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Mitochondria, Mood Lability, and Bone: mtSNPs' Surprising Relationship to Mental Homeostasis

Elizabeth Mingo* **and Chelsea Stephens**
Howard University Department of Biology and Quadgrid Data Lab Research Group

***Corresponding author:** Howard University Department of Biology and Quadgrid Data Lab Research Group

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Abstract

Mitochondrial DNA profiles comprise some of the most inclusive and broadly representative genomic databases publicly available, containing diverse haplogroups from all over the world; however, there is less emphasis on mutations' biochemical and neurological impact. Mitochondria's function in calcium regulation is often cited, but few weave in its roles in immunity, bone homeostasis, cytokinesis, and apoptosis. While this approach is apt for increasing statistical significance, it can miss the bigger picture. Currently, there are enough associations—such as the effects of calcium dysregulation, the role of ROS in circadian rhythm determination, and cytokines' interaction with mitochondria—to speculate on causality. This systematic review re-contextualizes previously reported haplotypes and single nucleotide polymorphisms (SNPs) in their biochemical environment, reports on potential systemic effects of altered mitochondria, explores common setbacks for studying bipolar disorders, and suggests new technologies that could ameliorate some of them using a novel graphic representation of each study's findings.

Keywords

mtDNA; SNP; Mitochondria; Homeostasis; Bone homeostasis; Calcium; Calcium regulation; TNF-α; Cytokines; TFAM; P2X7R; ROS production; CACNA1C; RANKL; MCU; α-CaMKII; CAMK2II; IL-6; CRP; C-reactive protein; ROS; IL-1β; Mitochondrial morphology.

Introduction

Mitochondria are organelles formed from the endosymbiosis of α-proteobacteria [1]. As soon as these endosymbionts entered an archeal cell, their evolutionary 'incentives' shifted, and they underwent a slew of changes: their gram-negative ancestors lost their interstitial peptidoglycan, the inner membrane folded into cristae, and much of the genome was transferred to the nucleus [2]. This process was heterogeneous across eukarya. In general, mtDNA may be linear or circular, have multiple types of molecules, and may retain different genes in mtDNA. [3]. Some eukaryotes even lose mitochondria entirely [4]. This mitochondrial heterogeneity is so intense that it exists within Homo sapiens alone.

Although humans' mtDNA is uniformly circular, everyone differs in the number of mtDNA molecules per mitochondrion (copy number) [5,6], the exact haplotype of the mtDNA, the level of heteroplasmy (intra-individual mtDNA haplotype diversity) [7], and even the shape of their mitochondria [8].

Such a varied structure suggests a multitude of functions, which proves correct. Mitochondria house the TCA cycle and the electron transport chain (ETC). Additionally, they engage in lipid metabolism, release ROS (signaling molecules on top of their damaging nature [9]), engage in calcium signaling [10,11], facilitate apoptosis [12], and regulate both nuclear and mitochondrial protein degradation [13].

This, together with mitochondria's systemic roles in cytokinesis [14]], immunity [14-17], neurology [5] [6,18], and bone homeostasis [19,20], make it a versatile powerhouse within the body. Free-floating mitochondria have been found in both human and fetal bovine sera, expressing genes that regulate immune function [21]. However, this means that any downtick in utility has the potential to cause complex, messy disorders that do not fit nicely into any other box. Due to neurons' steep energy demands, the brain is on the frontline of any metabolic disorder. This is seen clearly in altered mental statuses conferred by diabetic incidents [22] and the influence of eating disorders such as anorexia nervosa on confusion [23]. In other words, the symptoms of metabolic disorders bleed into psychiatry. Not everything that affects the brain occurs in the brain.

The etiologies of many mental illnesses, including bipolar, remain elusive. Bipolar is a group of mental disorders characterized by varying, prolonged, virtually unprompted periods of mania/hypomania, bipolar depression (as opposed to unipolar depression), and possibly mixed states. Psychosis and emotional blunting may occur throughout, and remission is known as euthymia. Euthymia is biochemically and mentally distinct from a normative mental state.

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Bipolar disorders are subject to the kindling effect [24], meaning that each episode is more extreme than the last. It shares this phenomenon (as well as potential treatment with lamotrigine) with epilepsy.

Bipolar is the sixth leading cause of disability worldwide [33]. However, it overlaps with other disorders and is difficult to diagnose, with 31.9% of probands suffering for 13 years before finding the true diagnosis [34] [25]. This lack of identification is a huge problem; 25% of bipolar probands will attempt suicide in their lifetime, and 11% will succeed [34]. This combines with other factors to decrease probands' lifespan by 11-20 years [35].

The list of comorbidities is lengthy, even putting aside other mental disorders: diabetes [26,27], low bone mass [28], decreases in visual motor perception [29], atrial fibrillation [30], asthma [31], dyslipidemia [36], hypertension [36], CVD [36], T. gondii infection [36], myocardial infarction [36], systemic lupus erythematosus [36], and temperature fluctuations [32]. When compared to healthy controls, bipolar probands present with activation changes in the thalamus [28], dorsolateral prefrontal cortex (DLPFC) [531*], hippocampus [28], and decreased volume in the anterior cingulate cortex [110*]. Many cytokines, such as TNF-α [39], vary significantly between states, as do serum and CSF calcium levels [40].

This prevalence, severity, and suicide risk all demand a convincing etiology—and mitochondria almost certainly play a role. Mitochondria interact with cytokines such as TNF-α [113], their count and morphology change in bipolar [114], and they are one of the main players in calcium signaling. Calcium homeostasis interacts with many of these comorbidities and symptoms [115]. However, this illness is complex. Solving the problem of its etiology will take a greater sample size than is reasonable from a singular study.

Although there are excellent reviews on bipolar disorders and mitochondrial physiology [41], there is no review of the utility of available databases. This review aims to integrate the physiology of mitochondria with the immune and skeletal system, explain salient existing database options, and clarify where they fall short for describing bipolar disorders.

Methods

PubMed was searched for the combinations of: "bipolar disorder," "mtDNA," "mitochondrial DNA," "cytokine," "bone," "calcium," and "mitochondria" on 12-21-2023. These searches provided 580 results, or 521 unique articles, which were then appraised by the methods outlined in Fig. 1A. Only primary sources were included. Other reviews and meta-analyses were excluded to avoid the possibility of evaluating outdated or duplicate studies. Studies were considered "relevant" if they met the following criteria.

In epidemiological studies, the bipolar group had to be the test group/cohort of at least 100 subjects. Thus, a study on the effect of alcohol dependence on bipolar was excluded due to the confounding variable of alcohol dependence. If the study investigating bipolar was one of a few cohorts, and the bipolar sample met the qualifications, it was included. However, the results for non-bipolar mental disorders (such as ASD) were not reported. Studies needed to evaluate a characteristic of bipolar and not suggest a

clinical course. If this epidemiological study was a genetic analysis, it had to specify a gene, not a haplogroup.

Mitochondrial haplotypes are broad categories, and results based on haplogroups are inconsistent. This does not mean that mtDNA is irrelevant—rather, smaller subgroups can influence the neurological risk of conditions such as Alzheimer 's disease [42]. While there are no studies directly addressing subgroup analysis in bipolar disorder, it would certainly make sense of the discrepancies in the literature. To ensure even reporting, only specific mutations were considered.

Mouse studies' requirements were similar: to have an appropriate strain and sample size. The appropriate sample size was met if the difference between the total animals and the total test groups was greater than 10.

In vitro studies needed slightly different inclusion/exclusion criteria. A list of comorbidities [43], medications, and biochemical markers associated with bipolar disorder were compiled. Relevant studies either investigated bipolar and one relevancy term or investigated three (or more) of the relevancy terms. The relevancy terms were as follows: childhood maltreatment/trauma, CVD, mitochondrial dysfunction, diabetes, dyslipidemia, senescence/aging, blood-brain barrier, metabolic syndrome, obesity, HPA disruption, bone mass, CKD, sleep deprivation, hippocampus, T. gondii, dentate gyrus, dorsolateral prefrontal cortex, prefrontal cortex, ROS/oxidative stress, mitochondrial copy number, mania/ hyperactivity (in mice), NF-κB, TNF-α, IL-6, IL-8, BRPF2, α-CaMKII, CRP, P2X7R, mitophagy, apoptosis, IL-1β, Lithium Lamotrigine, Valproate/valproic acid, Quetiapine, Olanzapine, Aripiprizole, Risperidone, any SSRIs, calcium, Complex 1, Complex 2, Polg1, LPS. iPSC studies claimed the correct significance, outlined in this review [44].

All relevant studies reported no author bias and had accurate abstracts. All were peer-reviewed.

Results from the relevant studies were tabulated in the supplementary table, which is the source for all the following figures to create 'etiological fingerprints' for each given variable—including comorbidities, cytokine elevations, ROS, cell cycle alterations, calcium alterations, and mitochondrial alterations. These were the columns of our table, with the exposure variables on the x-axis and our dependent variables on the y-axis. We then screened the following biometric databases for the qualities outlined in (Figure 1B) MITOMAP, MitBASE, MSeqDR, GnomA, PGC, and GWAS. The benefits and drawbacks of each were tabulated and compared to the literature review to estimate the efficacy of the available sources.

Results

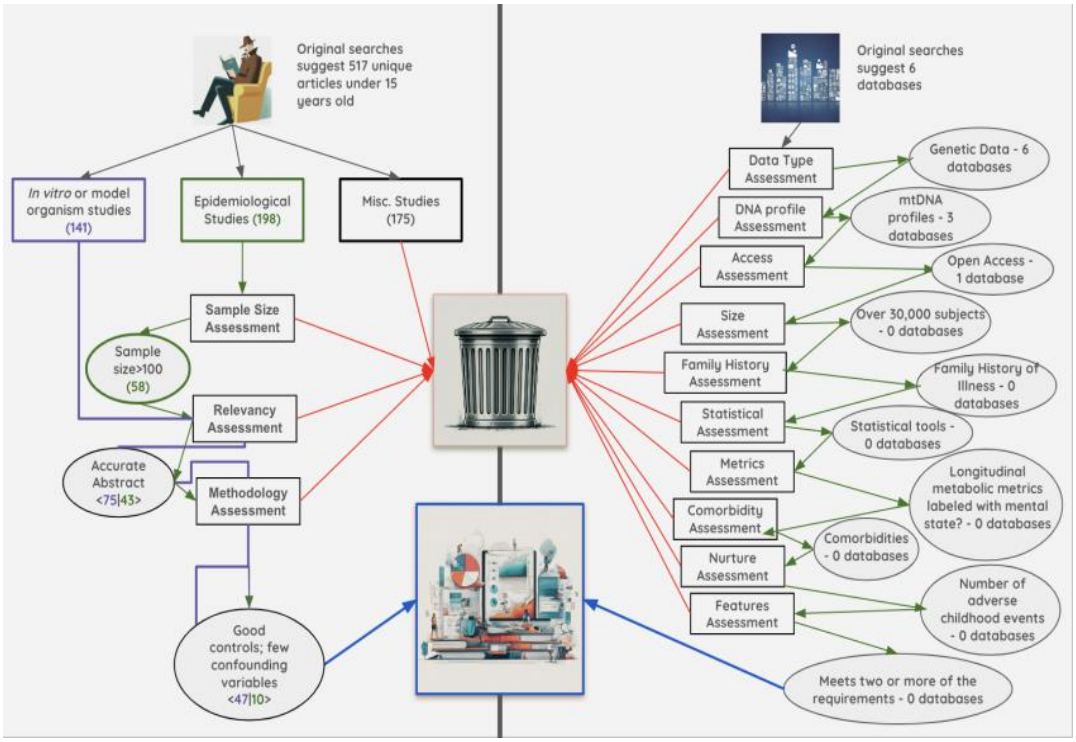

Figure 1: The results of the literature and database review.

Diagnoses and Symptoms

Dependent Variables	Exposure Variables						
	Bipolar Disorder	**Sleep Deprivation**	**YMRS**	**MADRS**	**Social Stress**	**Early Onset Bipolar**	**Memory**
TNF-α Activity	(After accounting for processing time) [47]	Lithium | Hippocampus; Frontal Cortex (C57BL/6J mice) [111] || (Male Sprague- Dawley) [106]	(sTNF- R1) [48]	(sTNF-R1) [48]			Logical | Verbal (sTNF-R1) [48]

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	(sTNF-R1) Duration | Psychotic Features [48]						
IL-6 Activity	(After accounting for processing time) [47] sIL-6r | Duration [48]	(Male Sprague-Dawley) [106]	(sIL-6r) [48] || Impuls- ivity [51]	(sIL-6r) [48]			
Misc. Monocyte-Activating Factors	IFN-γ (After accounting for processing time) [47] MCP-1 | Duration[48]	IFN-γ | IL-1 (Male Sprague- Dawley) [106]	MCP-1 [48]	MCP-1 [48]			
CRP	CRP | Duration [48]		CRP [48]	CRP [48]			
IL-1β	(After accounting for processing time) [47] [48]	Lithium | Hippocampus; Frontal Cortex (C57BL/6J mice) [111] || (Male Sprague- Dawley) [106]	[51]				
Complex I Genetic Variants	rs6506640 | rs906807 (NDUFV2, Han Females) [45] || rs1880924 (MGAM) | rs3915952 (ND4) [46]	mtND2 [110]				rs9933834 (IL34) | rs3915952 (ND4) [46]	
Anxious Behavior/Anxiety	Self-explanatory	(Male Sprague-Dawley) [106]			(EPM, Male Wistar Rats, Repeated Social Defeat) [77]		
IL-10 (Anti-inflammatory, inhibits MHC)	(After accounting for processing time) [47]	Lithium | Hippocampus; Frontal Cortex (C57BL/6J mice) [111]			Hippocampus (Adult Male Wistar Rats, Repeated Social Defeat) [77]		
Cortisol/Corticosterone Levels	(Early Childhood Trauma) [77]	(Male Sprague-Dawley) [106]			(Male Wistar Rats, Repeated Social Defeat) [77]		
Locomotor Activity	Self-explanatory	(REM Deprivation, Sprague– Dawley Rats) [110]			w/maternal PIC (Y maze and OFT, Adult Male Wistar Rats, Repeated Social Defeat) [77]		

IL-4	Suicidality [51]	Lithium | Frontal Cortex (C57BL/6J mice) [111]					
ROS (Complex I or III)	[100] || [70]	(Lipid Peroxidation, C57BL/6J mice) [111] || (iNOS, Male Sprague-Dawley) [106]					
mtDNA Copy Number	[110]	Hippocampus | Prefrontal Cortex (REM Deprivation, Sprague– Dawley Rats) [110]					
Cell Injury	Oxidative Damage to DNA [110]	Oxidative Damage to DNA (C57BL/6J mice) [111]					
Cyt-B Variants	rs1880924 (MGAM) |rs12733666 (AK5) | rs3088309 [46]					rs9933834 (IL34) | rs583990 (CTNNA2) | rs3088309 [46]	
Circadian rhythm associated factors	PER Abnormalities [106]	Daytime | Per1 | Cry1 | Bmal | CLOCK (Male Sprague- Dawley) [106] Daytime | Cry2 (Male Sprague-Dawley) [106]					
Presynaptic Markers	[74]				Maternal PIC; Frontal Cortex (Synaptophysin, Adult Male Wistar Rats, Repeated Social Defeat) [77]		
Body Mass	[47]				(Male Wistar Rats, Repeated Social Defeat) [77]		
Social Gregariousness	Self-explanatory				maternal PIC (Adolescent Male Wistar Rats, Repeated Social Defeat) [77]		

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Fracture Risk	History of Hospitalization | Lamotrigine | Carbamazepine | Valproic Acid | Antipsychotic Dosage [Fracture Risk, 98] || Anticonvulsants [Fracture Risk, 91] || Lithium | Antipsychotics | Valproate | Lamotrigine(Osteoporosis) [81]						
25OHD	[80]						
Depressive Behavior/Depression	Self-explanatory						
IL-2 Activity (T cells, anti Th17)	(After accounting for processing time) [47] sIL-2r | Duration [48]						
Misc. Neutrophil-Activating Factors	IL-8 [47]						
Misc. Eosinophil-Motivating Factors	RANTES [51]						
GSK-3β functionality (Pro-inflammatory)	[66]						
Maternal Infection	[77]						
Complex I expression/activity	[62] || Type I [110] || [70]						
Histone Deacetylase Activity (Intracellular Signaling, Cell Cycle Promotion)	(HDAC) [100]						
BDNF (Neuron survival, plasticity, and growth)	[100]						
rs1006737 (CACNA1C)	(only in males) [62]						

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Misc Apoptosis-Associated Factors	P2X7R Expression [76]						
Purinergic Cell signaling	P2X7R Expression [76]						
Calcium Regulation	rs1006737 (CACNA1C) [62]						
ER Calcium	[112] || [104]						
Mitochondrial Calcium	[112] || [104]						
Cytoplasmic Calcium	[112] || [104]						
Glial Activation		Cortex | Hippocampus (IBA-1, Male Sprague-Dawley) [106]					
Blood Brain Barrier Integrity		(AQP-4, Male Sprague-Dawley) [106] ZO-1 | Claudin5 (Male Sprague-Dawley) [106]					
Apoptosis		(Cytoplasmic Cytochrome C, COX 411) [110]					
Complex IV Expression / Activity		mt-CO1 | COX411 (Hippocampus, REM Deprivation, Sprague–Dawley Rats) [110]					
Hippocampal Volume							Verbal [78]
Glial Activation					(Short term, Male Wistar Rats, Repeated Social Defeat) [77] Maternal PIC (Long term, Adolescent Male Wistar Rats, Repeated Social Defeat) [77]		
Arginase-1		[106]					

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Cell Density					Maternal PIC; Frontal Cortex (Microglia, Adult Male Wistar Rats, Repeated Social Defeat) [77]		

Findings Map 1: A summary of dependent variables associated with bipolar and vetted symptoms of bipolar.

The finalists confirmed the existing notion that bipolar is an inflammatory disease. TNF-α, CRP, IL-1β, monocyte activators, and Complex I mutations all showed symptom profiles similar to bipolar. Both early and late onset bipolar were associated with mutations in Cytochrome B and Complex I, but the mutations differed. ND4 affected both phenotypes, whereas NDUFV2 was only associated with late onset [45] [46]. They also showed different epistasis—with late-onset preferring MGAM and early onset interacting with IL34 [46].

Although studies show consistent associations with TNF-α, IL-6, and IL-1β, these are dramatically affected by sample processing time, which may differ between collection sites [47]. While *in vitro* studies still support the involvement of these three cytokines, sample processing time remains a silent confounding variable for all epidemiological studies. The only cytokine that survived the correction was a decrease in IL-8. The effects of sample processing time on CRP were not tested. Even with this confounding variable, TNF-α, IL-6, CRP, and MCP-1 are all associated with the duration of bipolar and are differentially affected by depressive and manic states [48].

Medication

Dependent Variables	Exposure Variables									
	Bipolar Disorder	Sample Processing Time	d-Amphetamine			Lithium	Lamotrigine	Risperidone	Lithium Responsivity	Topiramate	Valproate/Valproic Acid
IL-6	(After accounting for processing time) [47]	[47]	Frontal Cortex | Sodium Butyrate | Valproic Acid [100] || Lithium(Male Wistar rats) [101]	Striatum | Sodium Butyrate | Valproic Acid [100] || Lithium(Male Wistar rats) [101]	Serum | Lithium(Male Wistar rats) [101]	Grape Seed/Skin Extract| Heart , pro-IL-6 (Wistar Rats) [90] Caffeine+ Theobromine+Catechin (RAW 264.7) [66] || Orbitofrontal Cortex (Male Long-Evans Rats) [51]	(Balb/c mice) [62] || [72] w/TGF-ß (astrocytes) [72]	Acute, transient (male C57BL/6J mice) [89]	Orbitofrontal Cortex (Male Long-Evans Rats) [51]		Striatum; Frontal Cortex (Valproic Acid) [100]

	[48]					Plasma | Medial Prefrontal Cortex | Nucleus Accumbens (Male Long-Evans Rats) [51]	w/TGF-ß (microglia) [72]				
IL-1β	(After accounting for processing time) [47]	[47]				Caffeine +Theobromine+Catechin (RAW 264.7) [66] || Orbitofrontal Cortex | Plasma (Male Long-Evans Rats) [51]	(Balb/c mice) [62]	(male C57BL/6J mice) [89]	Orbitofrontal Cortex (Male Long-Evans Rats) [51]		
	[48]					Medial Prefrontal Cortex | Nucleus Accumbens (Male Long-Evans Rats) [51]					
TNF-α	(After accounting for processing time) [47]	[47]	Frontal Cortex | Sodium Butyrate [100] || Lithium (Male Wistar rats) [101]	Striatum | Sodium Butyrate | Valproic Acid [100] || Lithium (Male Wistar rats) [101]	Serum | Lithium(Male Wistar rats) [101]	Caffeine+ Theobromine+ Catechin (RAW 264.7) [66]	(Balb/c mice) [62]		Orbitofrontal Cortex (Male Long-Evans Rats) [51]	(Astrocyte-microglia co-cultures) [72]	Striatum; Frontal Cortex (Valproic Acid) [100]
	[48]						(Astrocyte-microglia co-cultures) [72]				
IL-2 (T cells, anti Th17)	(After accounting for processing time) [47]	[47]				Plasma (Male Long-Evans Rats) [51]	(Balb/c mice) [62]	(male C57BL/6J mice) [89]			
	[48]										
Misc Apoptosis-Ascociated Factors	P2X7R Expression [76]					P2X7R (microglial N9 cells) [76]	TGF-ß1 (Astrocyte-microglia co-cultures) [72]			CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
										TGF-ß1 (Astrocyte-microglia co-cultures) [72]	

Misc. Eosinophil-Motivating Factors	RANTES [51]				IL-13 | Eotaxin (Plasma, Male Long-Evans Rats) [51]		IL-13 (3 Hours, male C57BL/6J mice) [89] Eotaxin | RANTES (male C57BL/6J mice)[89]	RANTES | Orbitofrontal Cortex (Male Long-Evans Rats) [51]		
Purinergic Cell signaling	P2X7R Expression [76]				P2X7R (microglial N9 cells) [76]				CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
Misc. Neutrophil-Activating Factors	IL-8 [47]	IL-8 [47]			IL-8 | Plasma | Orbitofrontal Cortex (CCL-5) (Male Long-Evans Rats) [51] IL-8 | Medial Prefrontal Cortex | Nucleus Accumbens (CCL-5) (Male Long-Evans Rats) [51] | Plasma, Male Long-Evans Rats) [51]		IL-17 (3 hours, male C57BL/6J mice)[89]			
Histone Deacetylase Activity (Intracellular Signaling, Cell Cycle Promotion)	(HDAC) [100]		Frontal Cortex | Sodium Butyrate | Valproic Acid(HDAC) [100]							Striatum; Frontal Cortex (HDAC, Valproic Acid) [100]
Locomotor Activity	Self-explanatory		Frontal Cortex & Striatum | Valproic Acid | Sodium Butyrate [100] || Lithium (Male Wistar rats) [101]	Frontal Cortex & Striatum | Valproic Acid | Sodium Butyrate [100] || Lithium (Male Wistar rats) [101]	Serum | Lithium (Male Wistar rats) [101]	(Male Long-Evans Rats) [51]				
IL-4	Suicidality [51]		Frontal Cortex | Sodium Butyrate | Valproic Acid [100] || Lithium (Male Wistar rats) [101]	Striatum | Sodium Butyrate | Valproic Acid [100] || Lithium (Male Wistar rats) [101]	Serum | Lithium(Male Wistar rats) [101]	Plasma (Male Long-Evans Rats) [51]			Orbitofrontal Cortex (Male Long-Evans Rats) [51]		Striatum; Frontal Cortex (Valproic Acid) [100]
IL-10 (Anti-inflammatory, inhibits MHC)	(After accounting for processing time) [47]	[47]	Frontal Cortex | Sodium Butyrate | Valproic Acid [100] || Lithium(Male Wistar rats) [101]	Striatum | Sodium Butyrate | Valproic Acid [100] || Lithium(Male Wistar rats) [101]	Serum | Lithium(Male Wistar rats) [101]. || Lithium (Male Wistar rats) [101]	Caffeine+ Theobromine+ Catechin (RAW 264.7) [66] Plasma (Male Long-Evans Rats) [51]			Orbitofrontal Cortex (Male Long-Evans Rats) [51]		Striatum; Frontal Cortex (Valproic Acid) [100]
Misc. Monocyte-Activating Factors	IFN-γ (After accounting for processing time) [47]	IFN-γ [47]				IFN-γ | MIP-1α | MCP-1 | CXCL10 (Plasma, Male Long-Evans Rats)		CXCL10 | MIP-1α (male C57BL/6J mice)[89]			

	MCP-1 [48]			[51]					
GSK-3β functionality (Pro-inflammatory)	[66]			Caffeine+ Theobromine+Catechin (RAW 264.7) [66]					
Post-Synaptic Markers	[74]			Grape Seed/Skin Extract | Heart (AChE, Wistar Rats) [90]					
Calcium Regulation	rs1006737 (CACNA1C)[62]							CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
Mitochondrial Calcium	[112] || [104]			8701A/10398A | 8701G/10398G(transmitochondrial cybrids) [112]					8701A/10398A | 8701G/10398G(valproate, transmitochondrial cybrids) [112]
ROS (Complex I or III)	[100] || [70]			Low glucose | High glucose (BMM) [63]. || (KOA mice) [85] || TCAIM (BMDC) [103] || Açai Extract (NO, Microglia) [70] || Grape Seed/Skin Extract | Heart (Lipid Peroxidation, Protein Carbonylation, Tyrosinase activity, Xanthine Oxidase Activity, Wistar Rats) [90] || 8-Iso [111]					
Cell Injury	Oxidative Damage to DNA [110]	Lactic Acid Dehydrogenase [47]		IL-1α (Plasma, Male Long-Evans Rats) [51] Lactic Acid Dehydrogenase | Grape Seed/Skin Extract | Heart (Wistar Rats) [90]					
Fracture Risk	History of Hospitalization | Lamotrigine | Carbamazepine | Valproic Acid | Antipsychotic Dosage[Fracture Risk, 98] || Anticonvulsants [Fracture Risk, 91] || Lithium | Antipsychotics | Valproate | Lamotrigine(Osteoporosis) [81]								Valproate (Bone Strength, Male Sprague Dawley Rats) [75]
Body Mass	[47]					(female C56BL/6J, w/ovarectomies) [93]			

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T-Cell Priming				IL-12p70 | CXCL10 (Plasma, Male Long-Evans Rats) [51]		IL-17 (3 hours) | CXCL10 (male C57BL/6J mice)[89] (Prolactin, plasma, female C56BL/6J, w/ovar-ectomies) [93] RANTES | (male C57BL/6J mice)[89]	RANTES | Orbitofrontal Cortex (Male Long-Evans Rats) [51]		
Cell Proliferation					TGF-ß1 (Astrocyte-microglia co-cultures) [72]	(Osteoblasts, Female C56BL/6J, w/ovar-ectomies) [93]		TGF-ß1 (Astrocyte-microglia co-cultures) [72]	
Blood Brain Barrier Integrity					Glial Cell Viability (Astrocyte-microglia co-cultures) [151]			Glial Cell Viability (Astrocyte-microglia co-cultures) [151]	
Apoptosis			dsDNA release, Cytoplasmic Cytochrome C [101]					[72]	
RANKL Release						RANTES | (male C57BL/6J mice)[89]	RANTES | Orbitofrontal Cortex (Male Long-Evans Rats) [51]		
Osteoclast Differentiation						(female C56BL/6J, w/ovarectomies) [93]			
Glial Activation					(Astrocyte-microglia co-cultures) [151]			(Astrocyte-microglia co-cultures) [151]	

Autophagy				Grape Seed/Skin Extract| Heart (p-62, Wistar Rats) [90]					
Autophagy-Associated factors								CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
Cell Signaling								CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
Angiogenesis								CX43 (Astroglia, Astrocyte-microglia co-cultures) [72]	
Cell Cycle Speed				PHA | Caffeine+Theobromine+Catechin (RAW 264.7) [66]					
Copper/ Zinc/ Iron Concentration				Grape Seed/Skin Extract| Heart (Wistar Rats) [90]					
Drug Metabolites, Plasma						1 hour (male C57BL/6J mice)[89]			
Drug Metabolites, Bone Marrow						3 hours (male C57BL/6J mice)[89]			
Catalase/ GSH/ GPx/ SOD Expression				(Wistar Rats) [65] || [76] || GPx | Catalase | Grape Seed/Skin Extract [Heart, Wistar Rats) [90] || GPx | SOD | Catalase (PHA-Treated Macrophages) [66] Frontal Lobe | Hippocampus | Plasma (GPx) [111]					

Findings Map 2: A summary of dependent variables associated with common medications for bipolar.

The etiological fingerprints of many medications prescribed for bipolar were also surveyed. Lithium and d-amphetamine were the most investigated drugs—lithium, because it is widely recognized as the gold standard for the treatment of bipolar (mania, in particular); d-amphetamine, because it can induce mania.

These drugs are appealing proxies for euthymia/mania *in vitro*. No drug seemed to simulate mixed states, rapid cycling, or bipolar (as opposed to unipolar) depressive episodes.

All investigated drugs (except valproate) act on cytokines—especially IL-6, IL-1β, TNF-α, and IL-2. However, each has a unique profile. Lamotrigine is more effective against bipolar depression than mania and is exceptionally effective against rapid cycling [49]. Therefore, building a unique etiological fingerprint for each drug could illuminate subtle differences between mood disorders. Valproate, the drug with the least measured anti-inflammatory action, was the only drug found to independently increase fracture risk.

Lithium demonstrated anti-inflammatory properties, even in cerebral and cardiac ischemia [50]. It partially diminished the etiological fingerprint of bipolar—and lithium response correlated with an innate ability to 'fill in the gaps.' For example, one study found lithium increased cardiac IL-6; lithium-responsive rats showed a decreased concentration of IL-6 in the orbitofrontal cortex [51]. These are different tissues, but the larger pattern suggests the potential of a findings map—even when the findings from one study are unilluminating, it is easy to see that lithium responsivity protects against a potential inconsistency in lithium's action. A findings map can identify intermittent problems quickly because they are all recorded in the same place.

Biochemical Findings

Dependent Variables	Exposure Variables										
	Bipolar Disorder	LPS exposure /TLR4 Engagement	PIC Exposure / TLR3 Engagement)	OH-dDHL	ATP exposure	RANKL Exposure	Antimycin A (Complex III Inhibitor)	Sodium Butyrate (histone deacetylase inhibitor)	Calcium Exposure	17β- estradiol	Ouabain Exposure (Na/K-ATPase Inhibitor)
IL-6	(After accounting for processing time) [47]	glucose (BMM) [63]. || Rice Bran Oil | Palm Oil(RAW 264.7) 84 || || Rice Bran Oil | Palm Oil (C57BL/6 male mice) 84. || Açai Extract(Microglia) [70] || TCAIM Expression [103] || Aspirin | Lithium | Lithium + Aspirin [97]	10ng/ml and 10 µg/ml | glucose (BMM) [63]	(BMM) [105]	CD39| 0.3 mM ATP (Bone Marrow-Derived Mast Cells) [82]. || CD39| 0.3 mM ATPγS (Bone Marrow-Derived Mast Cells) [82]		Trolox (prevents) |Cyclosporin A |BAPTA/AM (Osteoblastic MC3T3-E1 Cells) [64]	Striatum; Frontal Cortex [100]			Prefrontal Cortices | Plasma (ICV, Sprague- Dawley rats) [50]
	sIL-6r | Duration [48]	(N9 cells) [76]	Plasma | Hippocampus (C57BL6/N) [74]								

ROS (Complex I or III)	[100] || [70]	Lithium (NO2, N9 cells) [76] Lithium+ BzATP (selective to P2X7R, NO2, N9 cells) [76] || Rice Bran Oil | Palm Oil (iNOS, RAW 264.7, Spinal Cord) 84 || METP nanoparticles | DS16570511 (iNOS, Male C57BL/6, KOA model) [85] | Lithium (iNOS) [65] || MMP | Complex II Activity | SOD2 | mtGPx4 [63]		NAC (BMM) [105]	(NO2, N9 cells) [76]	ECSIT | 17β-estradiol (BMMs, C57BL/6 mice) [55]			Grape Seed/Skin Extract | Heart (Wistar Rats) [90] || (HT-22) [62]	(BMMs, C57BL/6 mice) [55]	
TNF-α	(After accounting for processing time) [47]	METP NPs | DS16570511 [85] || glucose | Complex I activity (w/o glucose) | Complex III activity (w/o glucose) | Complex IV Activity (w/o glucose) | mtROS | (BMM) [63] || IL-33 (Bone Marrow-Derived Mast Cells) [82]. || Rice Bran Oil | Palm Oil (RAW 264.7) 84. || Rice Bran Oil | Palm Oil (C57BL/6 male mice) 84. || Açai Extract (Microglia) [70] ||| Lithium+ Aspirin [97] || Lithium[86]	10ng/ml and 10 µg/ml | Complex I activity | Complex III activity | Complex IV Activity | glucose | mtROS (BMM) [63].	(BMM) [105]			Trolox (prevents) |Cyclosporin A |BAPTA/AM (Osteoblastic MC3T3-E1 Cells) [64]	Striatum; Frontal Cortex [100]			Prefrontal Cortices | Plasma (ICV, Sprague- Dawley rats) [50]
	(sTNF-R1) Duration | Psychotic Features [48]	TCAIM Expression [103]	Plasma | Hippocampus (C57BL6/N) [74] || TCAIM Expression [103]								
IL-1β	(After accounting for processing time) [47]	mat -IL-1β; intracellular; extracellular | IL-33 | ATP Exposure (Bone Marrow-Derived Mast Cells) [82]	10ng/ml and 10 µg/ml(BMM) [63] || Plasma (C57BL6/N) [74]	(BMM) [105]	mat -IL-1β; extracellular | CD39 Expression(Bone Marrow-Derived Mast Cells) [82]						Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
	[48]	pro-IL-1β; intracellular | IL-33 (Bone Marrow-Derived Mast Cells) [82] || Açai Extract (Microglia) [70]	[82] || Hippocampus (Maternal Exposure, C57BL6/N) || [74] ||[77] || [50]		pro and mat-IL-1β; intracellular (Bone Marrow-Derived Mast Cells) [82]						

Misc. Monocyte-Activating Factors	IFN-γ (After accounting for processing time) [47] MCP-1 [48]	CXCL10 | glucose | mtROS | cytROS (BMM) [63] ||| MCP-1 | IFN-γ | Rice Bran Oil | Palm Oil (RAW 264.7) 84 || MCP-1 (N9 cells) [76]	CXCL10| 10ng/ml and 10 µg/ml | glucose | mtROS (BMM) [63] || IFN-γ [50]	MCP-1 (BMM) [105]								IFN-γ | ICV ASA | Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
Cytoplasmic Calcium	[112] || [104]	METP nanoparticles (Male C57BL/6, KOA model) [85] || TCAIM | IL-2 (BMDC) [103]		(BMM) [105]			Trolox | Cyclosporin A |Dantrolene (Osteoblastic MC3T3-E1 Cells) [64]					
Misc Apoptosis-Associated Factors	P2X7R Expression [76]	Açai Extract | Casp 3 | Casp8 (Microglia) [70]		Casp 8 | Casp 9 (BMM) [105]		Casp 3 | Casp9 (BMMs, C57BL/6 mice) [55]					
Complex I expression/activity	[62] || [110] || [70]	High Glucose (NDUFB8, BMM) [63] Açai Extract (Microglia) [70] Low Glucose (NDUFB8, BMM) [63]	High Glucose (NDUFB8, BMM) [63] Low Glucose (NDUFB8, BMM) [63]			ECSIT Expression | 17β-estradiol (ECSIT is req'd) (BMMs, C57BL/6 mice) [55]					
ER Calcium	[112] || [104]	METP nanoparticles (Male C57BL/6, KOA model) [85]		(BMM) [105]			(Osteoblastic MC3T3-E1 Cells) [64]					
Body Mass	[47]		(Male Wistar Rats, Maternal Exposure) [77]							Risperidone |(female C56BL/6J, w/ovar-ectomies) [93]	
Misc. Non-Specific Immune Activators	CRP [48]	MHCII | Rice Bran Oil (RAW 264.7, Spinal Cord) 84									CRP | Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
IL-4	Suicidality [51]		Plasma | Hippocampus (C57BL6/N) [74]					Striatum; Frontal Cortex [100]			
Mitochondrial Calcium	[112] || [104]						(Osteoblastic MC3T3-E1 Cells) [64]				
BDNF (Neuron survival, plasticity, and growth)	[100]										Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]

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Presynaptic Markers	[80]		Adolescent Stress |Frontal Cortex (Synaptophysin, Adult Male Wistar Rats, Maternal Exposure) [77] || CA | Dentate Gyrus (Synaptophysin, C57BL6/N) [74] Bassoon, C57BL6/N								
Cortisol/Corticosterone Levels	(Early Childhood Trauma) [77]		Adolescent Stress (Adult Male Wistar Rats, Maternal Exposure) [77] Adolescent Stress(Adolescent Male Wistar Rats, Maternal Exposure) [77]								
Purinergic Cell signaling	P2X7R Expression [76]				CD39 (Bone Marrow-Derived Mast Cells) [82]						
Histone Deacetylase Activity (Intracellular Signaling, Cell Cycle Promotion)	(HDAC) [100]							Striatum; Frontal Cortex (HDAC) [100]			
Fracture Risk	History of Hospitalization | Lamotrigine | Carbamazepine | Valproic Acid | Antipsychotic Dosage [Fracture Risk, 98] || Anticonvulsants [Fracture Risk, 91] || Lithium | Antipsychotics | Valproate | Lamotrigine(Osteo porosis) [81]									(Bone Mass)[55]	
Social Gregariousness	Self-explanatory		Adolescent Stress (Adolescent Male Wistar Rats, Maternal Exposure) [77]								

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Locomotor Activity	Self-explanatory		w/Adolescent Stress (Y Maze and OFT, Adult Male Wistar Rats, Repeated Social Defeat) [77]								
Post-Synaptic Markers	[74]		Dorsal CA and Dentate Gyrus (PSD95, C57BL6/N) [74]								
IL-10 (Anti-inflammatory, inhibits MHC)	(After accounting for processing time) [47]	Rice Bran Oil | Palm Oil (RAW 264.7) 84 || Rice Bran Oil | Palm Oil (C57BL/6 male mice) 84 || (N9 cells) [76] Acai [70]						Striatum; Frontal Cortex [100]			Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
Autophagy		Low glucose | High glucose (p-62, BMM) [63]. || (p-62, KOA mice) [85] || TCAIM (p-62, BMDC) [103] || Açai Extract (p-62, NO, Microglia) [70]	Low glucose | High glucose (p-62, BMM) [63]				BAPTA/AM (an intracellular Ca2+ chelator) |Cyclosporin A(mtCalcium release inhibitor) | Dantrolene (Ryanodin Receptor Channel Inhibitor) (p-62, Osteoblastic MC3T3-E1 Cells) [64]		(HT-22) [62]		
Misc. Antiviral Immune Factors		IFN-α | glucose | mtROS (BMM) [63] IFN-β | mtROS (BMM) [63]	IFN-α | 10ng/ml and 10 µg/ml | glucose |mtROS (BMM) [63] || IFN-β | 10ng/ml and 10 µg/ml | mtROS (BMM) [63] || IFN-β [50]								TLR3 Expression | ICV ASA | Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
Casp1 Expression/ Activity		Açai Extract (Microglia) [70]									
TLR4 Expression/Activity (Inflammatory, Bacterial)		TCAIM | IL-2 (BMDC) [103] || Lithium(Expression, Primary Astrocytes) [86]									ICV ASA | Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]

T-Cell Priming		CD86 | Rice Bran Oil | Palm Oil | (RAW 264.7, Spinal Cord) 84 || CD86 | METP Nanoparticles [85] ||| CD80 | Rice Bran Oil | Palm Oil (RAW 264.7, Spinal Cord) 84 || CD80 | METP Nanoparticles [85] || TCAIM | IL-2 | IL-12p70 | Rice Bran Oil | Palm Oil (RAW 264.7) 84(BMDC) [103] ||| CXCL10 | glucose | mtROS | cytROS (BMM) [63] IL-17 (BMDC) [103]	CXCL10| 10ng/ml and 10 µg/ml | glucose | mtROS (BMM) [63]									
T-Cell Abundance		TCAIM | IL-2 (BMM) [103].									
Glial Activation		Lithium (GFAP, Primary Astrocytes) [86] || Rice Bran Oil | Palm Oil (COX-2 Transcription, RAW 264.7, Spinal Cord) 84	(Short Term, Male Wistar Rats, Maternal Exposure) [77] Adolescent Stress (Long Term, Adolescent Male Wistar Rats, Maternal Exposure) [77]		w/ P2X7R | Lithium (M1 switch, microglial N9 cells) [76]						PGE-2 | Prefrontal Cortices | Plasma (ICV, Sprague-Dawley rats) [50]
Maximal Respiration, Spare Respiratory Capacity, and Basal Respiration Rate		Maximal Respiration | Spare Respiratory Capacity | Basal Respiration Rate | (BMM) [63] || Rice Bran Oil | Palm Oil (RAW 264.7) 84 || DS16570511 | METP Nanoparticles (BMDM, KOA mice) [85]	Spare Respiratory Capacity | 10ng/ml and 10 µg/ml (BMM) [63]			Maximal Respiration | Spare Respiratory Capacity | ECSIT Expression | 17β-estradiol (ECSIT is req'd) (BMMs, C57BL/6 mice) [55]			Maximal Respiration | (HT-22) [62]		
Oxygen Consumption Rate (Mitochondrial ATP Production)		(BMM, mitoOCR/glycoPER) [63] || Rice Bran Oil |Palm Oil (RAW 264.7) 84 || TNF-α [69] (BMM) [85]	10ng/ml and 10 µg/ml (BMM) [63]			ECSIT Expression | 17β-estradiol (ECSIT is req'd) (BMMs, C57BL/6 mice) [55]			(HT-22) [62]	ECSIT Expression (ECSIT is req'd for E2's inhibition) (BMMs, C57BL/6 mice) [55]	
ECAR (Cytosolic ATP Production)		(BMM, %Proton Efflux Rate from glycolysis) [63] || DS16570511 | METP Nanoparticles (BMM) [85]	10ng/ml and 10 µg/ml (BMM, %Proton Efflux Rate from glycolysis) [63]			(BMMs, C57BL/6 mice) [55]				(BMMs, C57BL/6 mice) [55]	

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Total ATP Levels						(BMMs, C57BL/6 mice) [55]					
Proton Leak						(BMMs, C57BL/6 mice) [55]					
Catalase/ GSH/ GPx/ SOD Expression		High glucose | Low Glucose [63]	High Glucose (SOD2, mtGPx4) [63]		(Wistar Rats) [65]						
Mitochondrial Number											
Apoptosis		Açai Extract (dsDNA release, Microglia) [70]		(BMM) [105]	Lithium (microglial N9 cells) [76]	ECSIT (BMMs, C57BL/6 mice) [55]		[100]			
Cell Cycle Speed		Açai Extract (Microglia) [70]									
Complex II expression		High Glucose | Low Glucose (SDHB, BMM) [63]	High Glucose | Low Glucose (SDHB, BMM) [63]								
Complex III expression/activity		Low glucose | High glucose (UQCRC2, BMM) [63]	Low glucose | High glucose (UQCRC2, BMM) [63]				(Osteoblastic MC3T3-E1 Cells) [64]				
Complex IV expression/activity		Low glucose | High glucose (COX4, BMM) [63]	Low glucose | High glucose (COX4, BMM) [63]						(cytosolic, CACNA1C is req'd) [62]		
Mitochondrial Membrane Potential		Low glucose | High glucose (BMM) [63]	Low glucose | High glucose (BMM) [63]	(BMM) [105]			[64]				
ECSIT-TRAF6 interaction						17β-estradiol (BMMs, C57BL/6 mice) [55]					
Dentate Gyrus, Pyramidal Neurons (CA)			Dorsal CA (C57BL6/N) [74]								

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Osteoclast Differentiation										ECSIT Expression (ECSIT is req'd for E2's inhibition) (BMMs, C57BL/6 mice) [55]	
RANKL Release						Self-Explanatory	Trolox (ROS scavenger) |BAPTA/AM(Osteoblastic MC3T3-E1 Cells) [64]				
Hypothermia		Lithium | Lithium+ ASA (Sprague Dawley males) [97]									

Findings Map 3: A summary of biochemical findings in bipolar.

In vitro studies highlighted LPS and PIC as the most common mechanisms of inducing cellular inflammation. Both produced etiological fingerprints similar to bipolar, but their intracellular effects differed. PIC goes through the TLR3 pathway, while LPS goes through the TLR4 pathway. The latter has been implicated in bipolar, whereas the former is seldom mentioned.

IL-6, ROS, TNF-α, and IL-1β formed the etiological fingerprint for LPS activation, which could all be normalized by inhibitors of the mitochondrial calcium uniporter (MCU) and antioxidants such as rice bran oil, açai extract, and palm oil. Some preliminary studies have even suggested that antioxidants such as CoQ10 aid the recovery of bipolar depression [52, confirming that this is not just an invitro phenomenon.

PIC elicited IL-6, TNF-α, IL-1β, and miscellaneous monocyte-activating factors. Maternal PIC exposure during pregnancy altered the glial density in bipolar-associated areas, such as the pyramidal neurons of the dorsal dentate gyrus, which interacted with adolescent social stress to create phenotypes such as gregariousness and hypermobility—both key symptoms of mania/hypomania.

Analogous Conditions

Dependent Variables	Exposure Variables					
	Bipolar Disorder	Hypoxia (10)	T. Gondii Infection (11)	Sepsis (5)	Diabetes (16)	Age (6)
TNF-α	(After accounting for processing time) [47]	Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]	Temporary (C57BL/6 (H-2b)) [67]	Lithium (Wistar Rats) [65]		(Comparing Adolescent Mice to Healthy Adults, C57BL6/N) [74]

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	[48]					(C57BL/6J, plasma) [69]
IL-1β	(After accounting for processing time) [47]	Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]		Lithium (Wistar Rats) [65]		(Comparing Adolescent Mice to Healthy Adults, C57BL6/N) [74]
	[48]					[69]
ROS (Complex I or III)	[100] | | [70]	(iNOS) [108]		Low glucose | High glucose (BMM) [63]. | | Lithium (Wistar Rats) [65]	Adiponectin (2 µg/ml) | AICAR (Lipid Peroxidation, Osteoblasts, C57BL/6 db/db)[79]	
Cell Injury	Oxidative Damage to DNA [110]	Lactic Acid Dehydrogenase | Mesenchymal stem cells' cultured media | Hypoxic pre-conditioning (Sprague–Dawley) [108]			p-AMPK Adiponectin (2 µg/ml) | AICAR (Osteoblasts, C57BL/6 db/db)[79]	
					Oxidative Damage to DNA | Adiponectin (2 µg/ml) | Compound C (Osteoblasts, C57BL/6 db/db)[79]	
IL-6	(After accounting for processing time) [47]	Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]	Temporary (C57BL/6 (H-2b)) [67]	Lithium (Wistar Rats) [65]		
	[48]					
IL-10 (Anti-inflammatory, inhibits MHC)	(After accounting for processing time) [47]	Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]	Temporary (C57BL/6 (H-2b)) [67]			
Misc. Monocyte-Activating Factors	IFN-γ (After accounting for processing time) [47]		IFN-γ, Temporary | MCP-1 (C57BL/6 (H-2b)) [67]			
	MCP-1 [48]					
IL-2 (T cells, anti Th17)	(After accounting for processing time) [47]					

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	[48]					
Misc. Neutrophil-Activating Factors	IL-8 [47]					
Body Mass	[47]		(C57BL/6 (H-2b)) [67]			
Depressive Behavior/Depression	Self-explanatory		(C57BL/6 (H-2b)) [67]			
Anxious Behavior/Anxiety	Self-explanatory		(C57BL/6 (H-2b)) [67]			
Locomotor Activity	Self-explanatory		(C57BL/6 (H-2b), TST) [67]			
T-Cell Priming		Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]	IL-12, Temporary (C57BL/6 (H-2b)) [67]			
Oxygen Consumption Rate (Mitochondrial ATP Production)					Adiponectin (2 μg/ml) (Osteoblasts, C57BL/6 db/db)[79]	(Tfamfl/fl mice) [71]
Catalase/ GSH/ GPx/ SOD Expression				Lithium (GSH, SOD, Wistar Rats) [65]	Adiponectin (2 μg/ml) (Osteoblasts, C57BL/6 db/db) [79]	
Mitochondrial Number					Adiponectin (2 μg/ml) (Osteoblasts, C57BL/6 db/db)[79]	TNF-α (C57BL/6J, plasma) [69]
Casp1 Expression/Activity					Adiponectin (2 μg/ml) (Osteoblasts, C57BL/6 db/db)[79]	
Blood Brain Barrier Integrity			(C57BL/6 (H-2b)) [67]			
Maximal Respiration, Spare Respiratory Capacity, and Basal Respiration Rate						Maximal Respiration | (Tfamfl/fl mice) [71]

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ECAR (Cytosolic ATP Production)						[69]
Autophagy					Adiponectin (2 μg/ml) | AICAR (p-62, Osteoblasts, C57BL/6 db/db)[79]	
Mitochondrial Fragmentation/Fission					Adiponectin (2 μg/ml) | AICAR (Osteoblasts, C57BL/6 db/db)[79]	
Apoptosis					Adiponectin (2 μg/ml) | AICAR (p-AMPK) (Osteoblasts, C57BL/6 db/db)[79]	
Cell Signaling Associated Compounds		MMP-2 | Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]				
Angiogenesis Associated Compounds		MMP-2 | Mesenchymal stem cells' cultured media (Sprague–Dawley) [108]				
Mitochondrial Membrane Potential					Adiponectin (2 μg/ml) (Osteoblasts, C57BL/6 db/db)[79]	
Brain Edema			(C57BL/6 (H-2b)) [67]			
Cytoskeleton Organization					Adiponectin (2 μg/ml) | AICAR (p-AMPK) (Osteoblasts, C57BL/6 db/db)[79]	
Cell Area					Adiponectin (2 μg/ml) | AICAR (p-AMPK) (Osteoblasts, C57BL/6 db/db)[79]	

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Cell Density					Adiponectin (2 µg/ml) | AICAR (p-AMPK) (Osteoblasts, C57BL/6 db/db)[79]	
Bone Growth (including Calcium Deposiiton, Collagen Secretion, and ECM regulation)					Adiponectin (2 µg/ml) | AICAR (p-AMPK) | Calcium Deposition | Collagen Secretion | (Osteoblasts, C57BL/6 db/db)[79]	
Cell Proliferation					Adiponectin (2 µg/ml) | AICAR (p-AMPK) (Osteoblasts, C57BL/6 db/db)[79]	
Body Strength: Body Mass			(C57BL/6 (H-2b)) [67]			
Lifespan			(C57BL/6 (H-2b)) [67]			

Findings Map 4: A summary of dependent variables associated with bipolar.

Certain comorbidities appeared in the course of the review. Diabetes looks dissimilar to bipolar; however, the study did not focus on the cytokine profile associated with the disease. It should be noted that Diabetes Mellitus Type II is associated with inflammation [36]. Sepsis was included due to the comorbidity of chronic infections, age was included because of the correlation with accelerated aging [53], and hypoxia was included as hypoxic injury may play a role in mood disorders [54].

One point of interest was that lithium was able to reverse the inflammation brought on by sepsis. This study was done on osteoblasts of normal C57BL/6 db/db mice. Even without a bipolar model, that data point suggests lithium's anti-inflammatory mechanism is a direct effect of the drug and not a by-product of a purely psychological process.

Genetic and Transcriptive Anomalies

Dependent Variables	Exposure Variables													
	Bipolar Disorder	Functional Disc1-Q31L	TFAM Expression	CACNA1C (CamKIIα) Expression	Extracellular Acidity	Mitochondrial Calcium Import (MCU) Expression/ Activity	ECSIT	BI-1 Expression	rs7585543 expression (PDE11A)	Cytokine Withdrawl	PER 3 Functionality	Osteoclastogenesis	myo-Inositol	Mitochondrial Fission
ROS (Complex I or III)	[100] | | [70]			(HT-22) [62]		Cacna1c req'd (HT-22) [62]	(BMMs, C57BL/6 mice) [55]			(Cardiomyocytes injected with MIF BM-MSC-exo, post Hypoxia/ serum deprivation) [88]		(BMMs, C57BL/6 mice) [55]		
Locomotor Activity	Self explanatory		(Tfamfl/fl Cd4Cre mice) [71]	w/o Dars2 (Custom Mice) [94]					(C57BL/6J,)[96]		(C57Bl/6J vs. Per3 Knockout) [102]		Lithium (Ensures embryonic survival, correct mandibular formation) [95]	
TNF-α	(After accounting for processing time) [47] [48]	Hippocampus (Disc1-Q31L –/– vs C57BL/6N) [73]	(Tfamfl/fl mice) [71]		B1-1 required [83]	mt[Calcium] | METP nanoparticles | Cacna1c Polymorphisms (Male C57BL/6, KOA model) [85]								
IL-6	(After accounting for processing time) [47] [48]	Frontal Cortex (Disc1-Q31L –/– vs C57BL/6N) [73]	(Tfamfl/fl Cd4Cre mice) [71]		B1-1 required [83]				(C57BL/6J,) [96]					
Mitochondrial Calcium	[112] | | [104]			Required for import (HT-22) [62]	(pH=6.8, MG63 Osteoblasts) [83]	METP Nanoparticles | Cacna1c Polymorphisms (BMM, Male C57BL/6, KOA model) [85] | | (HT-22) [62] | | L(pH=6.8, MG63 Osteoblasts) [83]		(pH=6.8, MG63 Osteoblasts) [83]						
Misc. Monocyte-Activating Factors	IFN-γ (After accounting for processing time) [47]	IFN-γ| Hippocampus (Disc1-Q31L–/– vs C57BL/6N) [73]	(Tfamfl/fl Cd4Cre mice) [71]	w/o Dars2 (CD68, cortex, Custom Mice) [94]										

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	MCP-1 [48]	IFN-γ | Striatum | Frontal Cortex (Disc1-Q31L−/− vs C57BL/6N) [73]												
IL-1β	(After accounting for processing time) [47] [48]	Frontal Cortex | Hippocampus | Hypthalamus | Striatum (Disc1-Q31L−/− vs C57BL/6N) [73]			B1-1 required [83]	mt[Calcium] | METP nanoparticles | Cacna1c Polymorphisms (Male C57BL/6, KOA model) [85]									
Complex I expression/activity	[62] || [110] || [70]		(Tfamfl/fl Cd4Cre mice) [71]	w/o Dars2 (Cortex, Custom Mice) [94]			(BMMs, C57BL/6 mice) [55]							
ER Calcium	[112] || [104]				(pH=6.8, MG63 Osteoblasts) [83]	METP Nanoparticles | Cacna1c Polymorphisms (BMM, Male C57BL/6, KOA model) [85]									
Misc. Non-Specific Immune Activators	CRP [48]			MHCII (w/o Dars2) (CD68, cortex, Custom Mice) [94]										
Body Mass	[47]		(Tfamfl/fl Cd4Cre mice) [71]											
mtDNA Copy Number	[110]		(Tfamfl/fl Cd4Cre mice) [71]											
Cytoplasmic Calcium	[112] || [104]							(pH=6.4, MG63 Osteoblasts) [83]						
Misc Apoptosis-Ascociated Factors	P2X7R Expression [76]				Casp3 | Casp9 | Cytoplasmic Cytochrome C (pH=6.8, Osteoblasts) [83]									
IL-2 (T cells, anti Th17)	(After accounting for processing time) [47] [48]	Hippocampus | Hypothalamus | Striatum (Disc1-Q31L−/− vs C57BL/6N) [73]												
IL-10 (Anti-inflammatory, inhibits MHC)	(After accounting for processing time) [47]	Frontal Cortex (Disc1-Q31L−/− vs C57BL/6N) [73]												
Misc. Neutrophil-Activating Factors	IL-8 [47]	IL-17 | Hippocampus | Hypothalamus | Frontal Cortex (Disc1-Q31L−/− vs C57BL/6N) [73]												
IL-4	Suicidality [51]	Frontal Cortex (Disc1-Q31L−/− vs C57BL/6N) [73]												

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Purinergic Cell signaling	P2X7R Expression [76]													
B-Cell Abundance		CD19+ (Disc1-Q31L−/− vs C57BL/6N) [73]												
T-Cell Priming		IL-17 | Hippocampus | Hypothalamus | Frontal Cortex (Disc1-Q31L−/− vs C57BL/6N) [73]		w/o Dars2 (CST7, cortex, Custom Mice) [94]										
T-Cell Abundance		CD3+ | CD3+CD4+ | CD3+CD4+CD25+ (Disc1-Q31L−/− vs C57BL/6N) [73] CD3+CD8+ (Disc1-Q31L−/− vs C57BL/6N) [73]	CD4+, CD8+ (Fornix, Tfamfl/fl Cd4Cre mice) [71]											
Glial Activation				w/o Dars2 (CD68, CTSC, CST7, IBA-1, Cortex, Custom Mice) [94]										
Maximal Respiration, Spare Respiratory Capacity, and Basal Respiration Rate			Maximal Respiration | (Tfamfl/fl Cd4Cre mice) [71]	Maximal Respiration | Basal Respiration Rate (HT-22) [62]		Maximal Respiration | Spare Respiratory Capacity | DS16570511 | METP Nanoparticles | Cacna1c Polymorphisms (BMM, Male C57BL/6, KOA model) [85]								
Oxygen Consumption Rate (Mitochondrial ATP Production)			(Tfamfl/fl Cd4Cre mice) [71]				(BMMs, C57BL/6 mice) [55]							
ECAR (Cytosolic ATP Production)			(Tfamfl/fl Cd4Cre mice) [71]	(HT-22) [62]		DS16570511 | METP Nanoparticles | Cacna1c Polymorphisms (BMM, Male C57BL/6, KOA model) [85]	17β-estradiol (BMMs, C57BL/6 mice) [55]							
Total ATP Levels				(HT-22) [62]										
Autophagy				p-62 | LC3B-11 (HT-22) [62]			(p-62, BMMs, C57BL/6 mice) [55]							(p-62, Cardiomyocytes injected with MIF BM-MSC-exo, post Hypoxia/serum deprivation) [88]
Mitochondrial Fragmentation/ Fission				(HT-22) [62]										(Cardiomyocytes injected with MIF BM-MSC-exo, post Hypoxia/serum deprivation) [88]
Mitochondrial Number				w/o Dars2 Corpus Callosum (Custom Mice) [94]										

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Apoptosis				(HT-22) [62]	Apoptosis B1-1 Req'd | BAX B1-1 Req'd | (pH=6.8, Osteoblasts) [83]					BCL-XL | HAX-1(murine bone marrow) [99]				
Mitochondrial Membrane Potential				Hyperpolarization (HT-22) [62]										
Cell Area				w/o Dars2 | IBA+ microglia | Corpus Callosum Myelin Sheaths | Corpus Callosum Axon Thickness (Cortex, Custom Mice) [94]										
Cell Density				w/o Dars2 | IBA+ (Microglia, Cortex, Custom Mice) [94]										
Cerebellar Area				w/o Dars2 (Custom Mice) [94]										
Total Brain Area, Cortical Thickness, and Corpus Callosum				w/o Dars2 (Custom Mice) [94]										
Dentate Gyrus, Pyramidal Neurons (CA)				w/o Dars2 | CA1 (Custom Mice) [94]										
Hippocampal Volume				w/o Dars2 (Custom Mice) [94]										
Heart Function			(Tfamfl/fl Cd4Cre mice) [71]											
Heart Remodeling			(Tfamfl/fl Cd4Cre mice) [71]											
Lithium Responsivity									Dorsal CA1 (C57BL/6J, PDE11A4 is the homologous mutation) [96]					
Bone Growth (including Calcium Deposiiton, Collagen Secretion, and ECM regulation)													(Ensures embryonic survival, correct mandibular formation) [95]	
Cell Proliferation				(Hippocampal, HT-22) [62]										

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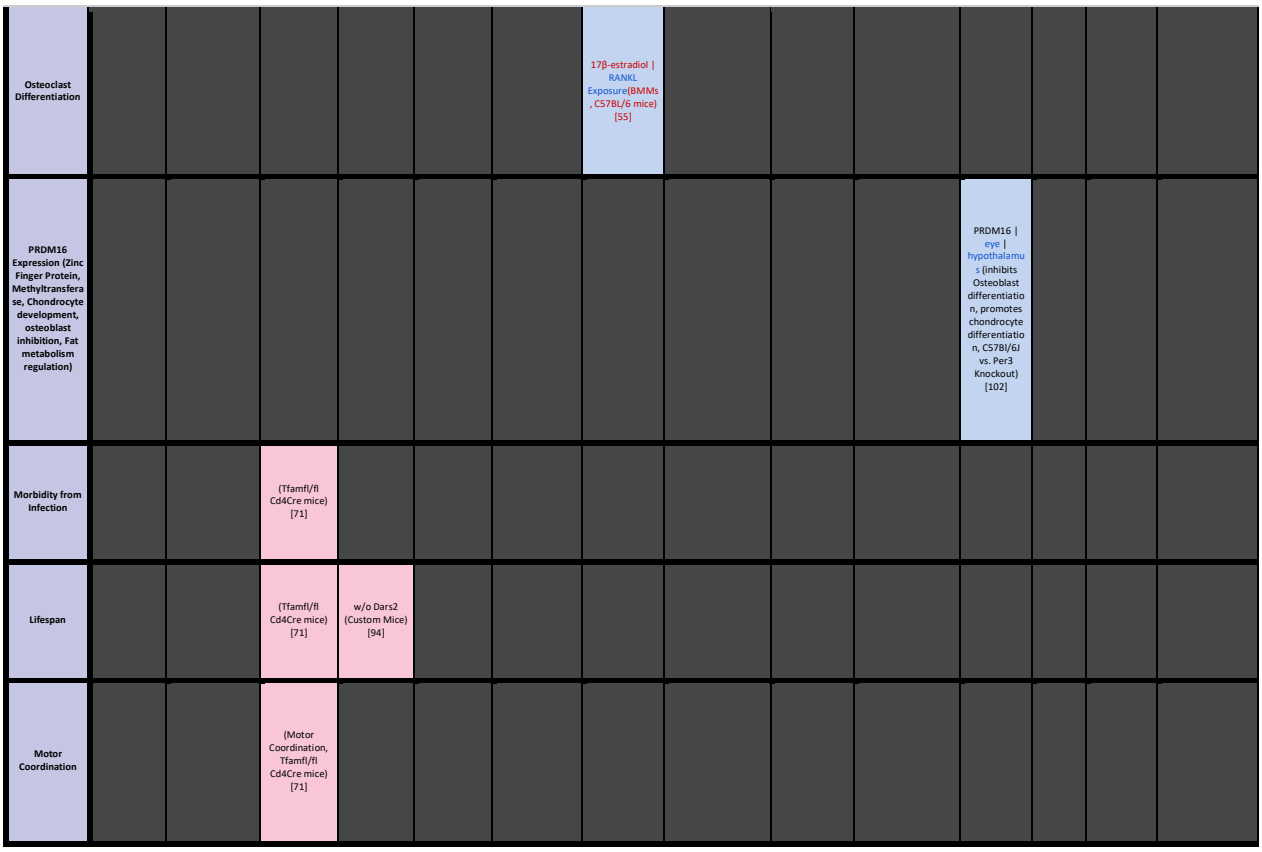

Findings Map 5: A summary of bipolar-associated genetic and transcription anomalies.

Genetic and transcriptive studies revealed important metabolic discrepancies—the most modified variables were ROS, locomotors activity, TNF-α, IL-6, and mitochondrial calcium. Disc1-Q31L interacted most with the elements of bipolar etiological fingerprint, followed closely by alterations in TFAM and CACNA1C. The MCU and CACNA1C showed the closest match for the etiological fingerprint of bipolar.

TFAM expression also affected many of bipolar important variables, but it had mixed effects. Sometimes, its cytokines would match bipolar' fingerprint; other times, it would deviate, but TFAM always affected bipolar' important elements. Differences in the expression and activity of MCU also created fingerprints similar to bipolar—MCU has a synergistic effect on the amount of ROS with CACNA1C. MCU and TFAM represent strong, under-researched links from mitochondria to neuropsychiatric disease.

Databases

Database Criteria	MITOMAP	MitBASE	MSeqDR	GnomAD	PGC	GWAS Integrator
Type of data?	Genetic data	Genetic data	Genetic data	Genetic data	Genetic data	Genetic data
Large sample size?	No	No	No	Yes (up to 140,000 exomes and 15,000 whole genomes)	Yes (tens of thousands of individuals and controls)	Depends on trait or disease being studied
Genetic data (mtDNA and/or nDNA profiles?)	mtDNA, no focus on nDNA	mtDNA, no focus on nDNA	mtDNA, no focus on nDNA	nDNA, no focus on mtDNA	nDNA, no mtDNA	nDNA, no focus on mtDNA
Family History of Illness?	No family history of illness beyond any DIRECTLY related to mtDiseases	No	No family history of illness beyond any DIRECTLY related to mtDiseases	No, focuses on whole populations	Yes, collected for studies; however, detail varies among cases and studies	Yes, related to trait or disease being studied
Comorbidities?	Only those directly related to mtDiseases	Only those directly related to mtDiseases	Only those directly related to mtDiseases	No	Yes, but only for some studies	No
Number of Adverse Childhood Events?	No	No	No	No	Yes, but only for some studies	No

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Longitudinal metabolic metrics labeled with mental state?	No	No	No	No	No	No
Open access?	Yes	Not accessible online	Basic features are available, some datasets have different access policies	Yes	Yes, however, some datasets are not available	Yes, however, specific datasets are not accessible
Forest plot generator? Statistical tools?	No	No	No	No forest plots - focuses on variant frequency	Offers extensive statistical tools but no forest plots	Offers extensive statistical tools but no forest plots

Table 1: A summary of popular databases and their utility.

Several open-access databases provided excellent options for data mining. PGC approached the stringent qualifications, but one would have to combine resources to investigate the role of mitochondria. PGC meets the nDNA requirement (which must be there to understand the role of molecules such as TFAM and the MCU) but omits mtDNA. MITOMAP is the leading open-access mtDNA database surveyed but still suffers from a small sample size. Depending on the study, utilizing multiple mtDNA databases may be advisable. None have the sort of longitudinal metabolic data required to capture the etiology of psychiatric disorders. None have automatic tools for generating forest plots. Although these open-access tools are extensive, more work is needed to investigate mitochondria's implications in neuropsychiatric disorders.

Discussion

The literature on bipolar is mixed, and it is not without its problems; however, enough agreement exists between *in vitro*, *in vivo*, and epidemiological studies to suggest that the link is not purely from sample processing time. Each study suffers from disparate confounding variables, but they all converge on a set of culprits: elevations in TNF-α., IL-6, IL-1β, and ROS; expression differences in CACNA1C (CamKIIα), TFAM, and Disc1-Q31L; and comorbidities of diabetes and insomnia. Including the action of common medications particularly strengthens this analysis—serving almost as a negative control.

Each medication has a different etiological fingerprint. Valproate interacts less with cytokines than lamotrigine, lithium, or topiramate; however, it is the only drug associated with an independent increase in fracture risk. Given TNF-α's role in bone resorption (through RANKL), RANKL's action on Complex I through ESCIT [55], Complex I's association with bipolar (Findings Map 1), and risperidone's long-term metabolism shift from plasma to bone marrow (Findings Map 2): bone physiology is heavily implicated in bipolar. Other affected processes included circadian rhythms, autophagy, apoptosis, angiogenesis, collagen deposition, osteoblast/clast differentiation, calcium regulation, cell signaling, ROS, bacterial immune response, T cell activation, and glial activation.

Epidemiological Studies

One silent problem in the psychiatric epidemiological world is diagnosis. The cultural reluctance of patients to come forward, symptomatic overlap with other conditions, and the presence of comorbidities make it difficult to distinguish bipolar from conditions like borderline personality disorder. Some studies sidestep this by having multiple psychiatrists confirm each diagnosis; however, this is not an option in many situations.

One easy variable to check is the sex of the probands. Bipolar is a sexually dimorphic condition on many levels—including the regulation of cytokines [56], whether mutations such as rs1006737 are risk factors [57], and the risk of rapid cycling [58]. The risk contributed by rs1006737 is particularly illustrating: in women, it is protective; in men, it is a risk factor. Had that study neglected to split its group by sex, they would likely have found no significant change. Many studies that found no significance in genetic or cytokine data did not split based on sex.

Finally, a large number of studies initially surveyed were inadequately controlled. The control group should exceed the test group, and it is ideal to use multiple controls if possible. Many studies that met the sample size requirement had disproportionately small control groups and thus were excluded.

Mouse Studies

The statistical problems found in epidemiological studies extend to mouse studies. Perhaps because most mouse studies represent a proof of concept, statistical rigor is lacking. Some studies were excluded because they neglected to include the strain and age of their rodents. Other excluded studies were as small as three mice per group, yet they tried to suggest an effect on an entirely different species. While it is essential to minimize waste of life and resources, there is a lack of standard statistical practices [59]—or, if they do follow statistical best practices, they were not reported in the methods sections. While consulting a statistician during the study design would be ideal, [59] provides excellent, open-access statistical resources for those interested in animal studies.

In vitro Studies

In vitro studies have their problems as well. iPSC studies fail to outrun statistical problems. Each cell line is derived from one individual, making it, at its root, a sample size of one. Many studies surveyed derived 3-5 iPSC lines (due to the difficulty of the procedure)—which is an incredible model, but it is not generalizable to the general public unless it is 1) an isogenic pair study, 2) a multiple isogenic pair study

or 3) meets the minimum sample size for an epidemiological study [44]. No iPSC studies survived these criteria.

As for the rest of the cell cultures, one detail stood out: the 1% mix of penicillin/streptomycin used to prevent bacterial contamination. Many antibiotics, including penicillin and streptomycin [60], are known to cause mitochondrial dysfunction and ROS overproduction. This puts cybrid/cell culture studies on shaky ground; are the given mutations indicating a native change in ROS production, or are they simply showing a difference in the mitochondrial response to penicillin? This overlooked factor threatens the validity of every *in vitro* study surveyed.

Limitations

The present study also suffers from constraints. The etiological fingerprint of bipolar was composed solely from the studies reviewed. Biomarkers and symptoms are inevitably omitted from the supplementary table. For example, there was no dedicated search for disturbances in the HPA axis, so 'cortisol levels' were undervalued. Future reviews would develop an even more extensive findings map, increasing the value of bipolar's "fingerprint."

Applying the rigorous standards for iPSC studies eliminated human neurons, whereas many approved cell culture lines are derived from rat neurons. This is not ideal. Future studies would provide a better framework for weighing cell lines against each other.

Another note—although not necessarily a limitation—is heterogeneity in the tissues studied. The tissue type affects medication intake and the efficacy of modifying factors (Supplementary Findings Map). Even tiny differences across brain regions significantly affect how the cells secrete, respond to, and are exposed to any given independent variable. This diversity is necessary; however, it is important not to take studies as a blanket elevation, decrease, or non-significance of cytokines.

Improved studies would survey more databases, represent certainty in each study more clearly, and increase the scope of the review to include childhood trauma, neurotransmitter abnormalities, and HPA axis disturbances.

Looking Forward

There is a demand for innovative, well-controlled studies on bipolar in all areas mentioned. One promising area for epidemiological cytokine studies is the development of wearable, real-time cytokine measurement [61]. With the caveat of caution against generalizing cytokine levels between tissues, this is a badly needed, low-maintenance option that completely avoids the sample processing time issue while yielding a time-dependent cytokine fingerprint. Future studies should avoid combining the sample into a coed cohort.

Promising areas for further *in vitro* and *in vivo* research include the role of RANKL, ESCIT, TFAM, and the MCU on bipolar. The advent of CRISPR-based manipulation of mtDNA also allows for more targeted studies on Complex I and III. Above all, a sterile, antibiotic-free growth medium is badly needed.

As we move into the age of precision medicine, more attention must be paid to statistical validity and the intuitive presentation of continuous data. This means providing stellar databases with combined mtDNA and nDNA, simple tools for illustrating relative statistical validity, and basic features such as forest plot generators and force-directed graphs. Many filters should be available, and updating the database with more samples should be possible. Bipolar requires a dizzying scope of data and effort, making it the ideal disorder to target through open-source databases.

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