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Case Report

Impaired mitochondrial function in bipolar disorder and alcohol use disorder: a case study using ^{18}F-BCPP-EF PET imaging of mitochondrial Complex I

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Abstract

Background: With bipolar disorder (BD) having a lifetime prevalence of 4.4% and a significant portion of patients being chronically burdened by symptoms, there has been an increased focus on uncovering new targets for intervention in BD. One area that has shown early promise is the mitochondrial hypothesis. However, at the time of publication no studies have utilized positron emission tomography (PET) imaging to assess mitochondrial function in the setting of BD. **Case Presentation**: Our participant is a 58 year-old male with a past medical history notable for alcohol use disorder and BD (unspecified type) who underwent PET imaging with the mitochondrial complex I PET ligand ^{18}F-BCPP-EF. The resulting images demonstrated significant overlap between areas of dysfunction identified with the ^{18}F-BCPP-EF PET ligand and prior functional magnetic resonance imaging (MRI) techniques in the setting of BD. That overlap was seen in both affective and cognitive circuits, with mitochondrial dysfunction in the fronto-limbic, ventral affective, and dorsal cognitive circuits showing particularly significant differences. **Conclusions**: Despite mounting evidence implicating mitochondria in BD, this study represents the first PET imaging study to investigate this mechanistic connection. There were key limitations in the form of comorbid alcohol use disorder, limited statistical power inherent to a case study, no sex matched controls, and the absence of a comprehensive psychiatric history. However, even with these limitations in mind, the significant overlap between dysfunction previously demonstrated on functional MRI and this imaging provides compelling preliminary evidence that strengthens the mechanistic link between mitochondrial dysfunction and BD.

Keywords: mitochondria; bipolar disorder; PET imaging; fronto-limbic circuit; ventral affective circuit; dorsal cognitive circuit; default mode network; central executive network; salience network; sensorimotor network

Background

Bipolar disorder (BD) has a lifetime prevalence of 4.4% and a significant portion of patients are chronically burdened by symptoms despite standard treatment (Vieta *et al.*, 2016; Merikangas and Lamers, 2012). Although pharmaceutical interventions have saved countless lives, much work remains to uncover improved targets for intervention. In recent years, the mitochondrial hypothesis of BD has been gaining increasing momentum in the scientific community, with mounting evidence supporting the key role of mitochondria in the pathogenesis of BD.

In post-mortem samples of BD patients, downregulation of mitochondrial electron transport chain (ETC) complexes I, IV, and V has been observed (Das *et al.*, 2022; Sun *et al.*, 2006). Furthermore, a study assessing leukocytes obtained from individuals with BD compared to those derived from healthy controls found lower mitochondrial DNA (mtDNA) copy number and higher degrees of oxidative damage in cells derived from individuals with BD (Chang *et al.*, 2014). Another study building on that work showed that mtDNA copy number was lower in cohorts of both manic and depressed individuals with BD when compared to individuals with BD in a euthymic state. They also found a negative correlation between mtDNA copy number and the number of relapses experienced by the participants in a manic state (Wang *et al.*, 2018). The CAMKK2 single nucleotide polymorphism (SNP), which regulates mitochondrial function, has also been associated with BD and correlated with impaired mitochondrial function in several studies (Atakhorrami *et al.*, 2016; Kaiser *et al.*, 2023). Induced pluripotent stem cells (iPSCs) generated from the fibroblasts of individuals clinically diagnosed with type 1 BD while in a manic state were found to have hyperexcitable neurons with increased mitochondrial activity and a corresponding up-regulation of mitochondrial genes; moreover, this hyperexcitability was capable of being reversed via administration of lithium (Mertens *et al.*, 2015). A study linking these findings and clinical symptoms found a significant negative correlation with lymphocyte ETC complex II activity and a Hamilton depression score (Valvassori *et al.*, 2018). Finally,

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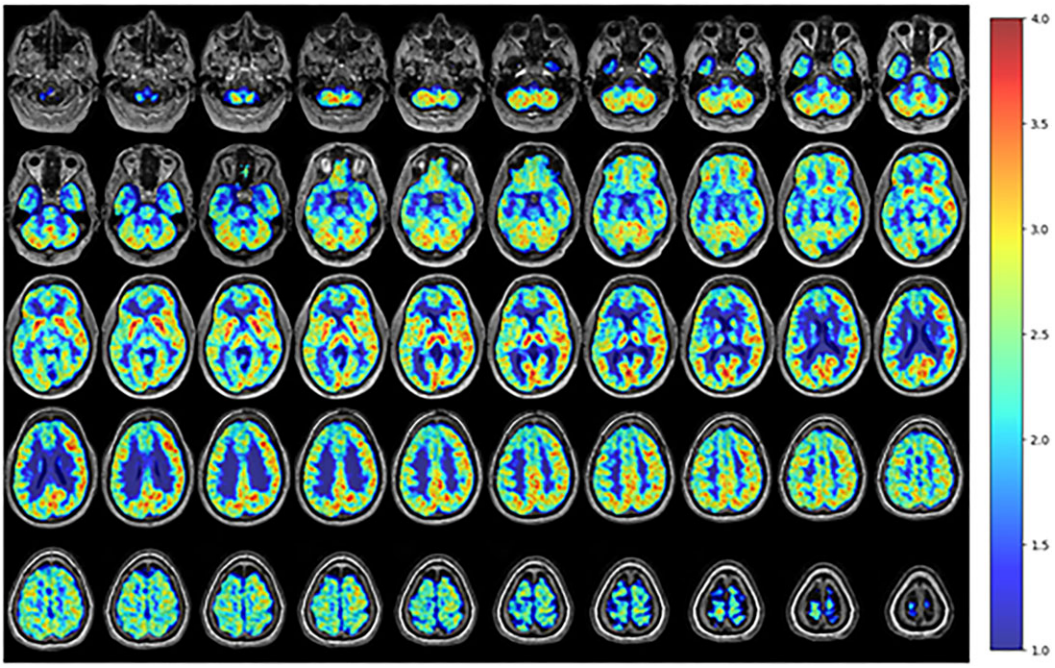

Figure 1: PET imaging of a 58-year-old male with BD disorder obtained via the ^{18}F-BCPP-EF mitochondrial Complex I PET ligand. Warmer colors represent greater mitochondrial activity in the brain and colder colors represent decreased mitochondrial activity.

clinical studies have revealed that individuals with mitochondrial cytopathies have a higher risk of developing BD (Marazziti *et al.*, 2012; Fattal *et al.*, 2007).

As a related consideration, the overlapping pharmacotherapies utilized for both BD and epilepsy suggest that a mechanistic overlap may exist between these conditions. Mitochondrial dysfunction has been implicated in various forms of epilepsy (Rahman, 2018; Madireddy, 2023). As a result, researchers have increasingly focused on elucidating the role of a parallel process, that of mitochondrial dysfunction in BD. With ~50% of a neuronal ATP utilized by the Na^+/K^+ ATPase (Zhang *et al.*, 2009), any deficiencies in mitochondrial-dependent ATP generation may result in altered membrane stability. Mitochondria also play a key role in the synthesis and regulation of neurotransmitters, epigenetic regulatory mechanisms, and calcium mechanisms central to neuronal excitability (Ly and Verstreken, 2006; Lee *et al.*, 2018; Guo *et al.*, 2017; Vos *et al.*, 2010; Storozhuk *et al.*, 2005; Csordás *et al.*, 1999, Thomas, and Hajnóczky, 1999; Jeanneteau and Arango-Lievano, 2016; Minocherhomji *et al.*, 2012). Alterations of these fundamental processes may drive dysfunctional patterns of neuronal activation and resultant changes in neural networks.

Despite the mounting evidence supporting a role for mitochondrial dysfunction in BD, no positron emission tomography (PET) imaging study to date has investigated this mechanistic connection. This gap in the current literature can be addressed by using the 2-*tert*-butyl-4-chrolo-5-(6-(2-(2-18F-fluoroethoxy)-ethoxy)-pyridin-3-ylmethoxy)-2*H*-pyridazin-3-one (^{18}F-BCPP-EF) PET ligand, which binds mitochondrial complex I to serve as a proxy for mitochondrial function. Prior research has investigated the application of this tracer in neurodegenerative disorders (Terada *et al.*, 2022; Terada *et al.*, 2021) and autism spectrum disorders (Kato *et al.*, 2023). However, no studies in mood disorders have utilized this imaging modality.

Case Presentation

The participant is a 58-year-old male with a past medical history notable for anxiety, depression, migraines, alcohol use disorder (AUD), BD (unspecified type), and COPD who notably enrolled as a control participant for a clinical trial that assessed brain mitochondrial function in the setting of neurological disorders via the ^{18}F-BCPP-EF PET ligand (a PET probe for mitochondrial complex I). On screening prior to enrollment, he indicated that he had no prior psychiatric history. However, in a subsequent interview, he disclosed that he has been diagnosed with BD (unspecified subtype) in the past and had been treated with various mood stabilizers (all of which he reportedly discontinued due to not "believing" in the disorder). He takes no medication for his anxiety, depression, and migraines but does take Trazadone, Benadryl, and melatonin to assist with sleep difficulties. He has a smoking history of 44 pack years, reports frequent marijuana use for the last 47 years, and reports drinking >10 drinks weekly from the age of 11. The participant reported a family history that includes a cousin's suicide and three siblings who have been diagnosed with BD (unspecified type).

On mental status exam, he exhibited pressured speech, irritability, and mildly elevated mood, in addition to reporting a sleep deficit (with a typical sleep duration of 5 hours per night). During the interview, he repeatedly insisted that he had enjoyed working long hours and had to leave as soon as possible so that he could get more work done (despite having scheduled the appointment at the earliest possible time slot that staff could accommodate, which fell outside of regular work hours). There was, therefore, limited time to undergo a more thorough diagnostic assessment in this setting, but the symptoms characteristic of BD evident during this exchange were noted by all staff with whom the participant interacted.

He also completed the Beck Depression Inventory (BDI-II) with a resulting score of 34 indicating severe depression in the preced-

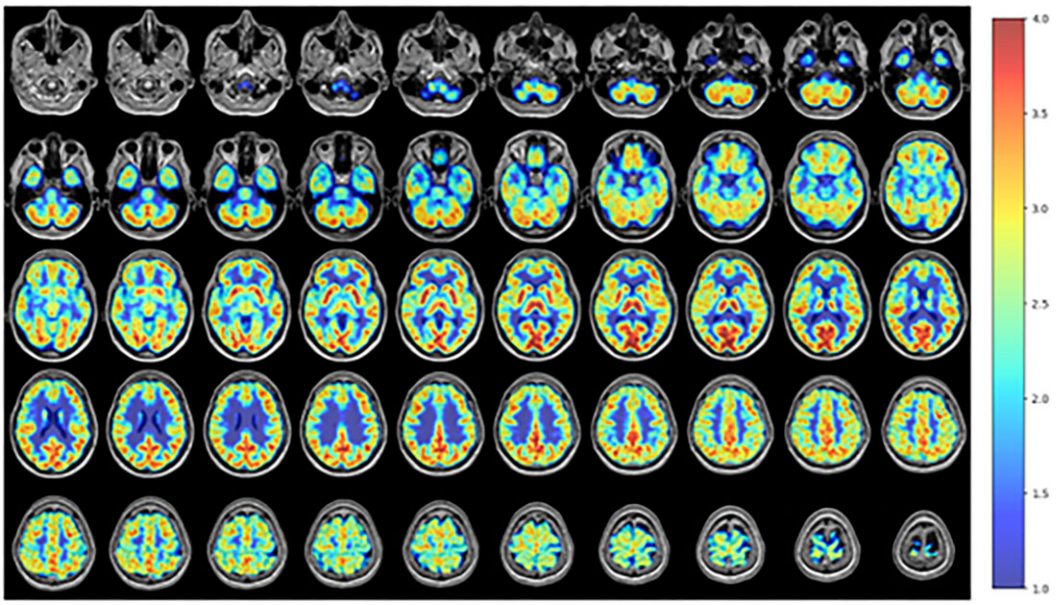

Figure 2: PET imaging of a 57-year-old female healthy control using the ^{18}F-BCPP-EF mitochondrial Complex I PET ligand. Warmer colors represent greater mitochondrial activity in the brain and colder colors represent decreased mitochondrial activity.

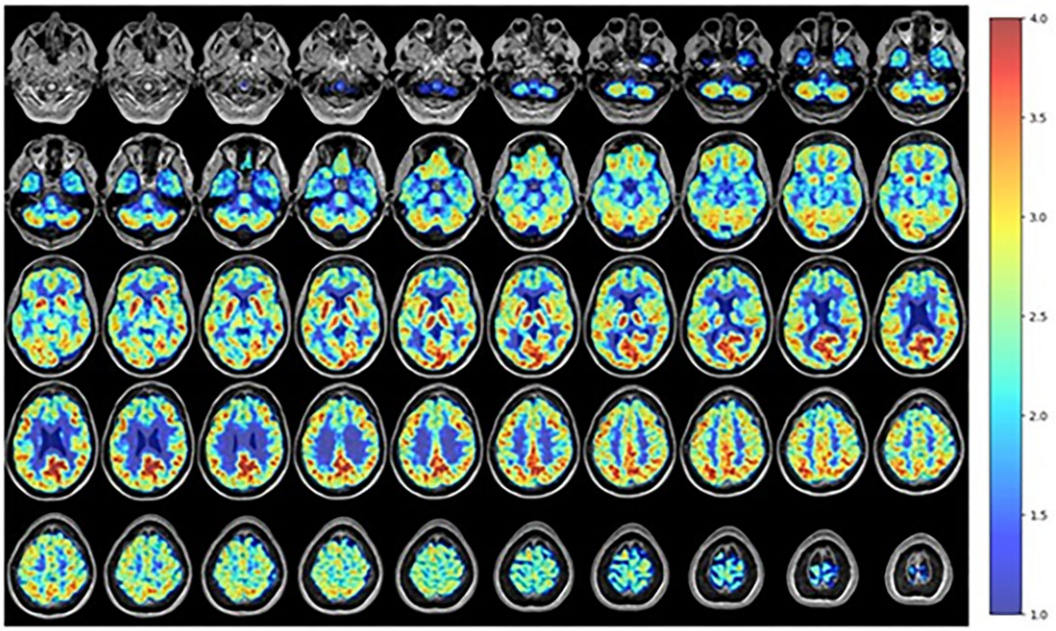

Figure 3: PET imaging of a 75-year-old female healthy control using the ^{18}F-BCPP-EF mitochondrial Complex I PET ligand. Warmer colors represent greater mitochondrial activity in the brain and colder colors represent decreased mitochondrial activity.

ing 2 weeks with predominant features of loss of interest, sadness, and agitation. Additionally, the participant got an alternating verbal fluency score of 9/20 and an action verbal fluency score of 17/30. Two healthy controls and the participant with BD additionally underwent PET imaging.

PET imaging was performed in 3D imaging mode on a Biograph 6 TruPoint PET/CT scanner (Siemens Molecular Imaging, Inc., Knoxville, TN, USA), which acquired 63 transaxial slices (slice thickness 2.4 mm) over a 15.2 cm axial field of view. Images were be corrected for scatter and motion. Sixteen frames of dynamic PET imaging data were acquired over 70 minutes from the time of injection. The last two frames of the dynamic acquisition were averaged and rigidly aligned to the participant's structural magnetic resonance imaging (MRI) scan using advanced normalization tools. The FreeSurfer software suite was used to generate segmentation labels for midsaggital corpus callosum from the structural MRI scans. The averaged PET frames were subsequently normalized by the mean value of the midsaggital corpus callosum to obtain standardized uptake value ratio images. Last, regional standardized uptake value ratio values were extracted using FreeSurfer labels, and between-subject percentage differences were calculated. Two female normal controls who underwent the same imaging protocol were available to provide approximate regional uptake comparisons. The other male normal

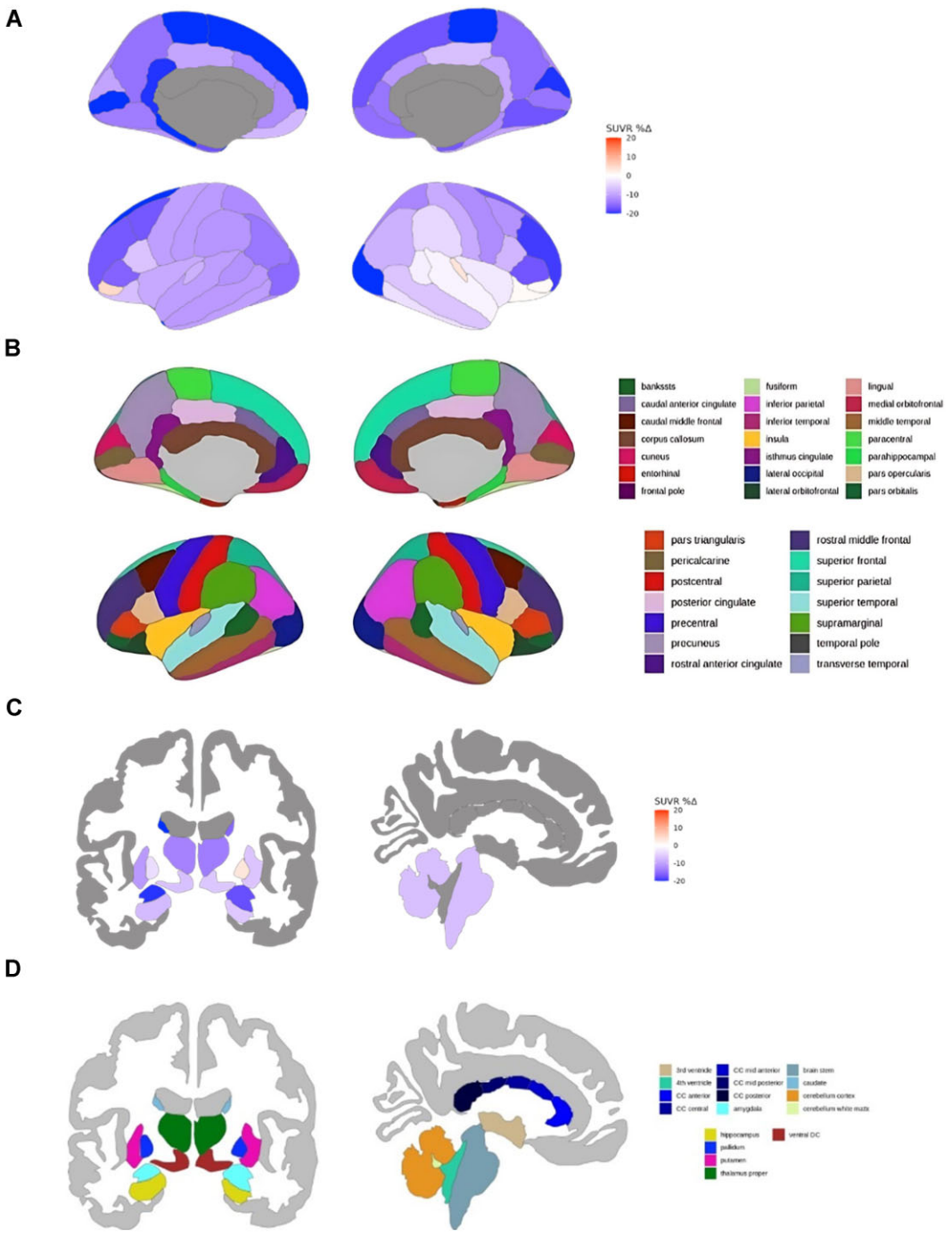

Figure 4: Relative degree of mitochondrial impairment: inter-participant comparisons. (**A**) and (**C**) The percentage differences in activity between our participant and the age matched 57-year-old healthy control. (**B**) and (**D**) A reference for the brain regions under investigation.

controls who participated in the clinical trial underwent different imaging protocols (as the diffusion protocol was still going through an interactive optimization process at the time of this trial given the recent advent of this technology). Therefore, while one of the normal controls with available comparative imaging data was age-matched, no gender-matched imaging data were available for comparison, representing a key limitation in interpreting comparative findings. Nonetheless, even when compared to the 75-year old female normal control with comparative imaging data available (for whom mitochondrial function would be expected to decline with age), mitochondrial function was significantly more impaired in the younger individual with a history of BD (as depicted in Fig. 1, Fig. 2, and Fig. 3 below).

For the participant presented in this case study, there was an ~20% reduction in mitochondrial complex I activity observed in the ventrolateral prefrontal cortex (vlPFC), the dorsolateral prefrontal cortex (dlPFC), and the precuneus region in comparison to mitochondrial complex I activity observed in the age-matched control. Additionally, a ~15% reduction was observed in the amygdala, thalamus, and caudate nucleus. There was mild laterality observed in the degree of deficit, but all within 5%. These findings are visualized in Fig. 4.

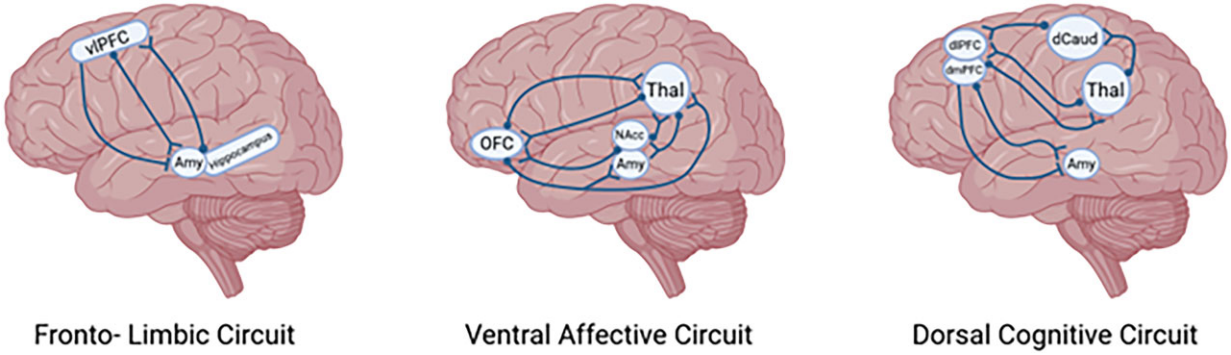

Figure 5: Interconnected circuits identified as major contributors to mood lability in BD.

Conclusions

It is important to note that an observed deficit in mitochondrial complex I activity does not allow us to definitively infer whether neurons in a given brain region are more or less active. Deficits in mitochondrial function would presumably affect neuronal membrane stability and result in altered resting membrane potential, which could manifest as increased frequency of action potentials (at least initially). Potential mechanisms include the accumulation of intracellular sodium, lowering the ATP-dependent resting membrane potential, or exhaustion of vesicular contents impairing synaptic transmission. The need to restore homeostasis may explain the temporal relationship observed between hypomanic and depressive episodes. Moreover, given the complex web of inhibitory and excitatory pathways throughout the central nervous system, inhibition of a given neural network may result in paradoxical excitation of associated regions.

When investigating dysfunctional neural circuits implicated in BD, neuroimaging researchers often categorically separate neural circuits into three domains: emotional regulation, cognition, and psychomotor changes (Bi *et al.*, 2022). When considering emotional regulation and function, there are three interconnected circuits that have been identified as major contributors to mood lability in BD. These are detailed in Fig. 5.

The first is the fronto-limbic circuit, which is primarily composed of connections between the amygdala and the vlPFC, with the vlPFC assessing whether the amygdala has properly responded to a situation and then adjusting its output (Kohn *et al.*, 2014). In individuals with BD, the amygdala shows increased activity, resulting from either dysfunction in the vlPFC, the amygdala, or both (Vai *et al.*, 2019). In our imaging case study, both the vlPFC and amygdala demonstrated significant decreases in mitochondrial function. It follows that such alterations may be related to symptoms involving emotional lability/impulsivity (e.g. pressured speech and irritability).

The second circuit depicted, the ventral affective circuit, is involved in identifying salient emotional stimuli and mediating resultant autonomic responses (Townsend and Altshuler, 2012; Blond *et al.*, 2012). It includes the orbital frontal cortex, the thalamus, and the ventral striatum. PET imaging of our participant exhibited significant mitochondrial dysfunction in both the thalamus and the frontal pole. Given the role of the orbital frontal cortex, these deficits point to a process that affects emotional reactions to both internal and external cues (Yamasaki *et al.*, 2002).

The third, dorsal cognitive circuit, is composed of the dlPFC, the dorsomedial prefrontal cortex, the dorsal caudate, and the thalamus. This circuit, which is responsible for selective attention, planning, and explicit emotional regulation, is broadly hypoactive in patients with BD independent of their current mood state (Kohn *et al.*, 2014; Kurtz *et al.*, 2021). In our case study, mitochondrial deficits are observed in all four of these regions, possibly contributing to deficits in cognitive regulation of emotion.

Beyond emotional regulation and function, symptoms related to both cognitive and psychomotor changes are hallmarks of BD. Cognitive changes include deficits in executive function, memory, social cognition, and response timing. Psychomotor changes seen are state-dependent, with mania involving symptoms of hyperactivity, reckless action, impulsivity, and agitation, whereas depressive episodes involve decreased activity levels, volitional inhibition, physical and mental sluggishness, and, in more extreme episodes, akinesia. These symptoms have been associated with four networks: the default mode network (DMN), the central executive network (CEN), the salience network (SN), and the sensorimotor network (SMN); the first three networks are predominant contributors to cognition, with the SMN primarily being responsible for psychomotor symptoms (Martino and Magioncalda, 2022; Martino *et al.*, 2016; Seeley *et al.*, 2007; Mamah *et al.*, 2013; Wang, Wang, Wu, *et al.*, 2020).

Coordination and switching among these four networks is considered to be an underlying framework for cognition (Park and Friston, 2013; Syan *et al.*, 2018). The DMN, composed of medial prefrontal cortex, the hippocampus, the lateral temporal cortex, the precuneal cortex, and the posterior cingulate cortex, is widely referred to as the "task-negative network" given that it exhibits activation at baseline and deactivation during engagement with a task. This is in contrast to the CEN, which is viewed as an antagonistic circuit to the DMN given that it is primarily active during activities (Smith *et al.*, 2009). The CEN comprises the dlPFC, the dorsal anterior cingulate cortex, the posterior parietal context, and the inferior temporal gyrus, and exhibits increased activity during attention-demanding and working memory tasks that require top-down modulation (Menon, 2011). At the center of these two networks is the SN, which plays a central role in switching between the DMN and CEN and comprises the insular cortex, the dorsal anterior cingulate cortex, the amygdala, and the temporal lobe (Seeley *et al.*, 2007). Dysfunctions in these networks have been shown to be correlated with the cognitive deficits observed in BD (Zovetti *et al.*, 2020; Liu *et al.*, 2021; Wang, Wang, Huang, *et al.*, 2020). Notably, in this case study, ^{18}F-BCPP-EF PET imaging revealed evidence of mitochondrial dysfunction within the precuneus cortex, which is a key part of the DMN. Additionally, the amygdala, which is a part of the SN, exhibited mitochondrial dysfunction. These

mitochondrial deficits could theoretically be contributing to the participant's alternating verbal fluency score of 9/20.

As with cognition, psychomotor behavioral features manifesting in BD are thought to be caused by alterations in networks, specifically the DMN and the SMN (Mamah *et al.*, 2013; Northoff *et al.*, 2021; Meda *et al.*, 2014). One study found that individuals with BD had reduced resting state cohesiveness of the SMN (Doucet *et al.*, 2017) and another found reduced functional within-connectivity in both the right and left primary somatosensory areas (clusters in the somatosensory network) in individuals with BD (Ishida *et al.*, 2017). The ratio between DMN activity and SMN activity as measured by blood flow has also been an area of investigation, with studies showing that the DMN/SMN activity ratio was significantly increased in depression and significantly decreased in mania, with computed ratios in both cases correlating with the degree of depressive or manic symptoms, respectively (Russo *et al.*, 2020; Martino *et al.*, 2016). For our participant in the case study, there were mitochondrial deficits observed in key regions in the DMN as detailed in the prior paragraph. However, calculating a DMN/SMN activity ratio to derive potential correlations with symptom severity would require a different imaging modality, which falls outside the scope of this case study.

While this case study establishes the first use of the ^{18}F-BCPP-EF PET ligand in the setting of BD, several key limitations must be noted. Namely, in addition to the limited statistical power inherent to a case study, no sex-matched controls were available for comparison. While matching for age is vital when assessing mitochondrial function, matching for biological sex may prove to be particularly important as well as more data emerge. A study examining mitochondrial enzyme activities in post mortem brains found that the activities of citrate synthase, succinate dehydrogenase, and mitochondrial reductase were higher in female vs male brains (Harish *et al.*, 2013). Accompanying this increased mitochondrial activity is evidence showing that female mitochondria produce fewer reactive oxygen species than male ones (Malorni *et al.*, 2007; Ventura-Clapier *et al.*, 2017). However, the effects of aging seem to have one of the largest effects on mitochondrial function (Chistiakov *et al.*, 2014) and substantial differences were still seen between the 75 year old healthy control and the 58 year old BD participant. Additionally, binge drinking behavior was comorbid with BD in this case study, making it difficult to discern to what extent observed mitochondrial deficits may be associated with underlying BD pathophysiology vs consumption of alcohol. Ethanol is a known mitochondrial toxin and much of the neurodegeneration seen in alcohol use disorder is thought to be secondary to oxidative damage, a biproduct of mitochondrial dysfunction (Kamal *et al.*, 2020; Crews *et al.*, 2015). This pattern of neurodegeneration is predominantly seen in the hippocampus, frontal lobe, and the corpus collosum that do overlap with several of the dysfunctional circuits seen in this case study (Harper and Matsumoto, 2005; Kapogiannis *et al.*, 2012). Finally, given the participant's mental status at the time of examination and preference to quickly return to work following the standard assessment, collecting a more comprehensive psychiatric history was not feasible.

Even with these limitations in mind, this case study provides exciting preliminary results due to the mounting evidence implicating mitochondria in the pathogenesis of BD. This has been established utilizing several techniques, including assessments pertaining to mtDNA copy number, SNPs, ETC complex activity in peripheral cells, post-mortem analyses of ETC function, and iPSC-derived biomarkers, among others. Despite this compelling evidence, at the time of this publication no studies have utilized PET imaging to assess mitochondrial function in the setting of BD. This renders the ^{18}F-BCPP-EF mitochondrial complex I PET ligand an exciting new tool to further characterize the role of mitochondrial dysfunction in BD. This case study opens the door for future lines of research to build on these preliminary results. Our imaging findings demonstrated significant overlap between areas of dysfunction identified with the ^{18}F-BCPP-EF PET ligand and areas of dysfunction previously identified in the setting of BD with functional MRI techniques. That overlap was seen in both affective and cognitive circuits, with mitochondrial dysfunction in the fronto-limbic, ventral affective, and dorsal cognitive circuits showing particularly significant differences. This was true even when comparing imaging with the much older healthy control, whom one would expect to have a greater degree of impairment as a function of aging. The compelling overlap between prior imaging outcomes and our findings in this case study warrant further investigation via an expanded study featuring an increased number of participants and measures aimed at controlling for confounding variables. Expanded research in this domain has the potential to better characterize the role of mitochondrial function in the pathogenesis of BD, with the ultimate goal of identifying clinically useful biomarkers and improved therapeutic targets to benefit patients suffering from BD.

Consent for publication

Consent for publication was acquired from the participant.

Author contributions

Travis P. Wigstrom (Conceptualization, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing), Stiven Roytman (Data curation, Formal analysis, Investigation), Jeffrey L. B. Bohnen (Methodology, Writing - original draft, Writing - review & editing), Rebecca R. Paalanen (Data curation, Project administration), Alexis M. Griggs (Conceptualization, Data curation, Project administration), Jaimie Barr (Conceptualization, Data curation, Project administration), Roger Albin (Funding acquisition, Project administration), Prabesh Kanel (Conceptualization, Investigation, Resources, Supervision), and Nicolaas I. Bohnen (Conceptualization, Funding acquisition, Investigation, Resources, Supervision).

Conflict of interest

None declared.

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Ethics approval and consent to participant

The trial from which these data were acquired received ethics approval from the University of Michigan IRBMED board. The participant consented prior to their involvement in the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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