Lipid metabolism is associated with temperament, corticosteroid, and hematological measures in infant rhesus monkeys (*Macaca mulatta*)

DEAR EDITOR,

Individuals can differ in how their behavioral and physiological systems are organized. The fact that these individual differences persist across life suggests they are supported by physical structures that may co-vary. Here, we explored three datasets associated with health and behavioral outcomes, which were obtained from infant rhesus monkeys during standardized assessment of biobehavioral organization. Variation in biobehavioral measures was related to variation in molecular pathways, as assessed by metabolomics. Plasma from infant male rhesus monkeys (*Macaca mulatta*) (*n*=52) was subjected to metabolite profiling. Principal component analyses identified multiple factors that explained 60%–80% of the variance in the metabolite measures. Correlational and regression analyses of corticosteroid, hematological, and temperament measures revealed significant relationships with indicators of lipid metabolism. Significant relationships were found for cortisol responses to stress and adrenocorticotropin (ACTH) stimulation, indicators of innate immunity (monocytes and natural killer (NK) cells), hemoglobin/hematocrit, and three measures of temperament. It will be important to replicate this first-of-a-kind study to determine whether the relationship between measures of biobehavioral organization and lipid metabolism are a general result, or one that is specific to early development.

The ability of individual organisms to achieve reproductive success is highly dependent on the organization of the individual's behavioral and physiological systems (referred to as its biobehavioral organization), which enable the animal to master essential tasks of life: e.g., finding and processing food successfully, finding prospective mates, rearing offspring, avoiding predators, and fighting pathogens. Individuals vary, however, in behavioral and physiological system characteristics. One concept that is valuable for describing and understanding variation in biobehavioral organization is temperament, whose definition often emphasizes its early appearance in development, its reflection of fundamental affective, motor, and attentional processes, its consistency across time and situations, and its presumed biological origin (Rothbart, 2012). The study of animal temperament/personality (both terms are typically used interchangeably in animal studies) has exploded in the past two decades, with investigations occurring in fields ranging from behavioral ecology to neuroscience to health and mortality (Barr, 2012; Blaszczyk, 2020; Capitanio, 2008). The fact that temperament, reflecting stable patterns of behavioral reactivity, is associated with health suggests that temperament patterns may themselves be associated with more global patterns of biological organization, as reflected in molecular pathways, which can impact disease processes.

Altered molecular pathway activities are frequently reflected in molecular constituent changes, which can be assessed by modern -omics technologies. The metabolome, a comprehensive list of small molecules, is believed to reflect the interaction between an organism's genome and its environment, which ultimately determines the phenotype. To date, however, only a handful of published studies have focused on the metabolome and temperament. In a population-based study, Altmaier et al. (2013) studied people with Type D personality, i.e., those high in negative affect and inhibited in social situations, which is linked to an increased risk of cardiovascular disease, greater stress reactivity, and metabolic syndrome. Their results showed that kynurenine is the principal metabolite found to differ between Type D and non-Type D individuals, and that four metabolic sub-networks can characterize Type D people. In a much smaller study, Ohnishi et al. (2017) found metabolite-level differences

associated with empathy in Buddhist priests and non-priest controls. Studies in nonhumans are similarly rare. Brand et al. (2015) studied metabolite profiles in the prefrontal cortex and serum of cattle and found 17 lipids and 10 other metabolites that could differentiate temperament types. Among rhesus monkey juveniles treated with fluoxetine, impulsivity is reportedly associated with three serum and five cerebrospinal fluid metabolites, which are related to two specific metabolic pathways (He et al., 2014; Su et al., 2016).

Here, we explored metabolite correlates of naturally occurring variation among indicators of biobehavioral organization. All data were obtained from a BioBehavioral Assessment (BBA) program (25 h long) conducted with healthy infant animals (3–4 months of age) at the California National Primate Research Center (CNPRC). We focused on three datasets from the BBA program that were relevant to disease processes. The first dataset comprised four temperament measures – Confident, Gentle, Vigilant, and Nervous – associated with diarrhea episodes (Gottlieb et al., 2018) and hyper-responsive airways, a major component of asthma (Capitanio et al., 2011b; Chun et al., 2013). The second dataset comprised plasma concentrations of the glucocorticoid cortisol, obtained from four blood samples drawn during a 25 h assessment period, and which reflect the initial stress response to separation and relocation (sample 1), response to sustained challenge (sample 2), and responses to dexamethasone (sample 3) and adrenocorticotropic hormone (sample 4). Our interest in cortisol stems from its central role in body metabolism, and that glucocorticoid concentrations are altered in a variety of diseases and psychiatric conditions (e.g., Glad et al., 2017; Staufenbiel et al., 2013). The third dataset involved a complete blood count and flow cytometry analysis performed on cells from sample 1, as leukocyte numbers are of importance in maintaining health and countering pathogenic infection.

In total, our study included 52 infant male rhesus monkeys born between 2003 and 2015 in 24 half-acre (0.2 ha) field corrals, each comprising 80–150 animals of all ages and both sexes. Each subject was born to a different dam and sire. Animals were tested under the BBA program (described in detail in Capitanio, 2017; Golub et al., 2009; see also Supplementary Information) at a mean age of 112.98 days (range: 103–120). All applicable international, national, and/or institutional guidelines for the care and use of animals were strictly followed, and all sample collection protocols complied with the current laws of the United States. All procedures were approved by the Institutional Animal Care and Use Committee of the University of California, Davis, USA.

Blood was drawn on four occasions during a 25 h period from non-fasted animals. In all cases, blood (1 mL for sample 1, 0.5 mL for the remaining three samples) was drawn from a femoral vein using non-heparinized syringes following manual restraint, then immediately transferred to tubes containing ethylenediamine tetraacetic acid (EDTA). Sample 1 (0.5 mL) was delivered to the CNPRC Clinical Laboratory for a complete blood count with manual differential and for

lymphocyte phenotyping using flow cytometry. The remaining 0.5 mL from sample 1, and samples 2, 3, and 4 were spun in a refrigerated centrifuge at 4 °C for 10 min at 1 277 g. Plasma was removed and frozen at −80 °C until cortisol assay (see Supplementary Information for details).

At the end of the 25 h testing period, the technician who performed the BBA rated the overall temperament of each animal using a list of 16 adjectives and a 1–7 Likert-type scale, with 1 reflecting the total absence of the behavior and 7 reflecting very high performance of the behavior. Exploratory and confirmatory factor analyses suggested a four-factor structure to the data: Vigilant (vigilant, not depressed, not tense, not timid), Gentle (gentle, calm, flexible, curious), Confident (confident, bold, active, curious, playful), and Nervous (nervous, fearful, timid, not calm, not confident). Adjectives preceded by "not" indicate that the item was reverse scored. Trait definitions and details on factor analyses and scale construction followed Golub et al. (2009).

For metabolite analysis, banked plasma samples from sample 1 were thawed, then centrifuged at 160 g for 5 min at 4 °C. Ice cold methanol (800 µL) was added to plasma (100 µL) and then vortexed. Samples were kept on ice for 1 h to allow proteins to precipitate. Afterwards, samples were centrifuged at 8 000 g for 10 min at 4 °C, with the supernatant dried in a SpeedVac and stored at −20 °C until further processing. Metabolite data were obtained using reversed-phase (RP) and hydrophobic interaction (HI) liquid chromatography online mass spectrometry and were processed as described in the Supplementary Information.

For the RP and HI mass spectrometry datasets, missing values were replaced by zeros, and individual items were retained for further analysis if at least 70% of the sample had non-zero values (three and four variables were deleted, respectively). Principal component analysis (PCA) with varimax rotation was performed on each dataset. A scree test identified five components in each dataset, and scales were constructed using a 0.5 cut-off for component loading and unit weighting. The five factors explained a total of 62.9% and 76.4% of the variance in the RP (363 variables) and HI data (1 172 variables), respectively. Factors were labeled R1 to R5 and H1 to H5. Relationships between metabolite scales and cortisol, hematology, and temperament were evaluated using Pearson product-moment correlations. Because of correlations between some metabolite scales, when more than one scale was significantly correlated with an outcome measure, we used multiple regression to identify which scale(s) remained a significant predictor once other scales were statistically controlled.

Metabolite scales H4 and H5 were associated with cortisol concentrations from samples 1, 2, and 4, but not 3. Scales H4 and H5 were significantly positively correlated with sample 1 (r=0.311, P=0.026; r=0.282, P=0.045, respectively), and follow-up multiple regression analysis revealed that H4 remained a significant positive predictor (P=0.033), while H5 became a trend predictor (P=0.056). For sample 2, the significant positive predictors in bivariate analysis were R4

($r=0.276$, $P=0.048$) and H5 ($r=0.498$, $P<0.001$). Regression analysis indicated that H5 remained a significant positive predictor ($P=0.001$), with R4 becoming non-significant ($P=0.523$). Finally, for sample 4, H5 was the sole significant positive correlate ($r=0.296$, $P=0.039$). Table 1 shows all correlations among BBA outcome measures and metabolite factors. Table 2 shows the principal metabolites loaded on each of the relevant factors.

Hematological measures were associated with H3, H5, and R4. Monocyte numbers were negatively correlated with H5 ($r=-0.295$, $P=0.036$), whereas lymphocytes and neutrophils showed no significant correlations. Among lymphocyte subsets, CD^{8+} CD^{3-} (which are principally NK cells: Ahmad et al., 2014) was negatively correlated with R4 ($r=-0.380$,

$P=0.007$) and H5 ($r=-0.371$, $P=0.010$); multiple regression analysis revealed that while the overall model was significant ($P=0.016$), neither regression coefficient was significant, suggesting that shared variance between R4 and H5 was associated with the NK cell percentage (bivariate correlation between R4 and H5 was $r=0.674$, confirming significant shared variance by these two components). No significant correlations were found with CD^{4+} (CD^{3+} CD^{4+}) or CD^{8+} (CD^{3+} CD^{8+}) T-cell numbers, or with percentages of B (CD^{3-} CD^{20+}) and T (CD^{3+} CD^{20-}) lymphocytes. Both hemoglobin and hematocrit values were each significantly correlated with three components: negatively with R4 ($r=-0.329$, $P=0.017$; $r=-0.345$, $P=0.012$, respectively), positively with H3 ($r=0.443$, $P=0.001$; $r=0.484$, $P<0.001$), and negatively with H5

Table 1 Summary of correlation and regression analyses

	R3	R4	H3	H4	H5	Regression
Cortisol						
Sample 1				$r=0.311^*$	$r=0.282^*$	H4: $P=0.033$ H5: $P=0.056$
Sample 2		$r=0.276^*$			$r=0.498^{**}$	H5: $P=0.001$
Sample 4					$r=0.296^*$	
Hematology						
Monocytes					$r=-0.295^*$	
NK cells		$r=-0.380^{**}$			$r=-0.371^{**}$	See note
Hemoglobin		$r=-0.329^*$	$r=0.443^{**}$		$r=-0.386^*$	H3: $P=0.005$
Hematocrit		$r=-0.345^*$	$r=0.484^{***}$		$r=-0.461^{**}$	H3: $P=0.002$
Temperament						
Vigilant			$r=0.278^*$			
Nervous		$r=0.475^{***}$	$r=-0.353^*$		$r=0.369^{**}$	R4: $P=0.013$ H3: $P=0.025$
Gentle	$r=0.280^*$	$r=-0.379^{**}$	$r=0.393^{**}$		$r=-0.292^*$	R4: $P=0.044$ H3: $P=0.030$

*: $P<0.05$, **: $P<0.01$, ***: $P<0.001$. Values in columns 2–6 are Pearson product-moment correlation coefficients and significance levels. Final column shows results of multiple regression when more than one factor was significant in bivariate correlations (direction remains the same as in bivariate analyses). Note: for NK cells, step was significant but individual coefficients were not, suggesting that shared variance between R4 and H5 was the significant predictor. See text.

Table 2 Components of five factors based on PCA of RP and HI datasets related to cortisol, temperament, and/or hematological data

R3	R4	H3	H4	H5
Pyroglutamic acid (C0 1879)[1]	L-Acetylcarnitine[4]	PC (34:3)[3]	PC (38:6)[3]	PE (38:5)[3]
	Hexanoylcarnitine[4]	PC (32:1)[3]	PC (36:5)[3]	Linolenic acid (C06426, C06427)[3]
Androsterone glucuronide (C11135)[2]	3-hydroxyoctanoyl carnitine[4]	LysoPC (18:1)[3]	DG (34:1)[3]	
Androsterone (C00523)[2]		LysoPE (22:6)[3]	DG (36`:0)[3]	
Androstanediol-glucuronide[2]		LysoPE (20:5)[3]	LysoPG (18:1)[3]	
			GalCer (30:1)[3]	
PC 44:7[3]		Pipecolic acid (C00408)[1]		
TG 55:7[3]		Asparaginyl-Lysine[1]		
TG 56:6[3]		Glucose (C00031)[1]		
		Glutamic acid (C00025, C00217)[1]		
		Glutamine (C00303)[1]		

[1]: Lipid metabolic pathways; [2]: Steroid hormones; [3]: Lipids; [4]: Intermediate products for energy generation from lipid tissue.

(r=–0.386, P=0.005; r=–0.461, P=0.001). Multiple regression analysis revealed that for both hemoglobin and hematocrit, H3 remained a significant positive predictor (P=0.005 and P=0.002, respectively).

Three of the four temperament measures were significantly correlated with the R3, R4, and/or H3 metabolite scales. Vigilant was positively correlated with H3 (r=0.278, P=0.048). Nervous temperament scores were correlated with R4 (r=0.475, P<0.001), H3 (r=–0.353, P=0.011), and H5 (r=0.369, P=0.008). Multiple regression analysis indicated that Nervous temperament remained positively associated with R4 (P=0.013) and negatively with H3 (P=0.025). Gentle temperament was positively correlated with R3 (r=0.280, P=0.044) and H3 (r=0.393, P=0.004) and negatively with R4 (r=–0.379, P=0.006) and H5 (r=–0.292, P=0.038). In regression analysis, Gentle temperament was predicted by negative scores on R4 (P=0.044) and by positive scores on H3 (P=0.030).

Our analysis identified various metabolite correlates in the three health-related datasets obtained from infant rhesus monkeys. Interestingly, all significant components were related to lipid metabolism. R4 consisted of intermediate products for energy generation from lipid tissue; the acylcarnitines L-acetylcarnitine, hexanoylcarnitine, and 3-hydroxyoctanoyl carnitine are essential compounds for the metabolism of fatty acids. H3 and H4 were mainly composed of lipid classes, including phosphatidylcholines, lysophosphatidylcholines, lysophosphatidylethanolamines, diacylglycerols (PC (34:3), PC (32:1), LysoPC (18:1), LysoPE (22:6), LysoPE (20:5), PC (38:6), PC (36:5), DG (34:1), DG (36:0)), lysophosphotidylglycerol LysoPG (18:1), and galactosylceramide GalCer (30:1)). H5 consisted of phatidylethanolamine PE (38:5) and the fatty acid linolenic acid. Lipids have many important functions in physiology, including energy metabolism and signal transduction mechanisms. In addition, they are part of the cellular membrane and post-translational protein modifications. The brain is made up of 20% lipids, and dysregulated lipid metabolism is implicated in several central nervous system (CNS) disorders (Crowe et al., 2007; D'Ambrosio et al., 2012; Hamazaki et al., 2013; Wei et al., 2013; Yadav & Tiwari, 2014).

Cortisol: Cortisol levels for samples 1 (reflecting stress associated with separation from mother and relocation to an indoor environment 2 h prior to sample collection), 2 (taken 5 h after sample 1, and reflecting responses to sustained disturbance), and 4 (taken after ACTH stimulation) were positively associated with H4 (sample 1 only) and H5 (all three samples). We note that the plasma used for metabolite analysis was drawn from sample 1; temporally, then, the metabolite and cortisol data from sample 1 were contemporaneous, whereas the metabolite data preceded the cortisol data from samples 2, 3, and 4. Because the metabolite data did not correlate with the dexamethasone-suppressed cortisol values from sample 3, the relationships between lipid levels and cortisol concentrations were not associated with

negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis.

The relationship between glucocorticoids and lipid metabolism is generally well known (e.g., McKay & Cidlowski, 2003). What is less well known, however, is how lipid metabolites relate to variation in adrenal function in normal subjects. Our results provide some of the first evidence that normal variation in cortisol concentrations is associated with fatty acid linolenic acid and phospholipid PE (main components of H5). Interestingly, an earlier study on rats demonstrated that administration of a mixture containing linolenic acid prior to exposure to stress can abrogate the cortisol response and learning deficits that typically accompany such experiences (Yehuda et al., 2000). Elevated fatty acid levels might protect neuronal membranes in the brain from the harmful effects of elevated corticosteroids. Intriguingly, therefore, our positive correlations between H5 and three cortisol measures may reflect an endogenous protective mechanism against neuronal damage. Clearly, however, more work is needed in this area.

Hematology: Both monocyte and NK cell numbers were negatively associated with H5 (NK cells were also negatively associated with R4), and hemoglobin and hematocrit values were positively associated with H3. Our data suggest that lipid/lipid metabolism indicators were more likely to be associated with innate immune system cells (monocytes and NK cells) than with adaptive immune system cells, none of which were correlated with metabolite data.

Given that hemoglobin and hematocrit are similar measures, they were associated with identical metabolite factors. Based on regression analyses, both showed significant positive correlation with H3. Very little is known about how these measures of gas transport are associated with lipid metabolism, although recent research on a large sample of hospital admissions showed an association between hematocrit and gross lipid profile – i.e., individuals with higher hematocrit values also had higher total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol (Lopes et al., 2018).

Temperament: Individuals with high values for H3 had higher scores for Vigilant and Gentle temperaments, but lower scores for Nervous temperament. In addition, R4 was a significant positive predictor of Nervous temperament and a negative predictor of Gentle temperament. All three temperament measures are reported to be associated with an increase in diarrhea events over a two year period (Gottlieb et al., 2018), and Nervous temperament is related to glucocorticoid desensitization and aggressive (rather than anxious) responses in challenging situations (Capitanio et al., 2011a). Vigilant temperament is associated with a pattern of blunted affective responses and cortisol responsiveness that generates a risk of poor respiratory function (Capitanio et al., 2011b; Chun et al., 2013). Gentle temperament reflects a coping style ranging from passive (high Gentle temperament) to more active coping (low Gentle temperament) (Koolhaas et al., 1999), and is linked to stereotypic behavior in monkeys

(Gottlieb et al., 2013). Unfortunately, little is known about the roles of lipids and lipid metabolism in temperament. The studies referenced earlier, relating dysregulated lipid metabolism with CNS disorders, were all carried out with blood serum or plasma specimens. Whether the observed lipid level differences are in fact mirroring the situation in the CNS or are due to alterations in the periphery or diet is unknown. In either case, they may represent biomarkers that, if confirmed, could have diagnostic applications. A recent study on the long-term treatment of juvenile macaques with the antidepressant fluoxetine revealed alterations in lipid classes, suggesting systemic changes in fatty acid metabolism that mirrored reported behavioral effects of treatment, including impulsivity (Tkachev et al., unpublished data). The same lipid change trend is apparent in both the cingulate cortex and cerebrospinal fluid of fluoxetine-treated macaques, suggesting that CNS lipid biosignatures may be reflected in the periphery, a prerequisite for eventual clinical translation.

Because there has been so little prior work examining metabolite differences in measures of biobehavioral organization in non-clinical populations, we consider our investigation exploratory and our results provisional. We note several limitations of this analysis. First, no females were assessed in this study. Second, it is possible that unmeasured variables, associated perhaps with growth or energy metabolism, may mediate the relationships found in our study. In addition, we note that the metabolomics analysis was untargeted, simply identifying metabolite classes associated with our outcome measures; thus, targeted analyses focusing on lipids are warranted. Finally, we reiterate that our subjects were infant rhesus monkeys, 3–4 months of age, which is roughly equivalent to a one-year-old human infant. This is a period of substantial brain development, particularly synaptogenesis (Granger et al., 1995) in which lipids, especially cholesterol, play an important role. Whether our results will generalize to older-aged animals is unknown.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

J.P.C. and C.W.T. designed the study; J.P.C. conducted BioBehavioral Assessment, performed data analyses, and wrote the bulk of the first draft of the paper. F.D. and C.W.T. performed metabolomics analyses and contributed to the writing of the manuscript. All authors read and approved the final version of the manuscript.

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