Full title: Systematic analysis of brain lactate and pH levels in 65 animal models related to neuropsychiatric conditions

Short title: Brain lactate and pH in neuropsychiatric disorder models

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Abstract

Altered brain energy metabolism associated with increase in lactate levels and the resultant decrease in pH have been increasingly implicated in multiple neuropsychiatric disorders, such as schizophrenia, bipolar disorder, autism spectrum disorder and neurodegenerative disorders. Although it is controversial, change of pH/ lactate level as a primary feature of these diseases, rather than a result of confounding factors such as medication and agonal state, has been evidenced. Animal models that can be studied without such confounding factors inherent to humans are a suitable alternative to understand the controversy. However, the knowledge in animal models regarding brain pH and lactate and their relation to behavioral outcomes is limited in the context of neuropsychiatric disease conditions. In this study, we investigated the common occurrence of changes in the pH and lactate levels in the brain in animal models by analyzing 65 animal models related to neuropsychiatric and neurodegenerative diseases with 1,239 animals. Additionally, we evaluated the behavioral phenotypes relative to the chemical changes in the brain. Among the models, 27 and 24 had significant changes in brain pH and lactate levels, respectively, including Shank2 KO mice, Clock mutant mice, serotonin transporter KO mice, mice with a paternal duplication of human chromosome 15q11-13, Fmr1 KO mice, BTBR mice, APP-J20 Tg mice, social defeat stress-exposed mice, corticosterone-treated mice, and streptozotocin-induced diabetic mice. Meta-analysis of the data revealed a highly significant negative correlation between brain pH and lactate

levels, suggestive of increased lactate levels causing decreased brain pH. Statistical learning algorithm based on the comprehensive data has revealed that the increased brain lactate levels can be predominantly predicted by the indices for the percentage of correct response in working memory test, with a significant simple, negative correlation. Our results suggest that brain energy metabolism is commonly altered in many animal models of neuropsychiatric and neurodegenerative diseases, which may be associated with working memory performance. We consider our study to be an essential step suggesting that the brain endophenotypes serve as a basis for the transdiagnostic characterization of the biologically heterogeneous and debilitating cognitive illnesses. Based on these results, we are openly accepting collaborations to extend these findings and to test the hypotheses generated in this study using more animal models. We welcome any mice/rat models of diseases with or without any behavioral phenotypes.

Introduction

Neuropsychiatric disorders, such as schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), autism spectrum disorder (ASD), and Alzheimer's disease (AD), are common with a prevalence of more than one-third of the population in most countries being diagnosed with at least one such disorder at some point in their life (1). Although these diseases clinically fall into different diagnostic categories, some biological features, such as genetic mutations, molecular changes, and brain activity alterations, are common among them (2–6), suggesting a common underlying biological basis. Increasing evidence suggests that metabolic alterations in the brain are shared by the multiple neuropsychiatric disorders. Increases in the levels of lactate, an end-product of glycolysis pathway, have been observed in the brain of patients with SZ, BD, ASD, MDD, and epilepsy (7–15). Increased lactate levels is considered to lead to decreased pH and are associated with brain energy deficits (12). Recent large-scale meta-analyses have confirmed increased brain lactate and decreased pH in SZ and BD (16,17). Such increased lactate and decreased pH have also been observed in the brains of patients with AD (18–24). However,

the observed phenomena are potentially confounded by secondary factors inherent in human studies, such as antipsychotic treatments (10). Agonal experiences associated with these disorders may also complicate the interpretation of postmortem study results (25–27). Although some human studies suggest that medication use is not a major factor for regulating brain pH and lactate levels (7,10,11,15,28), excluding the effects of other potential confounding factors in human studies especially using postmortem brain samples is technically difficult. Animal models, devoid of such confounding factors, may help to confirm whether increased brain lactate and decreased pH levels are associated factors.

Recently, increased brain lactate and decreased pH levels were demonstrated to be commonly found in five strains of neurodevelopmental mouse models of psychiatric disorders (29). As all of the mice used in the study were drug-naïve, with equivalent agonal states, postmortem intervals, and ages within each strain, those findings in mouse models suggest that increased lactate and decreased pH reflect an underlying pathophysiology, rather than mere artifacts, in at least a subgroup of patients with these

77 mental disorders. However, the knowledge of brain pH and lactate in the animal models is
78 limited to small numbers of models and systematic evaluations using the same platform
79 have not been conducted so far in animal models. Therefore, we have extended our
80 previous study (29) to a larger variety of animal models of neuropsychiatric disorders, as
81 well as of neurodegenerative disorder, AD, and peripheral diseases or insults that are
82 comorbid with psychiatric conditions (e.g., diabetes mellitus (DM), colitis, and peripheral
83 nerve injury). Those animal models include 65 strains or conditions of mice and rats with
84 genetic modifications, drug treatments, and other experimental manipulations (Table 1).
85 Combining the large-scale brain lactate data with behavioral data (e.g., working memory,
86 locomotor activity, anxiety-like behavior, and depression-like behavior), we also sought to
87 investigate the relations between alterations in brain lactate levels and behavioral
88 outcomes.

89

90 **Results**

91 **Altered brain pH and lactate levels in animal models**

92 The raw data of brain pH and lactate, and detailed information of animals (age, sex, and
93 treatment methods) are included in Supplementary Table 1. Among the 65
94 strains/conditions, 27 demonstrated significant changes in pH (5 increased, 22 decreased)
95 and 24 in lactate (19 increased, 5 decreased) in comparison with the corresponding
96 control animals ($P < 0.05$; Supplementary Figure 1 and Supplementary Table 2).
97 Hierarchical clustering based on effect size and direction of changes classified those 65
98 models into four groups: high lactate/low pH group, moderate high lactate/moderate low
99 pH group, low lactate/high pH group, and a group with minimal to no changes in lactate or
100 pH, consisting of 16, 6, 15, and 28 models, respectively (Figure 1), where high and low
101 mean higher and lower in mutant/experimental animals related to the corresponding wild
102 type/control animals, respectively. High lactate/low pH group included, for example, SZ
103 model Ppp3r1 KO mice and Nrgn KO mice, SZ/intellectual disability (ID) model Hivep2 (also
104 known as Shn2) KO mice, AD model APP-J20 Tg mice, and ASD model Chd8 KO mice. Low
105 lactate/high pH group included mainly mouse models for ASD or developmental delay,

such as Shank2 KO mice, Fmr1 KO mice, BTBR mice, Stxbp1 KO mice, Dyrk1 KO mice, Auts2 KO mice, and patDp mice (Figure 1).

The Z-score-based meta-analysis of 1,239 animals analyzed in this study revealed a highly significant negative correlation between brain lactate and pH levels individually (Figure 2, Supplementary Figure 2), supporting the idea that decreased pH is due to increased lactate levels in the pathological conditions related to neuropsychiatric disorders.

Poorer working memory performance predicts higher brain lactate levels

Most of the animal models we examined are known to show a wide range of behavioral abnormalities, such as deficits in learning and memory, and increased depression-like, anxiety-like behaviors or impaired sensorimotor gating. Thereafter, with our comprehensive lactate data, we examined potential relation of lactate alterations to their behavioral phenotypes. Therefore, we examined whether behavioral patterns could predict brain lactate levels by applying a statistical learning algorithm, which could

discover intrinsic links between the chemical signatures in the brain and behaviors. Of the 65 animal models, we collected comprehensive behavioral data of 24 mouse models, which were available in public source (e.g., published papers and database repository) or in-house studies (see Methods and Materials; Supplementary Table 3). We constructed an effect size-based model for predicting the brain lactate levels from behavioral data using leave-one-out cross-validation method. Statistical evaluation of the prediction accuracy of the model revealed a significant correlation between the actual and the predicted brain lactate levels (Figure 3a), indicating that behavioral measures have a potential to predict the brain lactate levels of individual models.

The prediction analysis was implemented to evaluate the behavioral measures most useful to characterize the brain lactate levels of individual strains. The prediction algorithm used identified behavioral signatures related to brain lactate levels by weighting behavioral measures according to their individual predictive strength. Thus, we identified the behavioral measures accompanying changes in brain lactate levels by examining the weighted behavioral measures used for the prediction in linear regression. Three out of

nine behavioral measures were selected to build the successful prediction model and in those measures for working memory was the most selected (Figure 3b). According to simple correlation analysis, the measures for working memory were negatively correlated with the brain lactate levels (Figure 3c). These results suggest that higher lactate levels in the brain are related to lower performance in working memory tests in mouse models of neuropsychiatric disorders.

Effects of age and sex on the brain pH and lactate levels

Ages at sampling were matched within each strain/condition, but varied among strains/conditions, ranging from 5 to 103 weeks old in mice (Supplementary Table 1). No significant correlation was found between pH and age in wild type/control mice. Brain lactate levels had a significant negative correlation with age (Supplementary Figure 5), consistent with a previous MRS study in mice (30). However, limitations need to be considered in interpretating our results, such as, differences in genetic background and handling conditions before sampling (some mice had received repeated intraperitoneal

151 injections or behavioral tests, and others had been kept undisturbed until sampling)
152 among strains/conditions. We further examined the effects of sex on the brain pH and
153 lactate levels. To minimize the effects of the limitations mentioned above, we used
154 Z-scores that were calculated within each strain/condition and focused on
155 strains/conditions with mixed gender. Female had significantly higher pH and lower
156 lactate levels than male in wild type/control animals (Supplementary Figure 6).

157

158 **Discussion**

159 We performed a comprehensive analysis of brain pH and lactate in 65 animal models. The
160 data suggested the diversity of brain-energy-metabolism among these model animals.
161 Some mouse strains considered to model different diseases were found to exhibit similar
162 pattern of changes in pH and lactate levels. Specifically, SZ models (Ppp3r1 KO and Nrgn
163 KO mice), SZ/ID model (Hivep2 KO mice), BD/ID model (Camk2a KO mice), ASD model
164 (Chd8 KO mice), depression models (mice exposed to social defeat stress,
165 corticosterone-treated mice and Sert KO mice), AD model (APP-J20 Tg mice), and DM

166 model (STZ-treated mice) commonly exhibited decreased brain pH and increased lactate
167 levels. A BD model Polg1 Tg mice showed no differences in pH or lactate levels. However,
168 other BD model (Clock mutant mice) and ASD models, such as Shank2 KO (31), Fmr1 KO,
169 Dyrk1 KO (32), Auts2 KO (33), and patDp mice (34), were classified into a group with
170 opposite changes, or decreased lactate and increased pH group. Animal models with
171 different patterns of changes in brain pH and lactate levels may represent subpopulations
172 of patients or specific states of the diseases (13). While increased brain lactate levels in
173 neuropsychiatric conditions are almost consistent in the literature, decreased lactate
174 levels has also been found in a cohort of patients with SZ (35) and in euthymic state of BD
175 (36). Our results from animal studies may also support the idea that the patients
176 categorized based on the symptoms to particular neuropsychiatric disorders are
177 biologically heterogeneous (37) from a brain-energy-metabolism viewpoint.

178 The present animal studies revealed an extraordinarily high negative correlation
179 between brain lactate and pH levels, strengthening our previous findings from small-scale
180 animal studies (29). Negative correlation between them has been found in human

181 postmortem study (10). These results suggest that brain lactate is a main regulator of the
182 tissue pH (12), although we could not exclude the possibility that other factors such as
183 neuronal activity-regulated production of carbon dioxide, another metabolic acid, may
184 also contribute to the changes in brain pH (38,39).

185 We observed no significant correlation between age and brain pH in wild
186 type/control mice. In human studies, inconsistent results have been obtained with regard
187 to correlation between brain pH and age. Some studies showed no significant correlation,
188 (40,41), whereas other studies showed a negative correlation (42,43). Sex effects on brain
189 pH is also inconsistent in human studies (40,41). Systematic analysis focusing on the
190 effects of age and sex on the brain pH using animal models may help explain the
191 inconsistency found in the human studies.

192 Does brain lactate exert favorable or unfavorable effects on learning and
193 memory functioning? Our prediction analysis highlighted that poorer working memory
194 performance may be predominantly associated with higher lactate levels in animal models
195 of neuropsychiatric disorders (Figure 3). Additionally, in human studies, higher lactate has

196 been associated with lower cognition in the individuals with SZ (14) and mild cognitive
197 impairment (44). Given these observations, lactate production may be expected to exert
198 negative impacts on brain functions, especially memory formation. However, lactate
199 production stimulated by learning tasks has been suggested as requisite for memory
200 formation. Lactate production by the astrocytic glycogenolysis and its transport to
201 neurons serves as an energy substrate for neuronal activity, referred to as
202 astrocyte-neuron lactate shuttle (ANLS). Animal studies have demonstrated that the
203 pharmacological disruption of learning task-stimulated lactate production and transport
204 via the ANLS immediately before the testing impaired memory formation as assessed by
205 the plus-shaped maze spontaneous alteration task (testing short-term memory) (45) and
206 in the inhibitory avoidance task (testing long-term memory) (46,47). Collectively,
207 considering that brain lactate levels increase during stimulations in a temporally (and
208 spatially) restricted manner under physiological conditions (48,49), pathologically
209 persistent elevation of brain lactate levels may exert negative impact on brain functions
210 including memory processing, although the causality is unknown. Other possibility is that

211 decreased consumption of lactate for energy production due to mitochondrial dysfunction
212 in neurons may underline the impaired learning and memory functioning in the disease
213 conditions. Mitochondrial dysfunction has been thought to lead to lactate accumulation
214 because of insufficient capacity of mitochondrial metabolism to metabolize lactate that
215 was produced (16,50,51). Mitochondrial dysfunction has been consistently implicated in
216 multiple neuropsychiatric disorders, including SZ, BD, MDD, ASD, and AD (52–54), among
217 which working memory deficits are common symptoms (55). In addition, given that lactate
218 rise reflects neuronal activation (29) and multiple brain regions are abnormally activated,
219 activation in the brain regions other than frontal cortex, one of the brain regions critical
220 for working memory (56), interfere with working memory performance, as proposed that
221 activity of core brain region could be interfered with noise from the rest on cognitive tasks
222 in patients with SZ (57). There is also the possibility that increased lactate may have a
223 beneficial effect to compensate for the impaired memory and cognition, as lactate
224 administration that increases brain lactate levels has been shown to attenuate cognitive
225 deficits in human patients (58) and rodent model (59) of traumatic brain injury.

Additionally, lactate administration has also been shown to exert antidepressant effects in depression model mice (60). We also cannot exclude the possibility that increased lactate is also involved in behavioral alterations other than memory deficit per se, such as anxiety, as we have found that increased brain lactate levels were associated with altered anxiety-like behaviors in social defeat stress model of depression (61). Further studies are required to address these issues, for example, by chronically inducing deficits of mitochondria function to manipulate endogenous lactate levels in a brain-region-specific manner and analyzing its effects on working memory.

As we used whole brain samples to measure the pH and lactate levels, we could not determine whether the observed changes in pH/lactate levels occur ubiquitously in the entire brain or selectively in specific brain region(s) in each strain or condition of the models. Indeed, brain region-specific increase in lactate levels was observed in human patients with ASD in the MRS study (8). The brain region-specific changes may occur even in animal models in which significant changes were not detected in the present study and, if so, such differences could be masked in the analysis using whole brain samples. Further

241 studies are required to address this issue, for example, by means of the measurements in
242 micro-dissected brain samples and in vivo analyses using pH- or lactate-sensitive biosensor
243 electrode (45,62) and MRS (63).

244 In conclusion, the present study demonstrated that altered brain pH and lactate
245 levels were commonly observed in many animal models of SZ, BD, ASD, AD and other
246 neuropsychiatric disorders. These findings provide further evidence supporting the idea
247 that altered brain pH and lactate levels are not mere artifacts such as medication
248 confounding, but rather implicated in the underlying pathophysiology of, at least
249 subpopulations of, patients with the diseases. Alteration in the brain-energy-metabolism
250 or hyper- or hypo-activity of neurons in the brain leading to abnormal lactate and pH
251 levels may serve as a potential therapeutic target of neuropsychiatric disorders (17). In
252 addition, detection of brain lactate, such as by MRS, may help to diagnose and
253 subcategorize such biologically heterogeneous diseases, as shown in mitochondrial
254 disease (64). Future studies to identify the effective treatment strategies specific to the
255 sets of animal models that could recapitulate diversity of brain-energy-metabolism in

256 human disease conditions may contribute to development of improved treatments for the

257 biologically defined subgroups of patients or disease states of the debilitating illnesses

258 beyond the clinically defined borders.

259

260 Table 1. Animal models used in this study

	Name	Description	Related diseases/conditions
1	APP Tg	Mice expressing familial Alzheimer's disease-mutant human amyloid beta precursor protein (PDGF-hAPP$_{swe/Ind}$, line J20) (65)	AD(66,67)
2	Arid1b KO	Mice with heterozygous knockout of the AT-rich interaction domain 1b (68)	ASD(69,70)
3	Auts2 KO	Mice with heterozygous knockout of the Autism susceptibility candidate 2 (33)	ASD(71–73), ID(74), SZ(75)
4	Barp KO	Voltage gated calcium channel beta-anchoring and -regulatory protein KO mice (76)	

5	Bdnf KO	Brain derived neurotrophic factor KO mice* (JAX, 004339)	
6	BTBR	Inbred mouse strain BTBR T+ tf/J (77,78)	ASD
7	Camk2a KO	Mice with heterozygous knockout of the calcium/calmodulin-dependent protein kinase II alpha (79–81)	BD(82–84), SZ(85)
8	Camkk1 KO	Mice with forebrain-specific constitutively active form of calcium/calmodulin kinase kinase 1 (86)	
9	Ccnd2 KO	Cyclin D2 KO mice (87)	
10	CFA treatment	Mouse model of chronic inflammatory pain induced by complete Freund's adjuvant (CFA) (88,89)	Chronic pain
11	Chd8 KO	Mice with heterozygous knockout of the	ASD(91–95)

		long isoform of chromodomain helicase DNA-binding protein 8 (90)	
12	Chn1 KO	Chimerin 1 (α-chimerin) KO mice (96)	ASD(96)
13	Clock mutant	Mice with N-ethyl-N-nitrosourea-induced mutation in circadian locomotor output cycles kaput (JAX, 002923) (97,98)	BD(99,100), SZ(101)
14	Corticosterone treatment	Mice chronically treated with corticosterone (102,103)	MD(104–106)
15	Crmp2 KO	Collapsin response mediator protein 2 KO mice (107)	AD(108), SZ(109)
16	Dextran treatment	Mice treated with dextran sulfate sodium (110)	Colitis
17	Disc1-L100P mutant	Mice with N-ethyl-N-nitrosourea-induced L100P amino acid exchange mutation in	SZ(112–114)

		exon 2 of Disrupted-in-Schizophrenia 1 (111)	
18	Disc1-Q31L mutant	Mice with N-ethyl-N-nitrosourea-induced Q31L amino acid exchange mutation in exon 2 of Disrupted-in-Schizophrenia 1 (111)	SZ(112–114)
19	Dyrk1a KO	Mice with heterozygous knockout of the dual specificity tyrosine phosphorylation regulated kinase 1a (32)	ASD/ID(70,115,116)
20	ECS treatment	Mice treated with electroconvulsive stimulation (117,118)	Treatment for MDD(119,120)
21	Fmr1 KO	Fragile X mental retardation protein translational regulator 1 KO mice (121)	ASD, FMR, SZ(85)
22	Gasc1	Gene amplified in squamous cell	ASD(124)

	hypomorph	carcinoma 1 hypomorphic mutant mice (122,123)	
23	Glra4 KO	Glycine receptor alpha 4 KO mice (125)	ID(126)
24	Grin1 KO (postnatal)	GABArgic neuron-specific glutamate receptor, ionotropic, NMDA1 KO mice (Protein phosphatase 1, regulatory subunit 2-cre; $Grin1^{loxP/loxP}$) (127)	SZ(128,129)
25	Grin1 KO (adult)	GABArgic neuron-specific glutamate receptor, ionotropic, NMDA1 KO mice (Protein phosphatase 1, regulatory subunit 2-cre; $Grin1^{loxP/loxP}$) (127)	SZ(128,129)
26	Gunn rat	Gunn rats (Gunn/Slc-j/j) (130)	SZ(131)
27	Hivep2 KO	Human immunodeficiency virus type 1 enhancer binding protein 2 (Schnurri-2) KO	ID(133,134), SZ(132)

		mice (132)	
28	Hyponatremia	Mice treated with 1-deamino-8-D-arginine vasopressin and fed with a liquid formula (135–137)	DS(138,139)
29	Il18 KO	Interleukin 18 KO mice (140,141)	DM(142)
30	Ketamine treatment	Mice treated with ketamine (143)	Psychosis(144)
31	Lurasidone treatment	Mice treated with lurasidone (145)	Atypical antipsychotic(146,147)
32	Mdga1 KO	MAM domain containing glycosylphospatidylinositol anchor 1 KO mice (148)	SZ(149–151)
33	Mdga2 KO	Mice with heterozygous knockout of the	ASD(153,154)

		MAM domain containing glycosylphospatidylinositol anchor 2 (152)	
34	Methampheta mine treatment	Mice treated with methamphetamine (155)	Psychosis(156)
35	Nhe5 KO	Na^+/H^+ exchanger 5 KO mice (157)	
36	Nlgn3-R451C KI	Mice with R451C amino acid exchange mutation in neuroligin 3 (77,158)	ASD(159,160)
37	Nr3c1 Tg	Mice overexpressing glucocorticoid receptor under the Camk2a promoter	MD(161)
38	Nrgn KO	Neurogranin KO mice (162–164)	SZ(165,166)
39	Oxamate treatment	Mice treated with sodium oxamate, an inhibitor of lactate dehydrogenase	
40	Pacap KO	Pituitary adenylate cyclase-activating	MD(168), SZ(169)

		polypeptide KO mice (167)	
41	patDp	Mice with a paternal duplication of human chromosome 15q11-13 (34)	ASD(170–173)
42	Phencyclidine treatment	Subchronic phencyclidine-treated mice (145,174)	SZ(175)
43	PCP+Lur	Phencyclidine (PCP)- and lurasidone (Lur)-treated mice (145,174)	
44	Polg1 Tg	Forebrain-specific catalytic subunit of mitochondrial DNA polymerase KO mice (176)	BD(177)
45	Ppp3r1 KO	Forebrain-specific protein phosphatase 3, regulatory subunit B, alpha isoform (calcineurin B, type 1) KO mice (178,179)	SZ(180)
46	Quinpirole	Mice treated with quinpirole, a dopamine	OCD(182)

	treatment	D2 receptor agonist (181)	
47	Reln Tg	Mice lacking the C-terminal region of Reelin (183)	ASD(184–186), BD(187), SZ(188)
48	Restraint stress	Mice exposed to chronic restraint stress (189)	Chronic stress
49	Sciatic nerve cuffing	The sciatic nerve cuffing mouse model of neuropathic pain (190,191)	Chronic pain
50	Scn2a KO	Mice with heterozygous knockout of the sodium voltage-gated channel alpha subunit 2 (192)	ASD(193,194), EP(195–197), ID(198,199)
51	Sert KO	Serotonin transporter KO mice (200)	ASD(201,202)
52	Shank2 KO	SH3 and multiple ankyrin repeat domain 2 KO mice (31)	ASD(154)
53	Shank3 KO	SH3 and multiple ankyrin repeat domain	ASD(204–206)

		3b KO mice (JAX, 017688) (203)	
54	Snap25-S187A KI	Mice with S187A amino acid exchange mutation in synaptosomal-associated protein of 25 kDa	ADHD(207–212), EP(213,214), SZ(215,216)
55	Social defeat stress (acute)	Mice exposed to social defeat stress (217,218)	Acute stress
56	Social defeat stress (chronic)	Mice exposed to social defeat stress (219,220)	Chronic stress
57	Streptozotocin treatment	Mice treated with streptozotocin (221)	DM(222)
58	Streptozotocin + restraint stress	Mice treated with streptozotocin and exposed to chronic restraint stress (189,221)	DM and DS comorbidity(223)

59	Stxbp1 KO	Mice with heterozygous knockout of the syntaxin-binding protein 1 (224)	ASD/ID(116,199,225), EP(226,227)
60	Syngap1 KO	Mice with heterozygous knockout of the synaptic Ras GTPase-activating protein 1 (228,229)	ID, SZ, ASD(154), EP(226)
61	Thalidomide treatment	Rats prenatally exposed to thalidomide (230,231)	ASD(232)
62	Tnx KO	Tenascin X KO mice (233,234)	EDS(235), SZ(236–238)
63	Trx1 KO	Rats with heterozygous knockout of the thioredoxin 1	EP
64	Tsc1 KO	Astrocyte-specific tuberous sclerosis complex 1 KO mice (Glial fibrillary acidic protein-cre; $Tsc1^{loxP/loxP}$) (239)	TSC(240)

65	Valproic acid treatment	Mice prenatally exposed to valproic acid (241)	ASD(242)

AD, Alzheimer's disease; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; BD, bipolar disorder; DM, diabetes mellitus; EDS, Ehlers-Danlos syndrome; DS, depression symptom; EP, epilepsy; FMR, Fragile X mental retardation; ID, intellectual disability, KI, knock-in; KO, knock out; MD, major depressive disorder; OCD, obsessive-compulsive disorder; SZ, schizophrenia; Tg, transgenic; TSC, tuberous sclerosis complex. *Mice with off-target deletion of conditional Bdnf allele derived from $Bdnf^{2lox}$ mouse line.

Materials and Methods

Experimental animals and ethical statement

Mice and rats used in this study are listed in Table 1. Animal experiments were approved by the Institutional Animal Care and Use Committee of Fujita Health University, based on the Law for the Humane Treatment and Management of Animals and the Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain. Every effort was made to minimize the number of animals used.

Sampling and handling of the brain samples

Upon the study, a standardized protocol regarding sampling and handling of the brain samples has been established to minimize potential confounding effects because of the technical differences among laboratories and performing blind studies, as follows:

Animals and samples

- Animals: Mouse and rat. For genetically engineered animals, mutants and their wild-type littermates should be used.
- Number of animals: ≧6 per group (identical genetic background, littermate), preferably.
- Sex of animals: All males, all females, or balanced among groups if mixed.
- Samples: Fresh-frozen whole brain.

Blind study

pH measurements were blinded: Upon sampling, the researchers were supposed to randomize the animals regarding genotype and collect brain samples into tubes labeled with serial numbers. The researchers were asked to provide the genotype information and the corresponding serial numbers for the following statistical analyses, after the measurements.

Brain sampling procedures

1. Sacrifice mouse/rat by cervical dislocation followed by decapitation, and remove whole brain from the skull. Do not immerse the brain in any buffer solutions or water.
2. Cut the brain along the longitudinal fissure of the cerebrum.
3. Collect the left and right hemispheres into a tube that can be tightly capped like Cryotube and seal the caps with Parafilm (to minimize the effect of carbon dioxide from dry ice on the tissue pH during transportation.).
4. Snap freeze in liquid N2, and store at -80C until the shipment.
5. Transport the frozen brain on dry ice.

The protocol is also publicly available at http://www.fujita-hu.ac.jp/~cgbb/en/collaborative_research/index.html.

310 **Measurements of tissue pH and lactate levels**

311 Whole brain was used to measure pH and lactate levels as previously described (29).
312 Briefly, snap-frozen tissues were homogenized in ice-cold distilled H_2O (5 ml per 500 mg of
313 tissue). The pH of the homogenates was measured using a pH meter (LAQUA F-72,
314 HORIBA, Ltd., Kyoto, Japan) equipped with a Micro ToupH electrode (9618S-10D, HORIBA,
315 Ltd.) after a three-point calibration at pH 4.0, pH 7.0, and pH 9.0. Subsequently, the
316 concentration of lactate in the homogenates was determined using a multi-assay analyzer
317 (GM7 MicroStat, Analox Instruments, London, UK) after calibration with 8.0 M lactate
318 standard solution (GMRD-103, Analox Instruments). A 20-µl aliquot of centrifuged
319 supernatant (14,000 rpm, 10 min) was used for the measurement.

320

321 Effect size (d) was calculated for each strain/condition and each measure (e.g., pH, lactate
322 value, and behavioral index), as followed:

323 $$d = (M_{mutants} - M_{controls})/S_{pooled}$$

$$S_{pooled} = [(S^2_{mutant} + S^2_{control})/2]^{1/2}$$

The heat map was depicted using the R (version 3.5.2) gplots package.

Z-score transformation, a traditional method of data normalization for direct comparison between different samples and conditions, was applied for each pH or lactate value using individual animal data within each of strain, according to the following formula:

$$\text{Z-score} = (\text{value}_P - \text{mean value}_{P1\ldots Pn})/\text{standard deviation}_{P1\ldots Pn} \quad ,$$

where P is any pH or lactate and $P1\ldots P_n$ represent the aggregate measure of all pH or lactate values.

Prediction analysis

We collected the comprehensive behavioral data as much as of animal models whose brain pH and lactate levels were examined in this study. The following behavioral data of 24 animal models were obtained from published papers, Mouse Phenotype Database

338 (http://www.mouse-phenotype.org/), or in-house studies (Supplementary Table 3):
339 number of transitions in the light-dark transition test, percentage of immobile in the
340 forced swim test, time spent in open arm in the elevated plus maze test, prepulse
341 inhibition at 78-110 dB and 74-110 dB, startle response at 120 dB, distance traveled in the
342 open field test, and correct percentage in the T-maze, Y-maze, or other maze test from
343 APP Tg mice, Arid1b KO mice mice, Barp KO mice, BTBR mice, Camk2a KO mice, complete
344 Freund's adjuvant-treated mice, Chd8 KO mice, corticosterone-treated mice, Disc1-L100P
345 mutant mice, Disc1-Q31L mutant mice, Gasc1 hypomorphic mutant mice, Hivep2 KO mice,
346 Nhe5 KO mice, Nr3c1 Tg mice, Nrgn KO mice, Pacap KO mice, patDp mice, Ppp3r1 KO mice,
347 Reln Tg mice, Scn2a KO mice, Sert KO mice, Snap25-S187A KI mice, social defeat
348 stress-exposed mice, and Syngap1 KO mice. The literature search was conducted in
349 PubMed and Google Scholar using relevant key words: name of strain or experimental
350 condition, species (mice or rats), and name of behavioral tests. Among the top hits at the
351 search, we used the data that were presented in actual values of the mean and SD or SEM,
352 as priority. For some behavioral measures, possible mean and SD values were estimated

353 from the graph presented in the paper. In the matrix of strains/conditions and behavioral
354 measures, those with any missing values were excluded, resulting in obtaining nine
355 behavioral measures from 24 strains/conditions of mouse models. Effect size was
356 calculated for each strain/condition and each measure and used for the prediction
357 analysis.

358 Leave-one-out cross-validation was employed to determine whether behavioral
359 measures can predict brain lactate levels for individual strain of mice. From the analyzed
360 behavioral dataset of 24 mouse strains, one sample was selected and excluded to serve as
361 test data of the cross-validation. Thereafter, a multivariate linear regression model was
362 trained on the remaining 23 samples using a stepwise variable selection procedure with
363 EZR software (version 1.38; Saitama Medical Center, Jichi Medical University, Saitama,
364 Japan) (243), and the test sample was predicted. This was repeated 24 times, in which all
365 samples were chosen once as the test data. Behavioral measures selected at least one
366 time in the prediction model were considered as predictive behavioral measures. The

prediction performance was analyzed by evaluating correlation between the predicted and actual values for the 24 mouse strains.

Statistical analysis

The pH and lactate data were analyzed using unpaired t-test, or one-way analysis of variance (ANOVA) or two-way ANOVA followed by *post hoc* Tukey's multiple comparison test using GraphPad Prism 8 (version 8.4.2; GraphPad Software, San Diego, CA).

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Figure legends

Figure 1. Hierarchical clustering of 65 strains/conditions of animals regarding brain pH and lactate levels. Effect size was calculated for each strain/condition and was used in this analysis. $^{\$}$The data of these mice have been reported previously (29).

Figure 2. Highly significant negative correlations between brain pH and lactate levels. Scatter plot showing correlations between pH and lactate levels of 1,239 animals. A Z-score was calculated for each animal within the strain/condition and used in this study.

Figure 3. Poorer working memory predict higher brain lactate levels. (a) Prediction of brain lactate levels from behavioral outcomes in the 24 mouse models related to neuropsychiatric disorders. The scatter plot shows significant correlations between predicted and actual lactate levels. (b) Feature preference for constructing the model to predict brain lactate levels. (c) Scatter plot showing correlations between working memory measures and actual brain lactate levels.

Supplementary Figure 1. Bar graphs showing the raw mean (± sem) of brain pH. Each plot represents individual value. Asterisks indicate significant effects of the genotype/condition. *p < 0.05, **p < 0.01; unpaired t-test, or one-way or two-way ANOVA followed by *post hoc* Tukey's multiple comparison test. Detailed statistics are presented in Supplementary Table 2. $The data of these mice have been reported previously (29).

Supplementary Figure 2. Bar graphs showing the raw mean (± sem) of brain lactate levels. Each plot represents an individual value. Asterisks indicate significant effects of the genotype/condition. *p < 0.05, **p < 0.01; unpaired t-test, or one-way or two-way ANOVA followed by *post hoc* Tukey's multiple comparison test. Detailed statistics are presented in Supplementary Table 2. $^{\$}$The data of these mice have been reported previously (29).

Supplementary Figure 3. Normal distribution of effect size values of 65 animal models (a, pH: D = 0.12, p = 0.30; b, lactate: D = 0.15, p = 0.093)

Supplementary Figure 4. No significant correlations between the number of transitions in the light/dark transition test (a), immobility in the forced swim test (b) and actual brain lactate levels of 24 mouse strains used for prediction analysis

Supplementary Figure 5. Scatter plots showing correlations between age at sampling and pH (a), and lactate levels (b) in wild type/control mice

Supplementary Figure 6. Dot plots showing pH (a) and lactate levels (b) of female and male animals in 17 mixed gender strains/conditions. Bars indicate means

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1257 **Table 1.** Animal models used in this study

1258 **Supplementary Table 1.** Raw data of brain pH and lactate, and detailed information of the

1259 animals (age, sex, and treatment methods)

1260 **Supplementary Table 2.** Detailed statistics of pH and lactate measurements in 65 animal

1261 models

1262 **Supplementary Table 3.** Source of behavioral data used for prediction analysis

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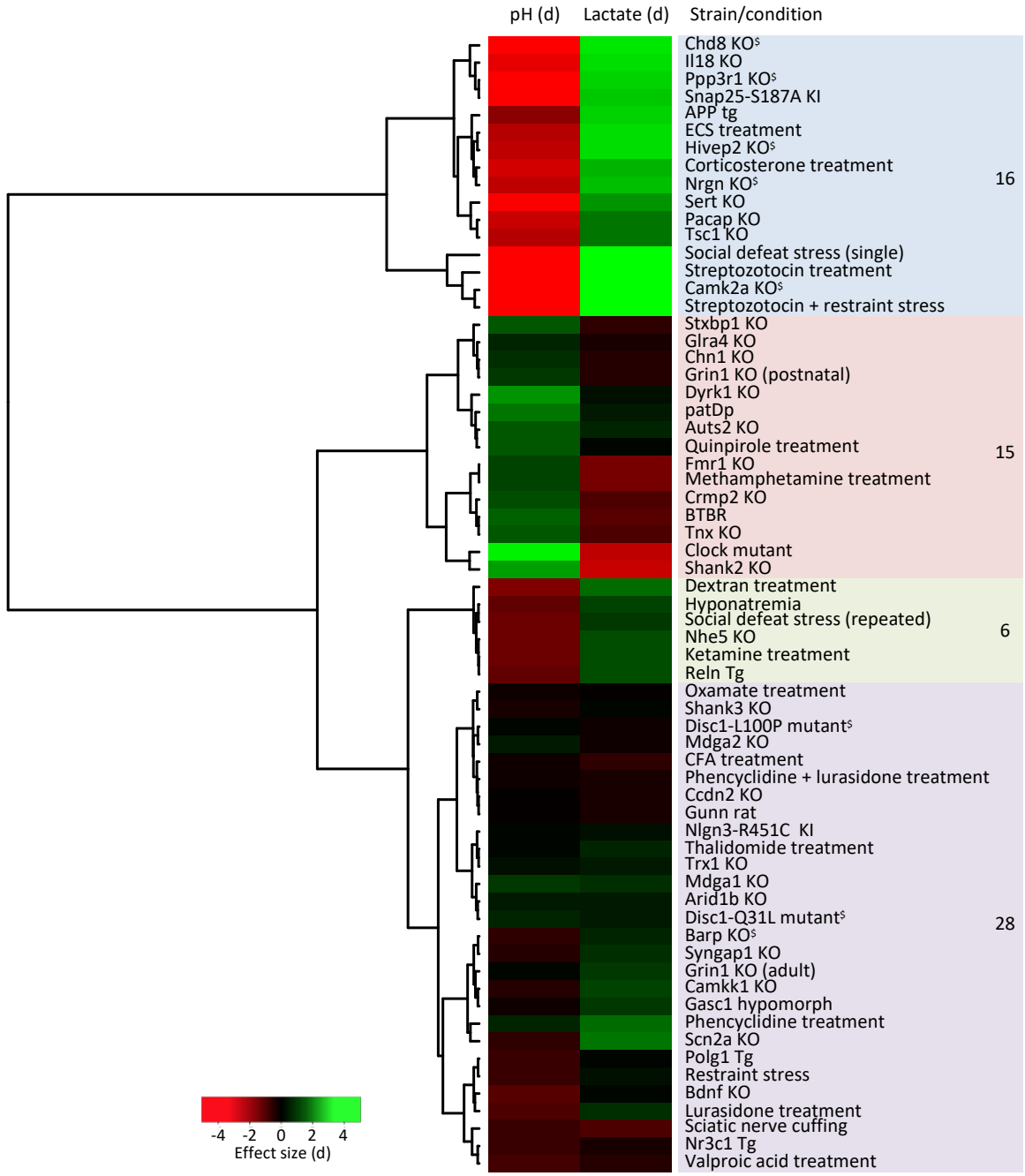
1264 Figure 1



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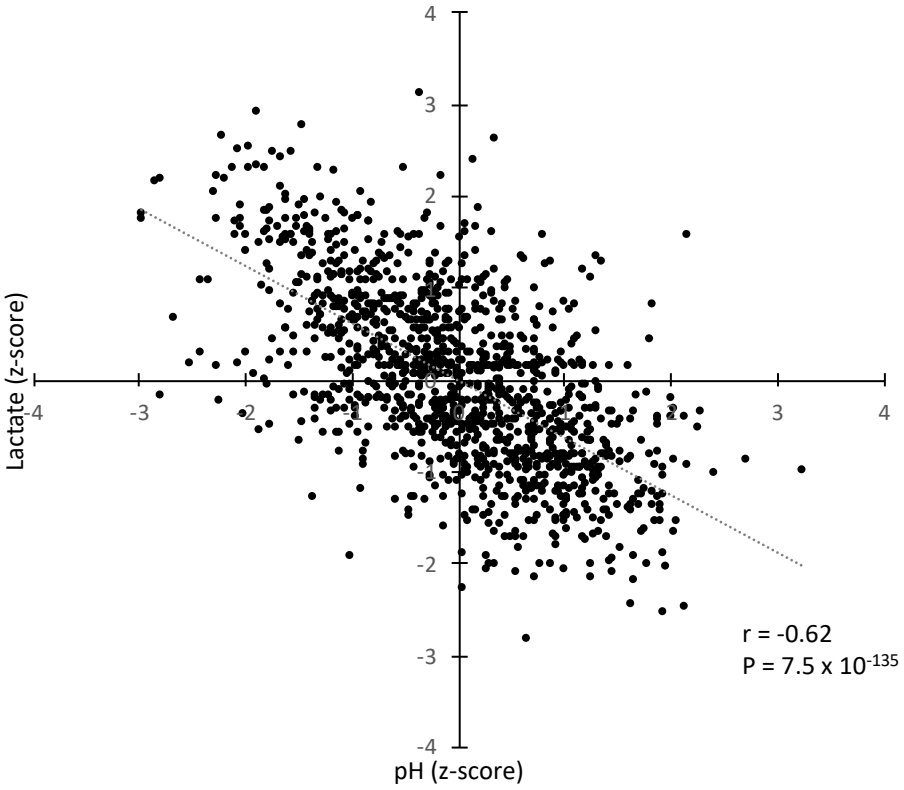
1267 Figure 2



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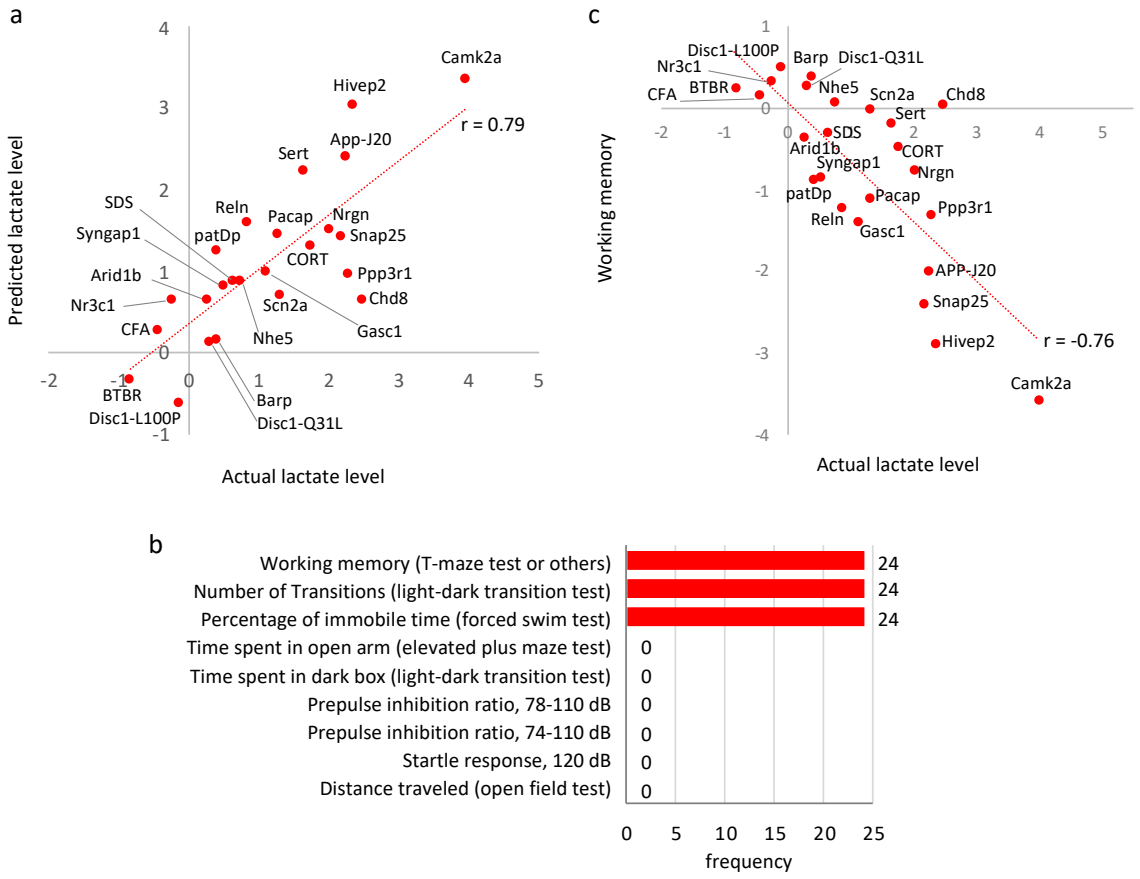
1270 Figure 3



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