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Greater Mitochondrial Polygenic Risk is Associated with Reduced Sustained Attention among Youth with Bipolar Disorder

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Abstract

Background

Bipolar disorder (BD) is a polygenic disease characterized by neurocognitive impairments and energy dysfunction, with potential mitochondrial involvement. We set out to examine whether mitochondrial polygenic risk scores (Mito-PRS) are associated with neurocognitive performance among youth with BD.

Methods

129 youth (17.0 ± 1.9 years; n = 72 BD, n = 57 controls) completed six Cambridge Neuropsychological Test Automated Battery tasks, evaluated as a composite and independently. Mito-PRS was derived from a BD genome-wide association study and variants were selected based on their location within/near genes annotated in expertly curated mitochondrial gene databases. Associations between Mito-PRS and neurocognitive composite scores were examined in the overall sample, and within BD and controls separately. Sex-stratified analyses, mood-stratified analyses, and PRS-by-diagnosis interaction effects were also examined. All analyses controlled for age, sex, IQ, and the first two genetic principal components, and sensitivity analyses additionally controlled for psychotropic medications and mood severity.

Results

Higher Mito-PRS was associated with poorer sustained attention in the overall sample (β=-0.19, p = 0.02) and within the BD group (β=-0.30, p = 0.01), but not within controls (β=-0.10, p = 0.44). Findings were significant in females only, and remained significant among symptomatic BD participants. Findings remained significant in sensitivity analyses.

Conclusions

This study provides preliminary evidence that Mito-PRS is associated with reduced sustained attention among youth. These findings were especially salient in youth with BD and among females. While sustained attention may be specifically impacted by Mito-PRS, larger studies are warranted to examine the full spectrum of neurocognitive domains and to discern brain mechanisms underlying the observed findings.

Introduction

Bipolar disorder (BD) is characterized by episodes of mania (BD-I), or less severe hypomania (BD-II), and depression [1]. BD onset typically occurs during adolescence and young adulthood [2], and is among the leading causes of functional disability among youth worldwide. Indeed, early-onset BD is associated with

substantial mood symptom burden and high rates of psychiatric comorbidities [3, 4]. There is also well-established evidence of neurocognitive dysfunction in both adults and youth with BD, even during euthymic/asymptomatic periods [5, 6]. Neurocognitive domains of emotion regulation and reward processing are most consistently impacted in BD, although there is evidence that memory, attention, and executive functioning are also highly affected [7, 8].

Another key aspect of BD in energy dysfunction. Energy disturbances are hallmark symptoms of both manic episodes (e.g., increased energy, hyperactivity) and depressive episodes (e.g., decreased energy, fatigue), persist during periods of normal mood (i.e. euthymia) [9–11], and have meaningful consequences for daily functioning and quality of life [12–14]. Indeed, BD has been conceptualized as a disorder of energy dysregulation, reflecting disruptions in the molecular and cellular systems that govern energy production and utilization [15].

Central to cellular energy production are mitochondria, the primary sites of adenosine triphosphate (ATP) synthesis and metabolic regulation. Mitochondrial dysfunction has long been recognized as a putative mechanism at the core of BD [16–18]. For example, adults with BD demonstrate differences in mitochondrial morphology (e.g., reduced size, altered shape) and function (e.g., respiration, oxidative phosphorylation) [19–24]. Both nuclear and mitochondrial genetics have been implicated in the observed mitochondrial dysfunction among individuals with BD. For instance, specific mitochondrial DNA (mtDNA) haplogroups (e.g., N9a, U) and variants (e.g., 10398 A > G) show associations with BD and BD treatment outcomes, although findings are heterogeneous [25–28]. The expression of nuclear genes involved in mitochondrial energy production also appear to be altered in BD, contributing to increased oxidative stress [21, 29, 30]. Emerging evidence suggests mitochondrial dysfunction may extend to poorer neurocognitive performance in BD. For instance, in first-episode, drug-naive patients with BD, elevated bioenergetic serum metabolites are associated with poorer performance on standardized neurocognitive assessments [31], and mtDNA copy number has been shown to mediate the relationship between insulin resistance and executive function in euthymic BD [32]. Furthermore, interventions that enhance prefrontal mitochondrial respiration via transcranial infrared laser stimulation have been shown to improve attentional control and working memory in individuals with BD [33, 34], suggesting that mitochondrial function may represent a promising target for improving cognitive deficits in BD.

Polygenic risk scores (PRS) reflect the combined effects of multiple single-nucleotide polymorphisms (SNPs) and have emerged as indices of genetic risk for polygenic disorders such as BD [35, 36]. One such study by Jiang and colleagues reported that a greater BD-PRS, derived from adult genome-wide association study (GWAS) summary statistics, was associated with poorer neurocognition, particularly sustained attention, in youth with BD vs controls [37]. However, the underlying mechanism driving this association was not examined. Recently, PRS that are based on nuclear-encoded genes involved in mitochondrial pathways (Mito-PRS) have been developed. Mito-PRS have been shown to predict disease risk, age of onset, and treatment response in Alzheimer's and Parkinson's diseases [38–41]. Thus far, there have been no published Mito-PRS studies in BD or in youth.

Using the same youth sample investigated by Jiang and colleagues [37], this study builds upon the prior neurocognitive findings by examining the association between Mito-PRS, derived from an independent adult GWAS of BD cases and controls, and neurocognitive performance in youth with and without BD. Examining Mito-PRS in youth with BD provides a unique opportunity to understand the genetic and mechanistic underpinnings of BD in a sample undergoing neurodevelopmental changes while minimizing the effects of aging and related diseases. The primary study hypothesis was that greater Mito-PRS would be associated with neurocognitive impairments among youth. While similar directions of effect were anticipated in both groups, stratified analyses also examined the BD and control groups separately to evaluate within-group effect sizes. These analyses are particularly relevant to BD, where mitochondrial genetic influences on brain bioenergetics and energy are of particular clinical relevance.

Methods

Participants

The current study included 129 genetically European youth, ages 13–21 years. BD participants (type I, II, or other specified bipolar and related disorder [OSBRD]) were recruited through a subspecialty clinic at an academic health sciences centre in Toronto, Ontario, Canada. Control youth were recruited from the community through advertisements. Exclusion criteria included: known cardiac conditions; autoimmune or inflammatory conditions; taking anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycemic agents; severe neurological or neurocognitive impairment, and/or inability to provide informed consent. Additionally, control participants had no major or recent psychiatric disorders (no lifetime mood or psychotic disorders, no recent alcohol or drug dependence in the past three months, and no recent anxiety disorders within the past three months) and no first- or second-degree family history of BD or psychotic disorders.

Participants and their parent/guardian(s) provided written informed consent. Ethical approval was granted by the research ethics board at Sunnybrook Research Institute. All data was collected at Sunnybrook Research Institute. However, all data was transferred with the Centre for Youth Bipolar Disorder's relocation to the Centre for Addiction and Mental Health (CAMH). Thus, ethics approval was also granted by CAMH Research Ethics Board.

Psychiatric and anthropometric measures

Diagnostic and clinical information was obtained using the *Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version* (K-SADS-PL) [42], which is a semi-structured interview that integrates information from both the participant and their parent/guardian(s), along with available medical records. The *K-SADS Depression Rating Scale* (DRS) and *K-SADS Mania Rating Scale* (MRS) were used in place of the K-SADS-PL mood sections [43]. Diagnoses in this study were based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, as

participants were enrolled from 2014 to 2019 and the DSM-5 version of the K-SADS-PL was not available until 2016. The diagnosis of OSBRD, previously referred to as bipolar disorder not otherwise specified (BD-NOS), incorporates operationalized criteria specified from the *Course and Outcome of Bipolar Illness in Youth (COBY)* study, including duration of symptoms (minimum of 4 hours per day) and the number of hypomanic days (minimum of 4 lifetime days) [44], while retaining DSM-5 symptom count requirements (≥ 3 symptoms when elation was the primary mood; ≥4 symptoms when irritability was primary). Details regarding clinical measures are described in Supplemental Materials.

All interviews were performed by trained study personnel with either Bachelor's or Master's degree in a health-related field and who completed comprehensive K-SADS-PL training under the supervision of the senior author (B.I.G.), a licensed child and adolescent psychiatrist. All diagnoses and symptom ratings were reviewed and confirmed by a licensed child and adolescent psychiatrist.

Body weight was measured in kilograms (kg) using a Tanita digital scale. Weight measurements were deducted by 1.3kg for participants wearing long pants and long-sleeved shirts, 1.1kg for short pants or short-sleeved shirts, or 0.9kg for both short pants and short-sleeves. Height was measured in centimeters (cm) using a wall-mounted stadiometer. Body mass index (BMI) was calculated using standard guidelines [45]. Blood pressure was taken using a Life Source Digital Blood Pressure Monitor after the participant had rested for 10 minutes. All measurements were repeated twice to ensure accuracy, and an average of the two measurements was computed; if there was a difference of >1cm (height) or > 0.3kg (weight) between the two measurements, a third measurement was taken.

Polygenic risk scores

A saliva sample (~ 2 mL) was collected from each participant in an Oragene OG-500 DNA kit (DNA Genotek Oragene-500 kits; DNA Genotek Inc., Ottawa, Canada). Participants were instructed to abstain from eating, drinking, smoking, and chewing gum 30 minutes prior to saliva collection. Detailed methods regarding DNA extraction, genotyping, genetic data quality control, and whole-genome imputation can be found in Supplemental Materials.

Initially, a BD-PRS was computed from ~ 5.9 million SNPs within BD GWAS summary statistics of > 2.4 million adults (effective sample size of 163,368) [46], all of European ancestry. The BD GWAS summary statistics was first adjusted using PRS-CS-auto, a Bayesian-based method that places a continuous shrinkage prior on the effects sizes of the SNPs [47]. PRS-CS-auto was implemented using the software default settings and with the 1000 Genomes European samples and HapMap3 SNPs as the LD reference panel provided with the PRS-CS software.

Mito-PRS was then derived from a subset of the adjusted SNPs (~ 21,000), which were selected for inclusion due to their location within genes annotated in MitoCarta v3.0 and/or Molecular Signatures Database (MSigDB), curated by the Broad Institute [48, 49]. MitoCarta comprises an inventory of nuclear genes encoding proteins with strong evidence of mitochondrial localization. MSigDB mitochondrial gene

sets reflect biochemical pathways and experimentally defined gene expression signatures (e.g., oxidative phosphorylation, mitochondrial dynamics). Mito-PRS SNPs are implicated in mitochondrial pathways that are directly (e.g., oxidative phosphorylation) and/or indirectly (e.g., mitophagy, fission/fusion) related to energy metabolism.

PLINK 1.9 was used to weigh all extracted SNPs by their effect sizes calculated using PRS-CS-auto and sum all extracted SNPs into a PRS for each individual in the target cohort. The derived PRS were subsequently standardized to a mean of 0 and a standard deviation of 1.

Neurocognitive testing

Specific domains of neurocognition were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB eclipse version 2.0; Cambridge Cognition, Ltd., 2005), a computerized battery of subtests that utilizes a touch screen and high sensitivity trigger buttons to record responses to neurocognitive tasks. The six neurocognitive tasks assessed were: Affective Go/No-Go (AGN) task, Cambridge Gambling Task (CGT), Rapid Visual Information Processing (RVP) task, Intra/Extradimensional Set Shift (IED) task, Spatial Span (SSP) task, and Stockings of Cambridge (SOC) task. Details regarding each task are presented in Supplementary Materials and Supplementary Table 1.

The scores on all outcome measures were re-coded where needed so that higher scores reflected better neurocognitive performance. Normality was assessed for each outcome measure. If data were not normally distributed, the data were either log-transformed or square-rooted based on the skewness of data. Extreme outlier values were winsorized to the closest non-extreme value. Z-scores were then computed for each outcome measure based on sample norms. Subsequently, the z-scores on outcome measures for each neurocognitive task were averaged to generate a composite score for each task (i.e. AGN, CGT, RVP, IED, SSP, and SOC). The Wechsler Abbreviated Scale of Intelligence was administered to all participants for an estimate of intelligent quotient (IQ) [50].

2.4 Statistical analysis

Demographic and clinical group differences were evaluated using IBM SPSS Version 27. Group differences were evaluated using *t*-tests for continuous variables, Kruskal-Wallis *H*-tests for ordinal variables, and chi-squared tests for categorical variables. Statistical significance was set at two-sided $p < 0.05$.

A general linear model (GLM) was used to examine the association of Mito-PRS with each of the six neurocognitive tasks. Primary analyses were conducted in the combined sample of youth with BD and controls to maximize power, and because we anticipated the direction of any association would be similar in both diagnostic groups. Secondary analyses further examined the associations within the BD group and control group separately. PRS-by-diagnoses interaction analyses and sex-stratified analyses were also conducted. Age, sex (as assigned at birth), IQ, and the first two data-derived genetic principal components [51] were included in the model as covariates. Sensitivity analyses additionally controlled

for psychotropic medications (binary outcomes of any medications, second generation antipsychotics [SGAs], lithium), BMI, mood symptom severity (depression [DRS score], mania/hypomania [MRS score]), and all 10 genetic principal components, respectively. Finally, associations in symptomatic BD participants (i.e. those experiencing current depression and/or hypomania; n = 55) and in euthymic BD participants (n = 17) were also examined in exploratory fashion.

Due to the modest sample size and the absence of prior literature examining associations between Mito-PRS and neurocognitive performance in BD or in youth, we report all results uncorrected for multiple comparisons.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics are presented in Table 1 and Supplementary Table 2. Compared to the control group (n = 57), the BD group (n = 72) was significantly older, with more advanced pubertal status, and higher BMI. Mito-PRS did not differ between groups.

Table 1
Demographic, physiological, and polygenic characteristics of participants in the overall sample.

	BD (n = 72)	**Controls (n = 57)**	**Statistic[a]**	***p***	**Effect size[b]**
Demographics					
Age, years	17.4 ± 1.8	16.5 ± 1.9	2.90	0.004*	0.52
Female	49 (68.1)	34 (59.6)	0.98	0.32	0.09
Socioeconomic status	4.4 ± 0.8	4.5 ± 0.6	0.94	0.33	< 0.001
Intact family	49 (68.1)	40 (70.2)	0.07	0.80	0.02
Tanner stage	4.5 ± 0.7	4.2 ± 0.7	6.38	0.01*	0.04
Physiological and polygenic characteristics					
Adjusted BMI (kg/m^2)	23.9 ± 4.2	21.6 ± 3.2	11.87	< 0.001*	0.09
Mito-PRS	0.1 ± 0.1	0.1 ± 0.1	0.05	0.96	0.008

Note: Values for all continuous and ordinal variables are written as mean±standard deviation or mean±standard error (only for polygenic risk scores). Categorical variables are written as n (% within

group).

[a]Statistic=t for dimensional variables, H (1 degree of freedom) for ordinal variables, or χ^2 for categorical variables.

[b]Effect size=Cohen's *d* for t test, partial η^2 for H test, or Cramer's *V* for χ^2 test. *=significance at α=0.05.

BD=bipolar disorder; BMI=body mass index; Mito=mitochondria; PRS=polygenic risk scores.

Primary neurocognitive analyses

The main effects of Mito-PRS in relation to neurocognitive performance are presented in Table 2 and Fig. 1. Higher Mito-PRS was associated with poorer sustained attention in the overall sample (RVP: β=-0.19, *p* = 0.02; Fig. 1A) and within the BD group (RVP: β=-0.30, *p* = 0.01; Fig. 1B), but not among controls (RVP: β=-0.10, *p* = 0.44; Fig. 1C). There were no significant PRS-by-diagnoses interaction effects, and no significant findings in any other neurocognitive composite scores.

Table 2
Association of Mito-PRS with neurocognitive performance.

Neurocognitive tasks	**β**	***p***
Main effect of Mito-PRS in the overall sample		
Affective processing (AGN)	-0.06	0.53
Decision-making (CGT)	-0.11	0.25
Sustained attention (RVP)	-0.19	0.02*
Cognitive flexibility (IED)	-0.09	0.33
Visuospatial working memory (SSP)	0.03	0.67
Spatial planning (SOC)	0.005	0.96
Global neurocognition composite	-0.13	0.14
Main effect of Mito-PRS within the BD group		
Affective processing (AGN)	-0.07	0.58
Decision-making (CGT)	0.005	0.97
Sustained attention (RVP)	-0.30	0.01*
Cognitive flexibility (IED)	-0.12	0.34
Visuospatial working memory (SSP)	0.05	0.68
Spatial planning (SOC)	0.09	0.48
Global neurocognition composite	-0.15	0.23
Main effect of Mito-PRS within the control group		
Affective processing (AGN)	-0.09	0.53
Decision-making (CGT)	-0.16	0.25
Sustained attention (RVP)	-0.10	0.44
Cognitive flexibility (IED)	-0.10	0.44
Visuospatial working memory (SSP)	0.06	0.67
Spatial planning (SOC)	-0.05	0.70
Global neurocognition composite	-0.13	0.31

Note: AGN=Affective Go/No-Go; BD=bipolar disorder; CGT=Cambridge Gambling Task; IED=Intra-Extra Dimensional Set-Shifting Task; Mito=mitochondria; PRS=polygenic risk scores; RVP=Rapid Visual Information Processing Task; SOC=Stockings of Cambridge; SSP=Spatial Span.

Sex-stratified analyses

The association between Mito-PRS and neurocognitive performance in females and males is presented in Table 3. Higher Mito-PRS was associated with poorer sustained attention in females only, both in the overall sample (RVP: β=-0.23, *p* = 0.04) and within the BD group (RVP: β=-0.35, *p* = 0.02). There were no significant associations in males.

Table 3
Association of Mito-PRS with neurocognitive performance, stratified by sex.

Neurocognitive tasks	Females		Males	
	β	*p*	β	*p*
Main effect of Mito-PRS in the overall sample				
Affective processing (AGN)	-0.007	0.95	-0.14	0.41
Decision-making (CGT)	-0.08	0.51	0.008	0.96
Sustained attention (RVP)	-0.23	0.04*	-0.19	0.22
Cognitive flexibility (IED)	-0.10	0.38	-0.07	0.66
Visuospatial working memory (SSP)	0.11	0.26	-0.10	0.49
Spatial planning (SOC)	0.12	0.29	-0.08	0.64
Global neurocognition composite	-0.08	0.44	-0.17	0.31
Main effect of Mito-PRS within the BD group				
Affective processing (AGN)	0.05	0.72	-0.29	0.22
Decision-making (CGT)	0.05	0.73	-0.04	0.87
Sustained attention (RVP)	-0.35	0.02*	-0.03	0.91
Cognitive flexibility (IED)	-0.10	0.55	-0.18	0.51
Visuospatial working memory (SSP)	0.03	0.82	0.13	0.58
Spatial planning (SOC)	0.12	0.46	0.22	0.38
Global neurocognition composite	-0.15	0.29	-0.05	0.86
Main effect of Mito-PRS within the control group				
Affective processing (AGN)	-0.12	0.50	-0.09	0.72
Decision-making (CGT)	-0.15	0.35	-0.05	0.81
Sustained attention (RVP)	-0.04	0.85	-0.28	0.22
Cognitive flexibility (IED)	-0.14	0.46	0.005	0.98
Visuospatial working memory (SSP)	0.27	0.09	-0.20	0.37
Spatial planning (SOC)	0.15	0.40	-0.28	0.19
Global neurocognition composite	-0.01	0.94	-0.27	0.20

Note: AGN=Affective Go/No-Go; BD=bipolar disorder; CGT=Cambridge Gambling Task; IED=Intra-Extra Dimensional Set-Shifting Task; Mito=mitochondria; PRS=polygenic risk scores; RVP=Rapid Visual

Information Processing Task; SOC=Stockings of Cambridge; SSP=Spatial Span.

Sensitivity and exploratory analyses

Sensitivity analyses are presented in Supplementary Tables 3–6. All findings remained significant when additionally controlling for any psychotropic medications, and specifically for SGAs and lithium respectively. Similarly, all findings remained significant when additionally controlling for BMI. Findings in the BD group remained significant when additionally controlling for depression and mania/hypomania mood severity. All findings remained significant when additionally controlling for all 10 genetic principal components, with some associations strengthened modestly after adjustment (e.g., RVP performance in the BD group). While these differences may reflect reduced residual confounding, they may also reflect model instability resulting from the significantly increased number of covariates, particularly in subgroup analyses with smaller sample sizes. Nevertheless, the overall pattern of findings was consistent across sensitivity analyses, with same direction of association and statistical significance maintained.

The associations between Mito-PRS and neurocognitive performance in symptomatic BD participants and in euthymic BD participants are presented in Supplementary Table 7. Similar to the primary analyses, higher Mito-PRS was associated with poorer sustained attention within the symptomatic group (RVP: β=-0.33, p = 0.02). There were no significant findings in the euthymic BD group.

Discussion

This study provides novel evidence that higher Mito-PRS was associated with poorer sustained attention in youth with BD but not control youth. These findings remained significant after additionally controlling for medications, current mood, and ancestry-related variation, and were observed in symptomatic youth with BD. Present findings add to a sparse body of genetics literature on this topic and suggest that Mito-PRS may comprise a static risk factor for impairments in sustained attention in BD, beyond the effects of traditional risk factors. The clinical relevance of these findings in underscored by the fact that these associations were observed in youth who have had far less exposure to the cumulative effects of BD symptoms and treatments, and far less medical comorbidity, than adult BD samples. As such, present findings provide preliminary evidence that the association between mitochondrial genetics and neurocognitive performance manifests early in the course of illness, rather than emerging only as a consequence of prolonged illness burden.

In the current study, the association between Mito-PRS and neurocognitive performance was only significant for sustained attention and was not other neurocognitive domains examined. This domain specificity was not hypothesized *a priori*, and may reflect sample size limitations. Indeed, the direction of association was also negative for the global neurocognition composite score, albeit non-significant (overall sample: p = 0.14, BD group: p = 0.23). Notwithstanding sample size, there are also elements of sustained attention that help contextualize this finding.

Sustained attention deficits in BD are consistently observed across the lifespan, during both symptomatic and euthymia intervals [52–56]. Moreover, prior familial and molecular studies suggest that genetic factors may contribute to these deficits [57–59]. This is consistent with an earlier study conducted by Jiang and colleagues in the same youth sample, in which BD-PRS was associated with poorer sustained attention, decision-making, and affective processing across youth with and without BD, with only the association with sustained attention remaining significant within the BD group [37]. Importantly, although Mito-PRS was derived from a subset of SNPs included in the BD-PRS, the correlation between the two scores was negligible in the current sample, suggesting that the association with sustained attention was not simply attributable to the broader genetic liability for BD captured by the overall BD-PRS.

The observed association of Mito-PRS with sustained attention highlights the theme of energy demands. Sustained attention requires prolonged maintenance of neural activity and relies on prefrontal-parietal networks that are highly energy-demanding, and may therefore be particularly sensitive to alterations in oxidative phosphorylation and ATP availability [60, 61]. Mitochondrial genetic variation may also affect neuronal calcium signaling and ion channel regulation [62, 63], processes implicated in the selective association between the *ANK3* bipolar risk variant and sustained attention [64], and may contribute to oxidative stress that disrupts synaptic proteins and neurotransmission. Additionally, given that mitochondrial function supports neurodevelopmental processes including synaptic pruning and myelination [65], mitochondrial genetic risk may exert particularly pronounced effects on attention-related circuitry during adolescence, a critical neurodevelopmental epoch [66].

Sex-stratified analyses demonstrated that all findings remained significant in females, whereas none remained significant in males. Findings from adults with BD indicate that females generally have superior performance on tests of visual and verbal learning and memory [67], though findings are mixed [68]. The differences in the current study may partly reflect the smaller sample size of males. However, effect sizes were larger in females, particularly in the BD group (RVP: $\beta_{females}$=-0.35 vs β_{males}=-0.03), suggesting a differential relationship between Mito-PRS and neurocognition across sexes rather than a purely power-driven difference. In addition to cognition-related sex differences, there are also sex differences in mitochondrial structure, function, and genetics [69, 70]. Our findings extend this literature and highlight the need for future studies to parse out biological factors underlying these putatively sex-specific associations.

When examining symptomatic and euthymic BD youth separately, associations between Mito-PRS and neurocognitive performance remained significant only in the symptomatic group. However, the euthymic group showed non-significant medium-large effect sizes for several composites, including RVP (β=-0.61). Given the small sample size of the euthymic subgroup (n = 17), this analysis was likely underpowered, underscoring the need for larger euthymic samples in future studies to parse out mood state vs disease trait effects.

Present findings should be considered alongside several limitations. First, the cross-sectional design precludes conclusions or inferences regarding the timing of the observed findings. Second, while the overall sample is relatively large for a single-site study focusing on youth with BD, it may not be sufficiently powered to detect small effect sizes in subgroup analyses (e.g., sex-stratified, euthymic BD) and may explain the null findings for other neurocognitive composite scores in the study. Relatedly, potential sources of residual confounding (e.g., psychiatric comorbidities, illness duration, family history) were not accounted for in the primary analyses. Third, an adult-based BD GWAS was used to generate PRS for the youth sample in this analysis due to a lack of youth-based BD GWAS. Relatedly, we recognize that Mito-PRS is only a genetic proxy of mitochondrial function in relation to BD risk. Finally, given that the GWAS summary statistics were based on individuals of European ancestry, analyses were restricted to participants of similar ancestry, limiting generalizability to more diverse populations. Larger, prospective studies in more diverse populations are needed to determine how and when the observed associations evolve, evaluate sex differences and mood-state effects, and support robust covariate modelling.

Conclusion

The current study demonstrates that higher Mito-PRS is associated with poorer sustained attention in youth with BD, suggesting that mitochondrial genetic variation at the molecular level may contribute to specific neurocognitive deficits early in the course of illness. This line of research positions mitochondrial function as a potential pathway underlying the neurocognitive deficits observed in BD and supports further research into bioenergetic targets for early intervention.

Declarations

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Author's contributions: NPK primarily wrote the manuscript and performed statistical analyses. CCZ conducted GWAS quality control and PRS calculations. MKD and AAS reviewed clinical data. BIG contributed to study conception, design, and assisted with manuscript preparation. All authors contributed to revisions of the manuscript and have approved the final manuscript.

Availability of data and materials: The dataset supporting the conclusions of this article is available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions. Supplementary Materials are available on the journal website.

Competing interests: Dr. Benjamin I. Goldstein acknowledges his position as RBC Investments Chair in Children's Mental Health and Developmental Psychopathology at CAMH, a joint Hospital-University Chair

between the University of Toronto, CAMH, and the CAMH Foundation. All other authors report no actual or potential conflicts of interest.

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Ethics approval and consent to participate: Participants and their parent/guardian(s) provided written informed consent. Ethical approval was granted by the research ethics board at Sunnybrook Research Institute (REB # 408-2011 and 409-2013). All data was collected at Sunnybrook Research Institute. However, all data was transferred with the Centre for Youth Bipolar Disorder's relocation to the Centre for Addiction and Mental Health (CAMH). Thus, ethics approval was also granted by CAMH Research Ethics Board (REB # 165/2020 and 168/2020).

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Figures

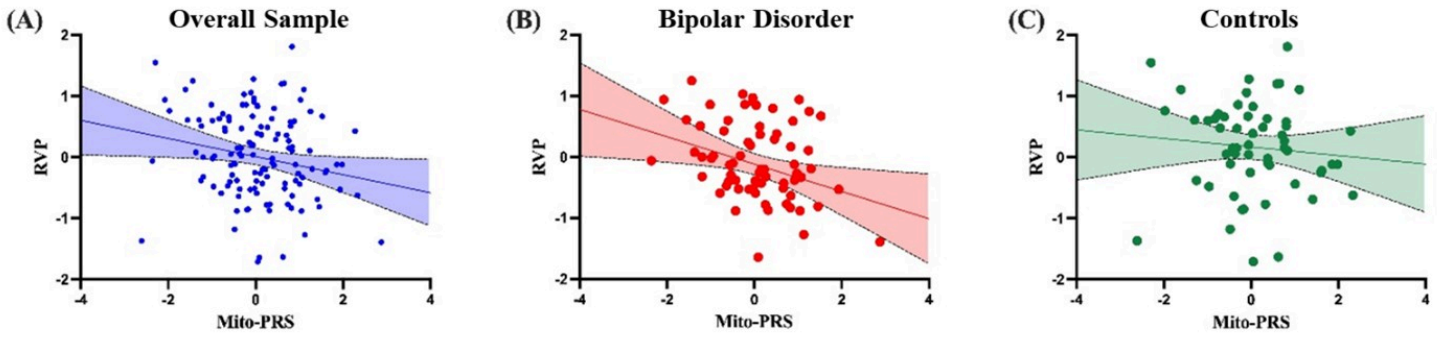


Figure 1

Association between mitochondrial polygenic risk scores (Mito-PRS) and the Rapid Visual Information Processing (RVP) task, a measure of sustained attention. Higher Mito-PRS was significantly associated with poorer performance on the RVP task in the overall sample (A) and within the bipolar disorder group

(B). There were was no significant association between Mito-PRS and RVP task performance in the control group (C).

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