies

Study	Subjects	Medication	FE/chronic	FS	Method	Region	Lactate
Machado-Vieira et al. [18]	20 BD I or II (depressive) 20 NC	All MF (at least 6 months)	Illness duration <5 years	3 T	2D CSI PRESS sequence TE = 288 ms, TR = 1500 ms Voxel size: $1 \times 1 \times 2$ cm^3 Quantification: STEMRW	Cingulate cortex	↑
Soeiro-de-Souza et al. [17]	37 BD I (euthymic) 35 NC	All medicated	Not mentioned	3 T	2D CSI JPRESS sequence Voxel size: $2 \times 2 \times 4.5$ cm^3 TE = 31 ms, TR = 1600 ms Quantification: ProFit	Dorsal ACC	↑
Xu et al. [19]	11 BD I (5 depressed + 6 manic) 13 BD II (7 depressed + 6 hypomanic) 20 NC	All MF (at least 2 weeks)	Not mentioned	3 T	2D CSI TE = 30 ms, TR = 1500 ms Sequence: not mentioned Voxel size: $13.75 \times 13.75 \times 15$ mm^3 Quantification: LCModel	ACC, PCC, thalamus	↑
Chu et al. [20]	21 BD (16 euthymic + 5 mixt episode) 10 NC	All medicated	Not mentioned	4 T	2D CSI LASER sequence Voxel size: $100 \times 80 \times 10$ mm^3 TE = 144 ms, TR = 2000 ms Quantification: LCModel	ACC, caudate	↑
Brady et al. [16]	15 BD I manic (follow-up: 7 euthymic) 6 NC	All medicated	Not mentioned	4 T	Single-voxel spectroscopy JPRESS sequence TE = 30–500 ms, TR = 2000 ms Voxel size: $2 \times 2 \times 2$ cm^3 Quantification: LCModel	ACC, POC	Mania → Euthym ↓
Dager et al. [15]	28 BD (11 BD I + 17 BD II) (depressed or mixed) 26 NC	All MF (at least 8 weeks)	Illness duration range: 6 months–33 years	1.5 T	2D CSI PEPSI sequence TE = 272 ms, TR = 2 s Voxel size: 1 cm^3 Quantification: LCModel	Frontal lobe, parietal lobe cingulate, caudate putamen, thalamus, insula	↑

BD bipolar disorder, *FE* first episode, *FS* field strength, *NC* normal control, *MF* medication-free, *Med* medicated, *CSI* chemical shift imaging, *PRESS* point resolution spectroscopy, *JPRESS* j-resolved point-resolved spectroscopy, *LASER* localization by adiabatic selective refocusing, *TE* echo time, *RT* repetition time, *LCModel* Linear Combination of Model Spectra, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *POC* parietal occipital cortex, *ProFit* prior knowledge fitting, *STEMRW* Spectroscopy Tool of the Extended MR Workspace R 2.6.3.5, *PEPSI* proton echo-planar spectroscopic imaging

Table 3. Schizophrenia and pH studies

Study	Subjects	Medication	Fe/chronic	FS (T)	Method	Region	pH
Du et al. [23]	26 SZ or SAD 25 NC	All medicated	Chronic	4	Magnetization transfer MRS Voxel size: 6 × 6 × 4 cm³ Quantification: AMARES	Frontal lobe	↓
Shirayama et al. [46]	11 SZ 15 NC	All medicated	Chronic	2	ISIS sequence TR = 3 s Voxel size: 35 × 45 × 70 mm³ Quantification: in-house method	PFC	↑
Riehemann et al. [24]	51 SZ 32 NC	8 MF 29 haloperidol 14 clozapine	Not mentioned	1.5	ISIS sequence TR = 3 s Voxel size: 28 × 28 × 50 mm³ Quantification: in-house method	PFC	Clozapine patients ↓
Volz et al. [47]	50 SZ 36 NC	47 medicated 3 MF	Not mentioned	1.5	ISIS sequence TR = 3 s Voxel size: 28 × 28 × 50 mm³ Quantification: in-house method	Frontal lobe	↑
Volz et al. [48]	13 SZ 14 NC	All medicated	Not mentioned	1.5	ISIS sequence TR = 3 s Voxel size: 28 × 28 × 50 mm³ Quantification: in-house method	DLPFC	↑
Volz et al. [49]	60 SZ 36 NC	10 MF 50 medicated	Not mentioned	1.5	ISIS sequence TR = 3 s Voxel size: 28 × 28 × 50 mm³ Quantification: in-house method	Frontal lobe	↑
Kato et al. [22]	27 SZ 26 NC	10 MF 17 medicated	Not mentioned	1.5	DRESS sequence TR = 3 s Quantification: in-house method	Frontal lobe	↑
Deicken et al. [50]	20 SZ 16 NC	6 MF 14 medicated	Chronic	2	TR = 350 ms, TE = 3.5 ms Voxel size:25 cm³ Quantification: in-house method	Frontal and parietal lobes	↑
Calabrese et al. [51]	11 SZ 9 NC	2 MF 9 medicated	Chronic	2	ISIS sequence TR = 2 s Voxel volume:4.5 × 5.5 × 3.5 cm³ Quantification: in-house method	Temporal lobe	↑
Fujimoto et al. [52]	16 SZ 20 NC	All medicated	Chronic	2	TR = 2 s Voxel size: 3 × 3 × 4 cm³ Quantification: in-house method	Frontoparietal region	↑
O'Callaghan et al. [53]	18 SZ 10 NC	Medication-free	Chronic	1.5	TR = 6 s Quantification: in-house method	Left temporoparietal region	↑
Pettegrew et al. [54]	11 SZ 10 NC	All drug-naive	FE	1.5	Voxel size: 20 cm³ TR = 2 s Quantification: GENCAP software	Dorsal PFC	↑
Williamson et al. [55]	10 SZ 7 NC	All medicated	Chronic	2	FROGS pulse sequence TR = 2 s Voxel size: 20 cm³ Quantification: in-house method	Left DLPFC	↑

FE first episode, FS field strength, SZ schizophrenia, SAD schizoaffective disorder, NC normal control, MF medication-free, AP antipsychotic, TE echo time, TR repetition time, ISIS image-selected in vivo spectroscopy, DRESS depth-resolved surface-coil spectroscopy, AMARES advanced method for accurate, robust and efficient spectral fitting, FROGS fast rotating gradient spectroscopy, PFC prefrontal cortex, DLPFC dorsolateral prefrontal cortex

Lactate & pH in schizophrenia and bipolar-systematic review...
AE Dogan et al.

1687

Table 4. Bipolar disorder and pH studies

Study	Subjects	Medication	FE/chronic	FS (T)	Method	Region	pH
Chouinard et al. [56]	32 psychosis (17 BD + 4 SZ + 4 SAD) 21 NC	All medicated	FE	4	Magnetization transfer spectroscopy TR = 14 s Voxel volume: $6 \times 6 \times 4$ cm^3 Quantification: AMARES	Frontal lobe	$\rightarrow$
Du et al. [34]	20 BD I (all psychotic) 28 NC	17 medicated	FE	4	Voxel size: $6 \times 6 \times 4$ cm^3 TR = 14 s Quantification: AMARES	Frontal lobe	$\rightarrow$
Shi et al. [36]	25 BD I (11 depressed + 14 euthymic) 23 NC	5 MF 20 medicated	Not mentioned	3	MT-ISIS pulse sequence Voxel size: $11 \times 8 \times 3$ cm^3 TR = 20.5 s Quantification: AMARES	Frontal lobe Corpus callosum Thalamus Occipital lobe	$\rightarrow$
Yuksel et al. [57]	23 BD I (21 euthymic + 2 depressed) 22 NC	All medicated	Not mentioned	4	TR = 3 s Quantification: AMARES	Occipital lobe	$\rightarrow$
Jensen et al. [35]	11 BD (5 BD I + 6 BD II) (depressive) 9 NC	All medicated	Not mentioned	4	TR = 3 s Voxel volume: $3 \times 3 \times 3$ cm^3 Quantification: in-house method	Whole brain	$\rightarrow$
Hamakawa et al. [28]	13 BD 10 NC	All medicated	Not mentioned	1.5	SPECREC sequence TR = 3000 ms Voxel size: $50 \times 35 \times 30$ cm^3 Quantification: in-house method	Basal ganglia Whole brain	$\downarrow$
Murashita et al. [31]	19 BD (13 BD I + 6 BD II) (euthymic) 25 NC	1 MF 18 medicated	Not mentioned	1.5	TR = 3 s Voxel size: 5 cm^3 Processing: OMEGA CSI software Quantification: in-house method	Occipital lobe	$\rightarrow$
Kato et al. [29]	7 BD (4 BD I + 3 BD II) (euthymic) 60 NC	All MF (at least 10 days)	Not mentioned	1.5	DRESS sequence TR = 3 s Quantification: in-house method	Frontal lobe	$\downarrow$
Deicken et al. [32]	12 BD (euthymic) 16 NC	All MF	Not mentioned	2	TR = 350 ms, TE = 3.5 ms Voxel size: 25 cm^3 Quantification: in-house method	Frontal lobe	$\rightarrow$
Deicken et al. [33]	12 BD (euthymic) 14 NC	All MF (at least 1 week)	Not mentioned	2	TR = 350 ms, TE = 3.5 ms Voxel size: 25 cm^3 Quantification: in-house method	Temporal lobe	$\rightarrow$
Kato et al. [27]	40 BD (31 BD I + 9 BD II) (euthymic) 60 NC	All medicated (all lithium)	Not mentioned	1.5	DRESS sequence TR = 3 s Quantification: in-house method	Frontal lobe	$\downarrow$
Kato et al. [30]	14 BD I (depressed or euthymic) 15 BD II (depressed, euthymic, or hypomanic) 59 NC	9 MF 20 medicated	Not mentioned	1.5	DRESS sequence TR = 3 s Quantification: in-house method	Frontal lobe	BD I euthymic $\downarrow$ BD II $\rightarrow$
Kato et al. [26]	17 BD (manic) 17 NC	All medicated	Not mentioned	1.5	DRESS sequence TR = 3 s Quantification: in-house method	Frontal lobe	$\rightarrow$

BD bipolar disorder, *FE* first episode, *FS* field strength, *NC* normal control, *MF* medication-free, *TE* echo time, *TR* repetition time, *MT-ISIS* magnetization transfer image-selected in vivo spectroscopy, *DRESS* depth-resolved surface-coil spectroscopy, *AMARES* advanced method for accurate, robust and efficient spectral fitting

1688

Brain region: There were seven studies collecting data in the frontal lobe and one study each collecting data in the temporal [33] and occipital lobes [34]. On the other hand, three studies [28, 35, 36] evaluated broader brain areas as detailed in Table 4. The regions of interest included the frontal lobe in all of the studies with a finding of decreased pH.

DISCUSSION

In our systematic review of studies measuring brain lactate and pH in schizophrenia and BD, we found mixed evidence related to bioenergetics abnormalities in both conditions. In BD, 5 out of 6 studies have found elevated lactate levels especially in the cingulate cortex and 4 out of 13 studies reported reduced pH in the frontal lobe. In schizophrenia, a single study has examined lactate and reported elevation, while only 2 out of 13 studies examining pH have reported reduction in this measure.

Mitochondrial and other bioenergetic abnormalities have been found in genetic, postmortem, and neuroimaging studies both in schizophrenia and BD. However, we have yet to put together the greater picture of related and underlying abnormalities of bioenergetic functioning in the brains of patients with schizophrenia and BD. We examined both lactate and pH results, because we consider these two measures to be markers of the same underlying process, specifically, the contributions of glycolysis and oxidative phosphorylation to ATP production. No study to date has collected data on lactate and pH levels together in schizophrenia or BD, with the addition of measures of ATP availability. This review highlights the need for such a study to directly address the proposed lactate–pH hypothesis.

For lactate results, there was only one study in schizophrenia at a very high field strength (7 T), which found elevated lactate levels compared to healthy controls. In this study, elevated ACC lactate level correlated with functioning. This can be interpreted as increased lactate levels reflecting mitochondrial dysfunction causes altered bioenergetics, which may interrupt high-energy-demanding processes like neurotransmission and synaptic plasticity. These altered mechanisms may contribute to cognitive and general functional impairments. In BD, all but one showed increased brain lactate. The study by Brady et al. [16] was the exception as it found no difference in lactate levels between patients and healthy controls when patients were manic. They re-examined the patients when they became euthymic and observed that lactate levels were significantly lower compared to healthy controls. Compared to their euthymic state their lactate levels were higher during mania. Motion artifact can be an issue for all MRS studies of lactate because the lactate resonance at 1.33 ppm is a low-amplitude peak, relatively broad due to J-coupling, mixed with larger resonances of macromolecules and lipids. The low signal-to-noise ratio (SNR) challenge can be compounded by motion, especially in studies of mania.

There were no remarkable patterns concerning the correlation of disease type, mood state, and symptom severity. Most of the studies did not find any difference between medication types. There was no study comparing medicated and medication-free patients. A longitudinal study [18], compared lactate levels before and after lithium treatment (6 weeks of lithium monotherapy), found a significant decrease in cingulate cortex lactate concentrations, which supports the evidence that elevated lactate levels in BD do not arise from medication use. Authors hypothesized that lithium normalizes cell energy metabolism by improving mitochondrial respiration, which leads to reduced lactate production. And these features may contribute to the well-known neuroprotective effects of lithium. A study by Friedman et al. [14] also evaluated patients before and after lithium or valproate treatment and did not find any difference in lactate levels. Both schizophrenia and bipolar studies measuring lactate focused mostly around the cingulate cortex region. Loss of affective control in BD

is a key factor and related to the dysfunction of critical structures (e.g., amygdala and caudate) within frontal-subcortical brain networks. Elevated lactate levels observed in ACC and caudate may suggest a possible relationship between affective dysregulation and metabolic abnormalities in these regions but none of the studies showed a correlation between symptom severity and either lactate or pH levels.

The sensitivity of lactate measurement differs across methods and the attribution of a peak to lactate is not straightforward because of lipid contamination from surrounding tissue. Two studies in our review [16, 17] used J-difference spectral lactate editing to address this issue, others [15, 18, 20] used longer echo time while two of them [19, 37] did not mention any lipid suppression method. Data acquisition techniques (single voxel vs chemical shift imaging (CSI)) also can impact lactate measurement. Except for the study by Brady et al. [16], which used single-voxel spectroscopy, all lactate studies used two-dimensional CSI, which provides larger coverage area and higher spatial resolution.

Elevated lactate levels in BD is the most prominent finding of this study. It is should be noted that lactate increase has also been observed in panic disorder (PD). Interventions such as sodium lactate infusion, hyperventilation, visual stimulation all caused greater increase in brain lactate compared to healthy controls [38–40]. More recently it has been suggested that the increased activity-dependent brain lactate accumulation is a trait feature of PD and this increase can be related to altered function of acid-sensitive fear circuits in PD [41].

For studies examining pH in schizophrenia, most of them are published in the 1990s and have lower field strength (1.5 or 2 T). There was only one study performed with 4 T magnetic field, which was also one of two studies that found decreased pH in schizophrenia. Although the study by Riehemann et al. [24] reported a significant pH difference between haloperidol- and clozapine-using patients, longitudinal measures did not confirm this medication effect. This difference may be due to disparate characteristics of patients in these groups. In contrast to schizophrenia, studies in BD, which used higher magnetic field (3 or 4 T), did not find any difference in pH levels. Four studies performed at 1.5 T demonstrated decreased pH especially at frontal lobe and during euthymia.

The study by Du et al. [23] found a negative correlation between BMI and pH levels. This finding may suggest a relationship between brain bioenergetics and peripheral bioenergetic status. Studies have shown that first-episode, drug-naive patients with schizophrenia have higher levels of plasma glucose and insulin levels together with higher insulin resistance [42, 43]. Triglycerides and lipoproteins, such as low-density and high-density lipoproteins, are also abnormal in first-episode, drug-naive patients [44].

The discrepancy of the pH findings might be at least partly due to methodological differences across studies. As seen in Tables 3 and 4, some of the studies used commercial software for quantification, whereas some of them used in-house methods. Intracellular pH is calculated from the chemical shift between PCr and Pi, and the precision of intracellular pH measured by ^{31}P-MRS is dependent on spectral resolution, how many data points are used for data processing, field strength, SNR, and shimming. We calculated an index of pH precision for each study and found a correlation with field strength (data not shown). Thus, data from lower field scanners (1.5 and 2 T) showed larger variation of measurements and lower reliability compared to 3 and 4 T.

Other MR-based approaches can also measure pH in vivo. Recently, ^{1}H MRI pulse sequences have been shown to detect H+ exchange between water and proteins. These techniques include amide proton transfer (APT) and T1 in the rotating frame (T1ρ). APT detects H+ exchange by taking advantage of differences in resonances between amide and water protons. The spin-lock preparation pulse used in T1ρ imaging sensitizes the magnetic

Lactate & pH in schizophrenia and bipolar-systematic review...
AE Dogan et al.

1689

resonance (MR) signal to relaxation effects arising from H+ exchange between free water protons and those bound to proteins and macromolecules [45]. These approaches may provide future opportunities for validation of the ^{31}P-MRS results discussed here.

It should be noted that both pH and lactate levels measured by MRS are the average of all cellular components available in the region of interest. Metabolite concentrations can differ between neurons and glial cells and this suggests that the observed findings could be due to differences in cellular composition in schizophrenia and BD. Furthermore, most of the studies did not distinguish white and gray matter differences regarding lactate and pH levels. So, the use of spectroscopic imaging approaches, allowing characterization of gray vs white matter metabolite differences, could additionally contribute to the interpretation of future findings.

This review and our interpretation of findings have certain limitations. First, the literature is small, methods and samples are heterogeneous, and much of it has been acquired at low magnetic field strengths where the intrinsic SNRs are low for both lactate and pH measurements. As seen in all four tables, data acquisition, processing, and quantification methods differ across different studies. Recent studies using modern scanners give higher quality, faster, and more objective results because shimming, scanner adjustments, and water suppression are incorporated into sequence. Second, incomplete reporting of clinical characteristics of patient population (disease duration, disease type, symptom severity, general functionality, etc.) and MRS techniques and procedures hamper our interpretation. Lastly, neuro-metabolite levels and brain pH can be affected by psychotropic medications and several other factors like sleep disturbances, psychological stress, smoking status, peripheral bioenergetic abnormalities, as well as by substances such as caffeine, nicotine, and alcohol. The majority of the studies in this review included patients medicated for various periods of time. Nevertheless, all of the studies with medication-free bipolar patients reported increased lactate, and lactate is decreased by lithium treatment in one study [18]. On the other hand, pH is found to be decreased in a small number of medication-free bipolar patients [29]. A single longitudinal study [26] with a sample size of six compared pre and post lithium treatment pH levels and did not find any changes in pH [27]. Taken together, while the influence of long-term medication cannot be excluded, the literature suggests it is unlikely that lactate abnormalities are solely due to acute medication effects. More studies with medication-free patients which also compare pre- vs post-treatment levels of pH are needed. Additionally, due to its low concentration, lactate measurement with MRS is technically quite challenging and multiple approaches used in different studies to quantify lactate may contribute noise to the literature. Also because of low gyromagnetic ratio of ^{31}P, field strength is critical for good SNR and spectral resolution in ^{31}P-MRS. So, future studies will likely benefit transitioning to high-field scanners.

Overall, our results show that the current literature is limited for now and bears mixed and insufficient findings to drive general conclusions. However, our findings also suggest that a pattern for lactate increase in BD might exist as it has been observed stably in the literature. Therefore, we believe that a thorough investigation of the energetics is necessary and these findings highlight the need for future studies combining ^{1}H-MRS and ^{31}P-MRS approaches, using longitudinal designs to examine lactate and pH in disease progression across both schizophrenia and BDs. Further insights into brain energy mechanisms can potentially lead to novel treatment modalities such as those targeting mitochondrial dysfunction or oxidative phosphorylation.

ADDITIONAL INFORMATION
Competing interests: DÖ served on a Scientific Advisory Board for Neurocrine Inc. in 2017. The reamining authors declare no competing interests.

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Lactate & pH in schizophrenia and bipolar-systematic review...
AE Dogan et al.

1690

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