**Supplement Information**

**Supplement Table 1.**
GLM with Maternal CSF CRF (ng/ml) Concentrations as the Dependent Variable and Controlling for Paternity

|                     | df | F   | p    |
|---------------------|----|-----|------|
| Rearing Group       | 1  | 8.74| 0.011|
| Maternal CSF Glutamate Concentrations(ng/ml) | 1  | 15.58| 0.002|
| Rearing Group * Maternal CSF Glutamate Concentrations(ng/ml) | 1  | 16.29| 0.001|
| Paternity (n = 4)   | 1  | 0.57| 0.465|
| Error               | 13 |     |      |

**Supplement Table 2.**
GLM with Change in CSF CRF Concentrations in Response to VFD as Dependent Variable and Controlling for Paternity

|                     | df | F   | p    |
|---------------------|----|-----|------|
| Proportional Change CSF Glutamine in Response to VFD Exposure (ng/ml) | 1  | 7.80 | 0.019|
| Paternity           | 1  | 0.01| 0.90 |
| Error               | 10 |     |      |

**Supplement Table 3.**
GLM with Difference between Final HFD and Final LFD Phase of Maternal VFD as Dependent Variable and Controlling for Paternity

|                     | df | F   | p    |
|---------------------|----|-----|------|
| Proportional Change CSF Glutamate Difference in Response to VFD Exposure (ng/ml) | 1  | 16.22| 0.002|
| Paternity           | 1  | 3.20| 0.10 |
| Error               | 10 |     |      |
Supplement Table 4: Correlation Matrix of VFD Offspring CSF Monoamine Metabolites and Proportional Maternal CSF Glutamate Concentration Change in Response to VFD Exposure

|            | MHPG  | 5-HIAA | HVA   |
|------------|-------|--------|-------|
| MHPG       | 1.000 |        |       |
|            | p=    | p=    | p=    |
| 5-HIAA     | .75   | 1.000  |       |
|            | p=.03 | p=    | p=    |
| HVA        | .72   | .97   | 1.000 |
|            | p=.04 | p=.001| p=    |
| Maternal ΔCSF Glutamate Concentrations | .92 | .85 | .83 |
| In Response to VFD Exposure | p=.001 | p=.001 | p=.009 |

MHPG = CSF 3-methoxy-4-hydroxyphenylglycol concentrations (noradrenergic metabolite)
5-HIAA = CSF 5-hydroxyindoleacetic acid concentrations (serotonin metabolite)
HVA = CSF homovanillic acid concentrations (dopamine metabolite)
### Supplement Table 5a.
GLM using Offspring CSF Monoamine Metabolite Concentrations as Repeated Measures Dependent Variable Controlling for Paternity

| Effect | df | F   | p    |
|--------|----|-----|------|
|        | 1  | 2.79| 0.155|
|        | 1  | 21.40| 0.005|
|        | 5  |     |      |
|        | 2  | 1.64| 0.24 |
|        | 2  | 13.25| 0.002|
|        | 10 |     |      |

R1= Repeated Measures. CSF Monoamine metabolites = CSF 5-HIAA, CSF HVA and CSF MHPG concentrations.

### Supplement Table 5b: Univariate Results for GLM of Offspring CSF Monoamine Metabolite Concentrations and Controlling for Paternity.

| Effect           | df | MHPG F | MHPG p  | 5-HIAA F | 5-HIAA p | HVA F | HVA p |
|------------------|----|--------|---------|----------|----------|-------|-------|
| Paternity        | 1  | 0.13   | 0.730   | 7.57     | 0.040    | 0.13  | 0.73  |
| ΔCSF Glutamate   | 1  | 27.27  | 0.003   | 33.76    | 0.002    | 15.75 | 0.01  |
| Error            | 5  |        |         |          |          |       |       |

ΔCSF Glutamate = Proportional Maternal CSF Glutamate Concentrations In Response to VFD Exposure
Supplement Table 6: General Linear Model Assessing the Effects of Maternal Variable Foraging Demand Versus Controls on Juvenile CSF 5-HIAA concentrations covaried for Sex, Weight and Age

| Effect          | df | F    | p    |
|-----------------|----|------|------|
| VFD             | 1  | 8.17 | 0.01 |
| Weight          | 1  | 0.04 | 0.85 |
| Age             | 1  | 0.60 | 0.45 |
| SEX             | 1  | 2.40 | 0.14 |
| Error           | 17 |      |      |

VFD effect = Partial $\eta^2 = 0.32 (>2$ fold a large effect size)

Supplement Table 7.
Spearman Correlation between Maternal ΔCSF Glutamate Concentrations in response to VFD Exposure and Juvenile Offspring CSF 5-HIAA Concentrations

| Valid N | Spearman R | t(N-2) | p-value |
|---------|------------|--------|---------|
| VFD-induced proportional mat glut response & Juv. CSF 5-HIAA | 8 | 0.94 | 7.15 | 0.0004 |
**Supplement 8.**

**Bootstrapping test for Bivariate Correlation between Maternal ΔCSF Glutamate Concentrations in response to VFD Exposure and Juvenile Offspring CSF 5-HIAA Concentrations**

| Bootstrap Specifications |
|--------------------------|
| **Sampling Method**      | Simple                        |
| **Number of Samples**    | 1000                          |
| **Confidence Interval**  | 95.0%                         |
| **Confidence Interval Type** | Percentile                 |

| Correlations          |              |              |
|-----------------------|--------------|--------------|
| **HIAA**              | **PRPGLUT**  |              |
| Pearson Correlation   | -855**      | 1            |
| Sig. (2-tailed)       | .007         |              |
| N                     | 8            | 8            |
| Bootstrapc Bias       | 0            | -.001        |
| Std. Error            | 0            | .099         |
| 95% Confidence Interval Lower | 1 | -.995 |
|                        | Upper        | 1 | -.655 |

**. Correlation is significant at the 0.01 level (2-tailed).
Supplement Figure 1. Juvenile Offspring CSF 5-HIAA Concentrations by Paternity.

Overlap is noted for each of four fathers. Father C is associated with a wide range of CSF 5-HIAA values not supporting a paternal contribution to offspring CSF 5-HIAA concentrations.

Potential Maternal Heritable Contributions

All mothers gave birth to their offspring during the same annual breeding cycle - therefore none of the offspring are siblings. However, it is possible that mothers participating in the study may be sisters. No new Bonnet Macaques have been added to the breeding colony in at least 30 years and the colony had its inception in the early 1960s, which at its peak was only 300 subjects. The relatedness of mothers could therefore be quite high. That would imply that offspring in the current study are conceivably at most second-degree relatives. The records available do not permit this potential confound to be quantified. However, because of random assignment of females to their specified social groups, hereditary bias by virtue of maternal genetic effects appears unlikely.
Supplement to Introduction (SI):

**SI1) Significance of CRF/Glutamate Interactions and Early Life Stress**

Translational reports in human, nonhuman primate and rodent subjects have collectively supported a critical role for activation of the central corticotropin-releasing factor (CRF) system in certain human anxiety and mood disorders [1-4]. Moreover, persistent activation of central CRF systems constitutes a putative marker of allostatic overload [5]. Central CRF neurotransmission, through its action at CRF2 receptors, facilitates glutamatergic synaptic transmission [6], suggesting a bidirectional excitatory relationship. Maternal CSF CRF over-expression in response to maternal variable foraging demand (VFD) is synchronized between mother and infant [7], with persistent increases observed at the young adolescent phase of development of VFD-offspring [4] which is sustained into adulthood [8]. In the current study, we wished to test the hypothesis whether relative activation of maternal CSF glutamate concentrations may be associated with a “transmission of stress-response” through a similar, putative “mirroring” process that would then predict other neurobiological alterations in grown offspring with relevance to a human affective vulnerability phenotype.

**SI2) Significance of Persistent Elevations of Cisternal 5-HIAA**

Several lines of evidence indicate that accumulation of serotonin in the extracellular space surrounding the dorsal raphe serotonin neurons may represent an important pathophysiological feature in major depression and SSRI-treatment resistance [9]. First, elevations of raphe serotonin along its full rostro-caudal extent are observed in the brains of suicide victims with proportional inverse decreases of serotonin observed in certain prefrontal cortical areas [10]. Second, in support of this view of serotonin system pathophysiology, we reported, in VFD-reared nonhuman primate subjects, specifically, an inverse relationship between elevated cisternal CSF-5-HIAA concentrations and hippocampal volume reductions [11]. Macaque CSF obtained from cisterna magna is in close proximity to the midbrain raphe nucleus and cisternal CSF 5-HIAA may be more reflective of serotonin accumulation surrounding the raphe nucleus than CSF 5-HIAA concentrations measured in distant lumbar areas, although direct evidence remains to be demonstrated. We hypothesized that elevations of peri-raphe extracellular serotonin would pose a significant impediment to the expected
action of SSRIs of increasing serotonin neurotransmission at projection areas, by increasing peri-raphe serotonin in an already flooded raphe nucleus [12]. Conversely, we hypothesized that drugs that block regionally specific release of glutamate would tend to rescue serotonin neurotransmission through reducing glutamate release into the vicinity of the dorsal raphe [12]. Thus, in a validated nonhuman primate model, based on disruption of the maternal-infant relationship, identification of plausible maternal origins for elevated cisternal CSF 5-HIAA in young adolescent VFD-reared subjects is warranted. Based on an intimate relationship between glutamate and serotonin [13], maternal CSF glutamate activation may provide an initial transgenerational impetus for persistently high peri-raphe serotonin in comparison to non-VFD subjects. The dopamine and serotonin metabolites -- homovanillic acid (HVA) and 5-HIAA respectively -- are consistently correlated [14] possibly due to serotonin modulation of the ventral tegmental area [15], making HVA an important corollary measure.

**Supplement to Methods (SM):**

**SM1) Subjects and Samples**

Due to blood-contaminated CSF samples, either prior to or following the VFD procedure, to avoid potentially inaccurate measurement of glutamate, data were unusable on four maternal subjects (fourteen subjects were available for longitudinal comparison). One pair of maternal CSF CRF values were also not available (thirteen subjects were available when analyses including glutamate and CRF were performed).

For the cross-sectional analyses, dyads from two pens with early VFD onset provided post-VFD samples whereas non-VFD exposed (pre-VFD) subjects were housed in two separate pens.

The SUNY Downstate Medical Center Nonhuman Primate Facility was utilized for subject housing and the Institutional Animal Care and Use Committees of SUNY Downstate Medical Center approved the study. Post-VFD experimental manipulations of offspring were not allowed to prevent confounding of the VFD-rearing effects [16]. Subjects were housed in pens approximately 2 m × 4 m × 2 m in dimension with the 4-m representing the depth of the pen. Perches were available at two levels within each pen. Water was available at all times from an automated watering system with animal-activated spigots. All pen walls were opaque. Two
large one-way hinged glass windows were located at the front of the pen for investigator observations.

SM2) CSF Sampling:
Sampling was performed between 11:00 AM to noon for all subjects. Maternal-infant dyads were ushered into carrying cages from their home pen, a weekly procedure required for cleaning the pens. Dyads were then released into a restraint cage where they received intramuscular ketamine (15mg/kg). Mothers were rapidly anesthetized in the squeeze cage and as the mothers underwent anesthetic sedation, infants were administered intramuscular ketamine shortly thereafter. Once the mothers’ CSF and bloods had been drawn, the infants had CSF and blood samples drawn immediately thereafter. Approximately 10cc’s of maternal blood (5 cc’s for infants) were drawn from the saphenous vein and three cc’s of maternal CSF (1.5cc’s for infants) were drawn at each sampling [for details of CSF sampling procedure, see Scharf et al [17]]. CSF samples were emptied into Gant tubes, and immediately placed on dry ice [18]. Capture stress was minimized in this procedure and timing of anesthetization meant there was no separation of mother-infant dyads at any time. Sedation of dyads was achieved in less than five minutes after exiting the carrying cage reducing the variance of stress response.

SM3) CSF Glutamate and CSF Glutamine Assays
Chromatographic separation is achieved using a reversed-phase 2 μ C-18 column (TSK-Gel), and a gradient mobile phase consisting of A: Sodium acetate and triethylamine (pH = 5.03) and B: 60% acetonitrile in water. A 40 μl sample of CSF is derived on-line with 60 μl of OPA reagent prior to injection of 20 μl. A linear gradient starting from 93% solvent A to 75% solvent A for 15 minutes eluted glutamate at approximately 9.2 minutes. The glutamate peak was observed using a fluorescence detector with the excitation and emission wavelengths set at 320 nm and 455 nm, respectively. Six calibration standards from 0.1 to 3.2 nm/ml were run with each batch of samples although coefficients of variation are not available. Similar methods were used for CSF glutamine.

SM4) CSF CRF Assays
The assay has a sensitivity of 2.5 pg per tube and intra- and interassay coefficients of variation of 3-6% and 10-13%, respectively. The laboratory personnel conducting the CRF
radioimmunoassay were blind to the rearing status of the subjects' samples. Infant CSF CRF was measured in the same batch as maternal CSF CRF.

**SM5) Maternal-Infant Proximity Scoring**

A score of 1 was given when mother and infant were in direct physical “ventral-ventral” contact. A score of 5 was given when the dyad was at a maximum distance in the pen, as permitted by the pen dimensions. A score of two was awarded when the mother and infant were less than one meter apart. A score of three was awarded if maternal-infant distance was one meter. A score of four was awarded when maternal-infant distance was in between a three and a five -- that is between maximal maternal distance from infant versus > 1 meter from infant. The distance measured was based on the initial observation of the dyad during the 5 separate observations. Although there was only one behavioral observer, staff performing behavioral observations had previously been trained to achieve an interrater reliability of >0.9.

**SM6) Statistical Analyses of Confounds including Heritability** As potential variability was introduced by certain confounds -- such as time to capture, time to sample retrieval and ketamine effects – which would tend to diminish effect sizes, as well as the risk of a type I error through exploratory testing, we determined the effect sizes (partial η²) of the primary findings of the study. Effect sizes exceeding 3 fold greater than a large effect size [19] would suggest that potentially confounding variables were not accounting for sufficient variance to obscure the primary findings. In addition, to exclude heritable paternity effects, analyses were rerun using paternity as a control variable.

**Supplement to Results (SR):**

**SR1) Cross-sectional analysis for maternal CSF glutamate and glutamine concentrations in relationship to Maternal CSF CRF Concentrations:**

Results remained significant following covarying for maternal age and then infant age. There were no paternity effects \( F_{(1,13)} = 0.57; p = 0.46 \) and results remained unchanged when controlling for paternity effects (Supplement Table 1). No effects were evident using CSF glutamine concentrations as a predictor variable.
Further Examination of Δ Maternal CSF Glutamate Concentrations

Based on the longitudinal analyses above, it must be considered how Δ maternal CSF glutamate concentrations can correlate with maternal and offspring neurobiology and dynamic maternal-infant attachment patterns when the net change from pre- to post-VFD exposure was close to 0. We therefore performed additional analyses to understand Δ maternal CSF glutamate concentrations under the prolonged and cumulative allostatic stress of VFD exposure. First, there was no correlation between pre-VFD and post-VFD maternal CSF glutamate concentrations ($r = -0.16, N = 14, p = 0.58$). Although the change of the group mean of maternal CSF glutamate concentrations comprised a negligible 0.5% increase over baseline following VFD exposure, the standard deviation of Δ maternal CSF glutamate concentrations represented 76% of the pre-VFD mean of maternal CSF glutamate concentrations, suggesting that although there was minimal mean group change, individual change was marked. In fact, the mean of the individual absolute % change of maternal CSF glutamate concentrations was 47% of pre-VFD levels. By contrast, for maternal CSF CRF concentrations ($N=13$) the mean group change over baseline comprised 31% (paired t-value $= -3.4, df = 12, p = 0.005$), while the standard deviation of Δ maternal CSF CRF concentrations represented 33.0% of the pre-VFD mean maternal CSF CRF concentrations. The mean of the individual absolute % change of maternal CSF CRF concentrations was 50% of the pre-VFD levels considered in the context of a mean group change of 31%. Unlike CSF glutamate, maternal CSF CRF concentrations showed a significant increase in response to VFD, but the standard deviation of Δ CRF/pre-VFD mean CRF was less than half of the corresponding measure for maternal CSF glutamate concentrations [$\chi^2 = 19.18; p< 0.0001$ for a CRF/glutamate comparison] using the following 2X2 table:

| % Δ group mean Glutamate | % Δ group mean CRF |
|--------------------------|---------------------|
| % SD/pre-VFD Glutamate   | % SD/pre-VFD CRF    |

Δ maternal CSF glutamate concentrations were not attributable to pen effects (subjects were housed in four separate pens) [$F_{(3106)} = 0.28; p = 0.84$]. Of note, pre-VFD maternal CSF glutamate inversely predicted Δ glutamate ($r = -.84; N = 14; p < 0.001$) whereas Δ glutamate positively predicted post-VFD maternal CSF glutamate ($r = .66; N = 14; p = 0.009$).

Maternal CSF Glutamate/Glutamine Ratios:
Ratios have been used in previous CSF studies examining both glutamate and glutamine concentrations [23]. Therefore we computed ratios using CSF glutamate/(CSF glutamine/1000) to create usable numeric units. No effects were observed over and above those described above.

**SR3) Dyadic Proximity:**
No paternity effects were observed and results remained significant when controlling for paternity (Supplement Table 3). There was no sex effect or infant age or maternal age effect on change in dyadic proximity from the final LFD to final HFD phase.

**Supplement to Discussion (SD):**

**SD1) Additional CSF Glutamate Points**
The within-subject longitudinal analysis of the same cohort demonstrate that mothers undergoing VFD exposure do exhibit a relative activation (or relative deactivation) of maternal CSF glutamate concentrations despite stability of the mean glutamate. Using pre-VFD glutamate as a denominator, proportional glutamate controlled for the magnitude of change in response to VFD in relation to the baseline. The lack of group differences for infant variables -- sex distribution, age or weight -- or maternal variables -- age or weight -- rendered it unlikely that the glutamate-CRF association observed post-VFD exposure was attributable to any of the independent variables. Moreover, controlling for infant age or maternal age did not affect the significance of the effects. Although multiple sites of intersection between glutamate and CRF exist [24], the cerebellopontine angle, from which cisternal CSF is drawn, is reasonably close to the dorsal raphe, where CRF and glutamate co-localization has been documented [25].

**SD2) Significance of 5-HIAA findings**
It should be noted that juvenile or young adolescent CSF 5-HIAA elevations were noted in two previous VFD cohorts [26, 27]. Elevations of CSF 5-HIAA have also been noted in subordinate rhesus females [28]. The origins of CSF 5-HIAA elevations can be assigned, at least in part, to alterations in maternal CSF glutamate during VFD exposure. No doubt there are multiple other sources for individual variation of CSF 5-HIAA concentrations, such as nonhuman primate serotonin transporter polymorphisms [29, 30], inflammatory processes [31] and epigenetic influences [32] to name a few. Nevertheless, that peri-raph human serotonin is increased in
suicide while cortical sites exhibit low serotonin levels [10] is noteworthy. CSF 5-HIAA
elevations in VFD-reared subjects are also associated with decreased hippocampal volume and
decreased white matter integrity [11]. In addition, of potential public health relevance,
elevated peri-raphe serotonin has been posited to set the stage for SSRI resistance [12].

**SD3 “Individual” versus “Social” Homeostasis of Maternal CSF Glutamate Concentrations**

Curiously, the anticipated depletion of maternal CSF glutamine concentrations expected in
stress-induced release of glutamate [20] was absent. These data suggest that, similar to the
absence of mean change in maternal CSF glutamate concentrations, homeostatic control over
the group mean of maternal CSF glutamate concentrations was maintained despite exposure to
conditions of allostatic overload (unlike CSF glutamate, numerical reduction in CSF glutamine
was observed in response to VFD exposure). Although group mean change of maternal CSF
glutamate concentrations was minimal, *individual* activation (or de-activation) of maternal CSF
glutamate concentrations in response to VFD-exposure was an important predictor central to
the study. A similar absence of plasma cortisol group mean change in response to VFD
exposure has been noted [21, 22].

In the current study, negligible differences for mean dyadic-distance between the final LFD and
final HFD phases were also noted, indicating the importance of consideration of individual
differences for both biology and behavior. These data link proportional Δ maternal CSF
glutamate concentrations in response to VFD to specific features of dyadic attachment further
prompting examination of long-term neurobiological sequelae.

The data, taken collectively, suggest a process of *individual* homeostatic adjustment of
maternal CSF glutamate concentrations while nevertheless concomitantly adjusting each
individual to achieve a biologically-determined maintenance point of the “social group” mean.
Although there are sizeable individual shifts in maternal CSF glutamate in response to VFD-
exposure, either represented as the standard deviation of Δ glutamate/ pre-VFD mean (76%) or
individual absolute % change divided by pre-VFD levels (47%), the group mean is maintained
within an extremely narrow range. It should be noted that subjects came from different pens,
but were aware of other subjects in neighboring pens through frequent vocalizations.
Although maternal CSF glutamate concentrations appear to be under a “homeostatic control”
process during VFD-induced allostasis, by contrast, CRF release into the cisternal CSF responds
directly to the VFD-induced allostatic load with a 31% increase in the group mean for maternal CSF CRF concentrations and a less pronounced effects on individual variability -- with the standard deviation of Δ maternal CSF CRF concentrations representing only 33.0 % of the pre-VFD maternal mean concentrations. Statistical comparison of the differential patterns of response to VFD exposure – homeostasis of glutamate and increases in CRF – were significant.

**SD4 Limitations including Lack of control for Multiple Testing**

Concerns that multiple testing in the current study may lead to a Type 1 error are addressed through demonstration that the key findings described above each yield effect sizes at least three-fold greater than a large effect size. Similarly, the very large effect sizes observed in the study despite the limited number of subjects, a constraint inherent to nonhuman primate studies, counters the view that other potential confounding factors that relate to the variability in time to capture or time to specimen retrieval are influencing the findings.
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