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Developmental Ambient Air Pollution Exposure in Mice Alters Fronto-Striatal Neurotransmitter System Function: Male-Biased Serotonergic Vulnerability

Deborah A. Cory-Slechta *, Katherine Conrad, Elena Marvin, David Chalupa, Gunter Oberdörster and Marissa Sobolewski

Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY 14642, USA; bachmannkatherine@gmail.com (K.C.); elena_marvin@urmc.rochester.edu (E.M.); david_chalupa@urmc.rochester.edu (D.C.); gunter_oberdorster@urmc.rochester.edu (G.O.); marissa_terry@urmc.rochester.edu (M.S.)
* Correspondence: deborah_cory-slechta@urmc.rochester.edu

Abstract: Air pollution (AP) exposures have been associated with autism (ASD), schizophrenia (SCZ), and attention deficit hyperactivity disorder (ADHD), male-biased neurodevelopmental disorders that are linked to alterations in brain fronto-striatal neurotransmitter systems. The current study sought to assess how developmental exposures of mice to inhaled ambient ultrafine particle (UFP) air pollution, considered its most reactive component, alters fronto-striatal functional correlations. Mice were exposed via inhalation to concentrated ambient UFPs from postnatal days (PND) 4–7 and 10–13. Frontal cortex, striatum, and serum were collected at PND14 and PND50 to evaluate both acute and persistent effects. UFP-induced changes, more extensive and persistent in males, included elimination of frontal cortical kynurenine correlations with striatal neurotransmitter function, persistent immunosuppression of approximately 50%, and striatal neurotransmitter turnover correlations with serum corticosterone. More limited effects in females did not show persistence. Collectively, these findings depict an apparently physiologically-integrated UFP-induced persistent male-biased vulnerability to brain fronto-striatal system dysfunction that could contribute to behavioral deficits associated with neurodevelopmental disorders. Further studies are needed to ascertain the interactive physiological mechanisms of male fronto-striatal vulnerability and their relation to behavioral impairments, mechanisms of apparent female compensation, and specific contaminants of AP that underlie this vulnerability.

Keywords: ultrafine particles; fronto-striatal system; kynurenine; glutamate; neurodevelopment

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1. Introduction

An accumulating body of evidence indicates that prenatal exposure to air pollution (AP) has adverse impacts on brain and neurodevelopment. Findings have included such consequences as neurodevelopmental delays [1], impaired cognitive functions [2], behavior problems [3], and memory and attention-related impairments [2], as well as structural alterations in the brain [4,5]. Such effects in children have been described across a range of extant ambient exposure concentrations, with levels of $PM_{2.5}$ (particulate matter $\leq 2.5\ \mu m$ or less) exposures, where reported, being as low as 11 $\mu g/m^3$ [6]. These effects of AP likely contribute to the corresponding increase in evidence that AP increases risks for neurodevelopmental and psychiatric disorders [7,8] that, to date, as supported by systematic reviews, include autism spectrum disorder (ASD) [9,10] and attention deficit hyperactivity disorder (ADHD) [11,12], as well as schizophrenia (SCZ) [13]. Questions remain as to specific periods of gestational vulnerability.

While distinct conditions, these neurodevelopmental and psychiatric disorders also share multiple characteristic features [14] and male-biased prevalence rates, and can be highly co-morbid [15,16]. Other shared characteristics include ventriculomegaly, hypomyelination, interhemispheric dysconnectivity [17], and cytokine alterations [18–20], as well as behavioral impairments including cognitive and impulsivity deficits [21,22].

Correspondingly, studies from our laboratory in mice have demonstrated that impacts of inhaled air pollution, specifically concentrated ambient ultrafine particulate (UFP) matter, considered the most reactive component of air pollution, can reproduce many of these shared features of neurodevelopmental disorders when exposures occur during the early postnatal period, a time period considered equivalent to the human third trimester for brain development [23]. Exposures to concentrated ambient ultrafine particle air pollution for 4 h/day from postnatal days 4–7 and 10–13, for example, have resulted in effects that include ventriculomegaly [24], hypomyelination [25], cytokine alterations [24], and impulsive behaviors [26,27] that were male-biased, consistent with the male bias in the prevalence of these neurodevelopmental disorders [28] that likely reflects sex differences in the trajectories of brain development and regional network integration [29].

Another shared feature of ASD, ADHD, and SCZ is the modification of brain fronto-striatal systems. Frontal cortical systems develop an organization of parallel networks with subcortical regions, including both dorsal and ventral striatum [30], within which interactive actions of glutamatergic, dopaminergic, and serotonergic neurotransmitters serve to mediate behavioral functions [31]. As a network of distinct but overlapping systems, fronto-striatal circuits are critical to the mediation of multiple behavioral processes, such as rewarded behaviors and cognitive functions [32,33], i.e., behavioral domains that are modified in these neurodevelopmental disorders [34–36].

With respect to specific neurochemical changes within these systems, alterations in glutamatergic signaling in fronto-striatal circuitry are reported in individuals diagnosed with ASD that appear to be related to inhibitory control [37,38]. In the case of ADHD, an insufficient GABAergic response of the fronto-striatal circuitry has been linked to reduced attention control [39], and glutamatergic dysfunction to hyperactivity and impulsivity, in adult ADHD [40]. Functions such as timing and attention and working memory deficits in SCZ have been reported to be likely due to dysfunction of dopamine and GABA in cortico-striatal circuitry [41]. Alterations in glutamatergic functioning and an excitatory–inhibitory imbalance are seen in ASD [42] and are prominent in SCZ [43] and ADHD [40]. In addition, dopaminergic system alterations are involved in these neurodevelopmental disorders [44,45], with methylphenidate, a dopamine reuptake blocker, used in the treatment of ADHD [46]. Alterations in dopaminergic systems have also been proposed as a basis for ASD [47,48] and have long been considered to contribute to SCZ [49]. In addition, alterations in serotonergic function characterize each of these neurodevelopmental disorders, including the hyperfunction of serotonergic pathways in SCZ [50]. Reductions in brain serotonin levels have recently been described in ASD [51], while studies using PET imaging have shown alterations in interregional molecular associations of the serotonin transporter in individuals with attention deficit disorder [18].

Similarly, as described above, early postnatal exposures of mice to inhaled concentrated ambient UFP lead to alterations in brain neurotransmitter levels. These include changes in levels of glutamatergic, serotonergic, and dopaminergic neurotransmitters in the frontal cortex and in the striatum, with outcomes dependent upon brain region, sex, and the UFP exposure concentration [24,52] as well as potential co-occurring risk factors [53]. However, what remains unclear is how these neurotransmitter changes are related between the frontal cortex and striatal regions and thereby potentially relate to fronto-striatal function. Such an understanding is ultimately requisite to predicting behavioral aberrations and defining the mechanisms of UFP-induced behavioral toxicity.

The current study therefore sought to further advance the understanding of UFP exposures on brain fronto-striatal systems' development and trajectory across time. For that purpose, correlational patterns of changes in the brain's frontal cortex and striatal neurotransmitter systems were determined both immediately after postnatal UFP exposures, i.e., acutely at postnatal day 14 (PND14), and again at PND50 to determine the persistent effects through development, potential reversibility of early changes, and/or latent onset of effects in response to earlier exposures. To determine these relationships, multivariate correlation analyses of the frontal cortex with striatal neurotransmitters at each time point were examined.

Inflammation is a shared risk factor for neurodevelopmental and psychiatric disorders [54–56], and inflammation can also be related to activation of the hypothalamic–pituitary–adrenal (HPA) axis [57]. Air pollution is an inflammatory stimulus that has been shown to influence inflammation-related proteins, even in young children [58], that is also associated with HPA axis activation [59]. Consequently, as cytokine and corticosterone changes have also been found to be critical to fronto-striatal systems in terms of brain development and function and thus to indirectly influence behavioral functions [60,61], measures of peripheral cytokines and corticosterone were also examined in relation to neurotransmitter changes.

2. Materials and Methods

2.1. Animals

C57BL6/J mice were kept, bred, and exposed as previously described [24–26,62]. Briefly, mice were bred monogamously, the pups were housed solely with the dam and were weaned on postnatal day (PND) 25. Mice were housed in standard mouse caging with 1/8″ high performance bedding (BioFresh, Ferndale, WA, USA), under a 12 h light-dark cycle maintained at 22 ± 2 °C, and fed standard Purina rodent chow, at the University of Rochester Medical Center. Following weaning, mice were pair-housed by sex and treatment group for the duration of the study. To preclude litter-specific effects, only single pups/sex/litter were used for each endpoint in these studies. Sample sizes were $n = 10$–12 per sex per treatment group. All mice were used and treated via protocols approved by the University of Rochester Institutional Animal Care and Use Committee and Committee on Animal Resources (Protocol number 102208/2010-046E), and in accordance with NIH guidelines. Mice were euthanized at either PND 14 or PND50 when brain tissue and serum were harvested for various analyses. Group mean ± standard error body weights at PND14 in grams were 6.23 ± 0.17, 6.02 ± 0.17, 6.24 ± 0.18, and 6.42 ± 0.15 for female Air, female UFP, male Air, and male UFP, respectively, and did not differ by treatment group.

2.2. Exposure

Pups were placed in small groups by litter in compartmentalized whole-body exposure chambers and exposed to filtered air (Air) or concentrated ambient ultrafine particles (UFPs) air pollution using the Harvard University Concentrated Ambient Particle System (HUCAPS) fitted with a size-selective inlet and a high-volume ultrafine particle (≤100 nm) concentrator (10–20×) that takes in outdoor air at 5000 L per minute and concentrates the ambient UFP component, as previously described [24,26,52,63]. Exposures lasted for 4 h per day from 0700–1100 for 4 days per week from PND (postnatal day) 4–7 and PND10–13, with exposure timing corresponding to peak vehicular traffic outside the intake valve of the HUCAPS instrumentation (Monday–Thursday). PND 4–14 is considered equivalent to the human third trimester for brain development [23]. A condensation particle counter (TSI, Shoreview, MN, 3022A) provided particle counts. Mass concentration was calculated using idealized particle density (1.5 g/cm^3). A Scanning Mobility Particle Sizer (SMPS) was used to determine particle size distribution and median particle diameter + geometric standard deviation. The flow of UFP-enriched and filtered air was maintained at 35–40% relative humidity and 77–79 °F. Ultimate exposure concentrations are dependent upon air pollution levels at the time of exposure. In the current studies, the exposure mass concentrations from these exposures averaged 44 μg/m^3 and the average particle size was 87.7 nm (Figure 1).

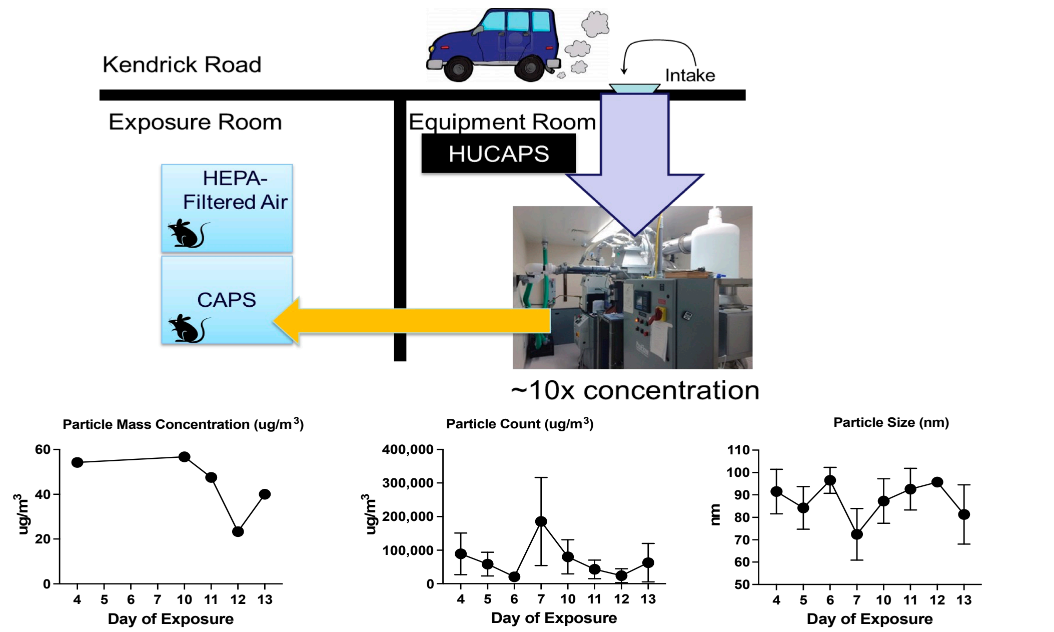

Figure 1. Group mean ± SE values for particle size, particle mass concentration (μg/m^3), and particle counts (μg/m^3) across days of concentrated ambient UFP exposures.

2.3. Neurotransmitter Analyses

Frontal cortex and striatal concentrations of various neurotransmitters were quantified by the University of Rochester Mass Spectrometry Core: DA (dopamine), DOPAC (3,4-dihydroxyphenylacetic acid), HVA (homovanillic acid), Tyr (tyrosine), Glu (Glutamate), GABA (γ-aminobutyric acid), Gln (glutamine), Kyn (kynurenic Acid), 5-HT (serotonin), 5-HIAA (5-Hydroxyindoleacetic acid), and Trp (tryptophan). Tissues were thawed, weighed, diluted in 75 μL of ice-cold acetonitrile (50%, *v*/*v*), and homogenized for 10 s via ultra-sonication (SLPe digital sonifier, Branson Ultrasonics Corp., Danbury, CT, USA). The homogenate was centrifuged at 10,000× *g* (4 °C) for 20 min. The resulting supernatant was collected and centrifuged at 10,000× *g* (4 °C) for 20 min, after which the new supernatant was collected and stored at −80 °C until analysis.

Stock solutions of DA, DOPAC, HVA, Glu, GABA, Glu, Kyn, 5-HT, 5-HIAA, and Trp (Sigma Aldrich, St. Louis, MO, USA) were made at 5 mg/mL in ddH_2O, with the exception of Tyr, which was made in 0.2 M HCl. A standard mixture was created in ddH_2O, with analyte concentrations varying in accordance with prior range-finding studies, in order to account for region-specific variations in endogenous neurotransmitters. This stock solution was derivatized using 13C6 benzoyl chloride (BzCl, Sigma Aldrich) using a method adapted from Wong et al. [64], to create internal standards for each individual neurotransmitter. The derivatized internal standard mixture was aliquoted and frozen at −80 °C for long term storage. Internal standard aliquots were thawed, then diluted in 50% acetonitrile with 1% sulfuric acid prior to being added to the samples. Prior to analysis, samples were derivatized following the same procedure. In brief, samples were centrifuged at 16,000× *g* for 5 min to remove debris, then 20 μL of the resulting supernatant was placed in a clean LoBind tube (Eppendorf, Leipzig, Germany). Next, 10 μL of 100 mM sodium carbonate, 10 μL of 2% BzCl in acetonitrile, and 10 μL of the respective internal standard were added in sequence. Then, 50 μL of ddH_2O was added to reduce the organic concentration prior to injection. Samples were centrifuged once more to pellet any remaining protein, and the supernatant was added to a clean autosampler vial.

LC-MS/MS analysis was carried out by a Dionex Ultimate 3000 UHPLC coupled to a Q Exactive Plus mass spectrometer (Thermo Fisher, Waltham, MA, USA). Analytes were separated on a Waters Acquity HSS T3 column. The mobile phases were (A) 10 mM ammonium formate in 0.1% formic acid and (B) acetonitrile. The flow rate was set to

400 μL/min and the column oven was set at 27 °C. After 5 μL of each sample was injected, the analytes were separated using a 12 min multi-step gradient. The Q Exactive Plus was operated in positive mode, and a parallel reaction monitoring method (PRM) was used to detect derivatized molecules. Fragment ions were extracted with a 10 ppm mass error using the LC Quan node of the XCalibur software (4.3, Thermo Fisher). Endogenous analyte peak areas were compared to those of each internal standard to determine relative abundance. Further normalizing abundance to the wet weight of the tissue yielded mass specific concentrations of the neurotransmitters (ng/g).

2.4. Serum Cytokines and Corticosterone

Serum cytokines (IL-1α, IL-1b, IL-2, IL-6, INF-γ, and TNFα) were measured using Bio-Rad, Mouse Cytokine Group l (Bio-Rad, Hercules, CA, USA; which has been discontinued). The kit was run according to the manufacturer's Bio-Plex Pro Assays protocol and run on a Bio-Plex 200 (Bio-Rad, Hercules, CA, USA). Samples were run in duplicate and counter-balanced across the plate based on sex and treatment group. Sample replicates with CVs higher than 15% were excluded from analysis. Serum corticosterone levels (Arbor Assays, Ann Arbor, MI, USA) were measured in duplicate using commercially available enzyme immunoassay kits according to manufacturer's specifications.

2.5. Statistical Analyses

Data were analyzed using JMP Pro17. Changes in brain neurotransmitter levels (normalized to tissue weight) and serum cytokine levels were analyzed separately by sex and time point using two factor ANOVAs with treatment group and time point (PND14 or PND50) as factors, with post hoc comparisons conducted if significant interaction effects were found. To assess fronto-striatal function, i.e., the relations between frontal cortical and striatal neurotransmitters as well as the relations of cytokines and corticosterone with neurotransmitters, multivariate correlation analyses based on Pearson coefficients were utilized. Statistically significant effects were defined as $p \leq 0.05$ and marginally significant effects as $p \leq 0.10$.

3. Results

3.1. Trajectory of Brain Fronto-Striatal Neurotransmitter Functions

Frontal Cortex—Changes in frontal cortical glutamatergic neurotransmitters (Figure 2; Table 1) were primarily reflective of time point, with significant increases between PND14 and PND50 in levels of glutamate turnover (glutamine/glutamate) and of reductions in GABA in females, while males also showed increases in glutamate turnover (glutamine/glutamate), as well as reductions in levels of glutamate and of GABA across this time period. Females did show significantly reduced levels of glutamate in response to UFP exposures at PND14, which persisted to PND50 (main effect of UFP, F(3, 35) = 2.4, $p = 0.022$).

In the case of frontal cortical serotonergic function (Figure 3; Table 1), females showed time point-related significant reductions in levels of tryptophan and kynurenine and increases in both 5HT and 5HIAA between PND14 and PND50, but these changes were not influenced by UFP exposures. Males likewise demonstrated reductions between PND14 and PND50 in levels of tryptophan and kynurenine, but UFP exposure resulted in a persistent reduction in levels of tryptophan (main effect of UFP: F(3, 39) = 2.19, $p = 0.034$). In addition, UFP exposure in males resulted in a latent increase of >50% in levels of serotonin (5HT) as observed at PND50 (UFP × Time Point, F(3, 39) = 2.18, $p = 0.035$).

Changes across time points were also found in frontal cortical dopaminergic neurotransmitter systems (Figure 4; Table 1), including reductions in levels of tyrosine, HVA, HVA/DA, and DOPAC/DA, and marginally in DOPAC, along with increases in the ratio of DA/tyrosine and marginally of DA in females, as confirmed by significant effects of Time Point in the statistical analyses. While UFP exposure reduced levels of frontal cortical tyrosine in females at PND14, recovery was seen by PND50 (UFP × Time Point, F(3, 35) = 2.58,

p = 0.014). However, a latent reduction of >30% was found in UFP-exposed females in the DA/tyrosine ratio at PND50 (UFP × Time Point, F(3, 35) = −2.06, p = 0.046). In males, time point-related reductions in tyrosine, HVA, HVA/DA, and DOPAC/DA, and corresponding increases in DA and DA/tyrosine occurred between PND14 and PND50. However, no consistent changes in responses to UFP exposures were found.

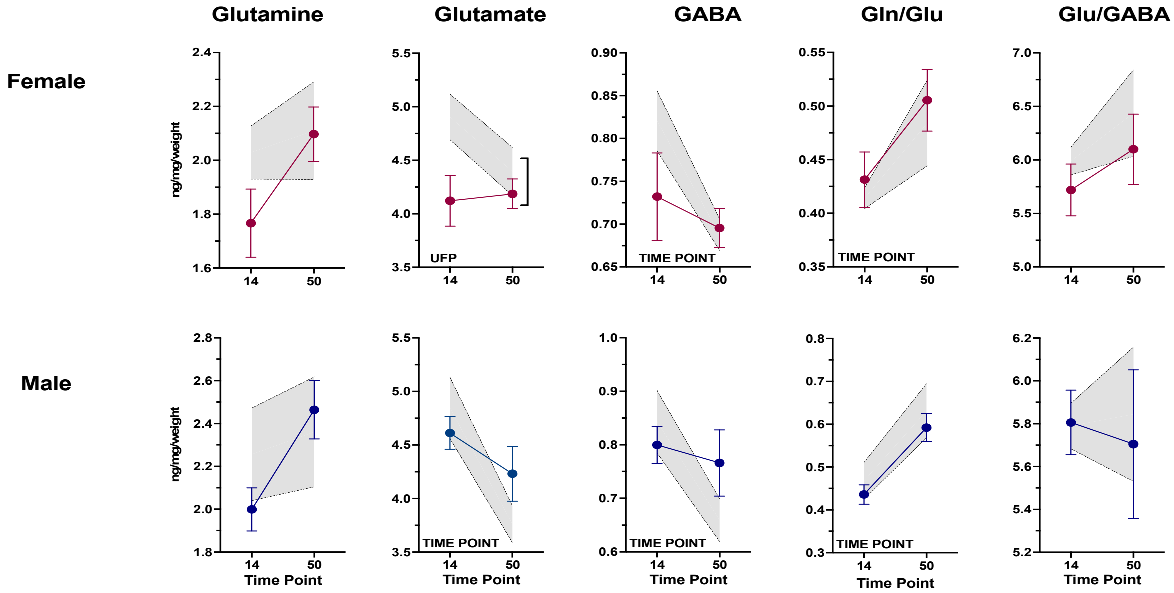

Figure 2. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of frontal cortex glutamatergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFPs. Sample sizes were n = 10–12/sex/treatment group. Symbols and lines show effects of UFP-treated mice, while shaded gray area represents filtered air control. Time Point = main effect of time point in the analysis of variance; UFP = main effect of UFP exposure in the analysis of variance.

Table 1. Summary of effects of UFP exposures.

	FEMALE		MALE	
	PND14	**PND50**	**PND14**	**PND50**
FC Neurotransmitters				
Glutamine				
Glutamate	↓	↓		
GABA				
Gln/Glu				
Glu/GABA				
Tryptophan			↓	
Kynurenine				
5HIAA				
5HT				↑
5HIAA/5HT				
HVA				
DOPAC				
DA				
NE				
Tyrosine	↓			
HVA/DA				
DOPAC/DA				
DA/Tyrosine		↓		

Table 1. *Cont.*

	FEMALE		MALE	
	PND14	**PND50**	**PND14**	**PND50**
STR Neurotransmitters				
Glutamine	↓		↓	↓
Glutamate				
GABA	↓			
Gln/Glu			~↓	~↓
Glu/GABA				
Tryptophan	↓		~↓	~↓
Kynurenine			↓	↓
5HIAA	↓		↓	
5HT				
5HIAA/5HT			↓	
DOPAC	↓			
DA				
NE		↑		
Tyrosine	↓			
DOPAC/DA			↓	
DA/Tyrosine		↓		
Cytokines				
IL1-α				
IL1-β			↓	↓
IL-2				
IL-6			↓	↓
IL-10				
IFN-γ			↓	↓
TFN-α			~↓	~↓

~ = marginally significant effect.

Striatum—Time point-related changes in levels of glutamatergic neurotransmitters (Figure 5; Table 1) were not particularly evident in the striatum between PND14 and PND50 in either sex. However, UFP-induced changes were found in females that included significant reductions at PND14 in both the levels of glutamine and of GABA, but both had recovered to filtered air control levels by PND50 (glutamine: UFP × Time Point, F(3, 35) = 2.47, p = 0.019; GABA: F(3, 35) = 2.29, p = 0.028). Males likewise evidenced changes in striatal glutamatergic function in response to UFPs that included reductions in levels of glutamine and marginally of glutamate turnover, but unlike changes in females, these effects were persistent and still evident at PND50 (glutamine: UFP, F(3, 38) = 2.46, p = 0.019; glutamine/glutamate: UFP, F(3, 38)1.85, p = 0.073).

Changes in striatal serotonergic function were seen in response to UFP in both sexes (Figure 6; Table 1). In the case of females, UFP marginally altered levels of tryptophan and 5HT and significantly reduced levels of 5HIAA. Levels of both tryptophan (marginally) and of 5HIAA were reduced by UFP at PND14, but in both cases had recovered to filtered air control values by PND50 (tryptophan: UFP × DAY, F(3, 35) = 1.97, p = 0.057); 5HIAA: UFP × Time Point, F(3, 35) = 2.91, p = 0.006). Similar but non-significant trends were seen with kynurenine and with levels of 5HT. In the case of males, significant reductions were found in levels of tryptophan, kynurenine, 5HIAA, and 5HIAA/5HT. In the case of 5HIAA and of 5HIAA/5HT, these effects were seen at PND14 but had recovered by PND50 (5HIAA: UFP × Time Point, F(3, 39) = 2.4, p = 0.021; 5HIAA/5HT: UFP × Time Point, F(3, 39) = 2.17, p = 0.036). In the case of both tryptophan and kynurenine, however, these effects were persistent and evident at both PND14 and PND50 (tryptophan: UFP (F(3, 39) = 1.86, p = 0.071); kynurenine: UFP (F(3, 39) = 2.37, p = 0.023).

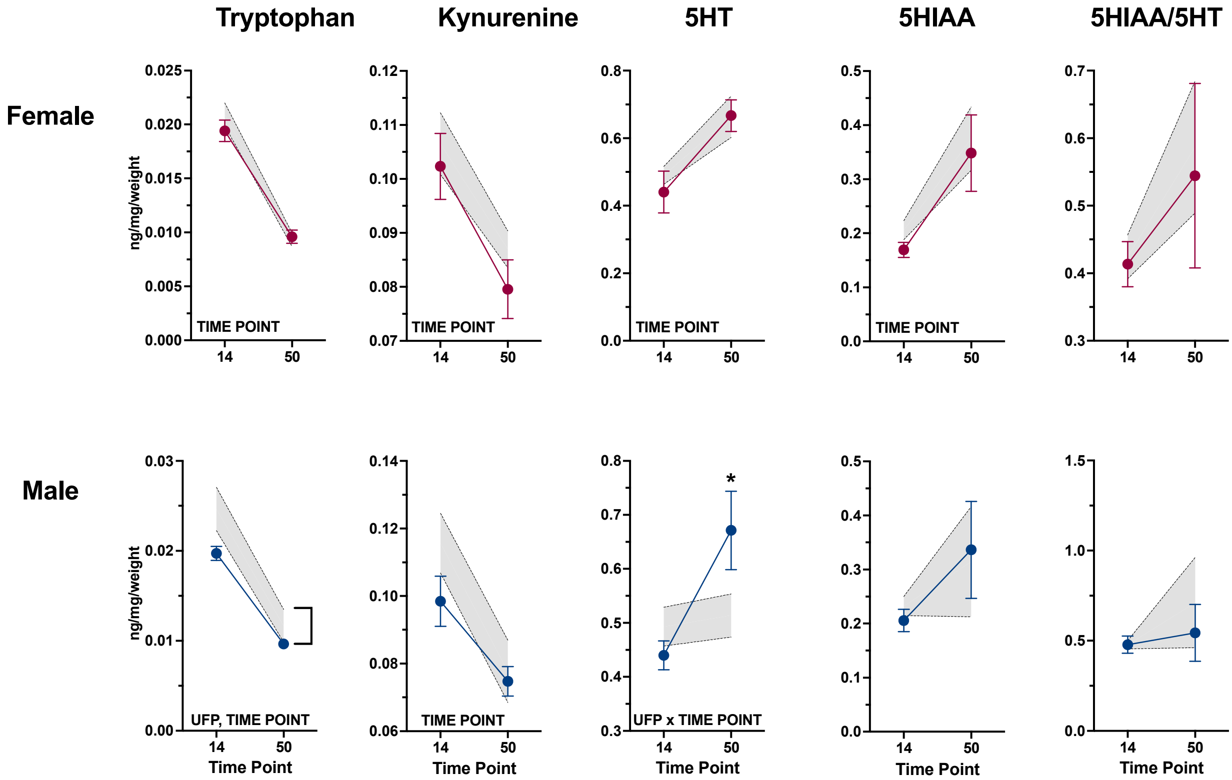

Figure 3. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of frontal cortex serotonergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFPs. Sample sizes were n = 10–12/sex/treatment group. Symbols and lines show effects of UFP-treated mice while shaded gray area represents filtered air control. Time Point = main effect of time point in the analysis of variance; UFP = main effect of UFP exposure in the analysis of variance; UFP × Time Point = interaction effect of time pint by UFP exposure; * significantly greater than filtered air control.

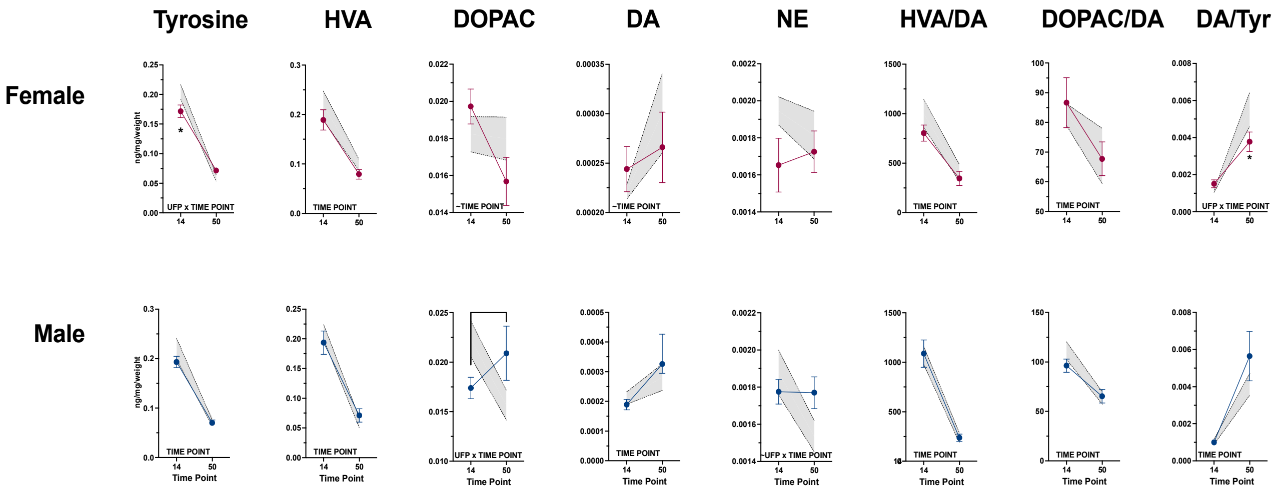

Figure 4. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of frontal cortex dopaminergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFPs. Sample sizes were n = 10–12/sex/treatment group. Symbols and lines show effects of UFP-treated mice while shaded gray area represents filtered air control. Time Point = main effect of time point in the analysis of variance UFP × Time Point = interaction effect of day by UFP exposure; ~ = marginally significant, $p \leq 0.10$; * = statistically significant at $p \leq 0.05$; bracket indicates significant difference between UFP DOPA level at PND14 vs. PND50.

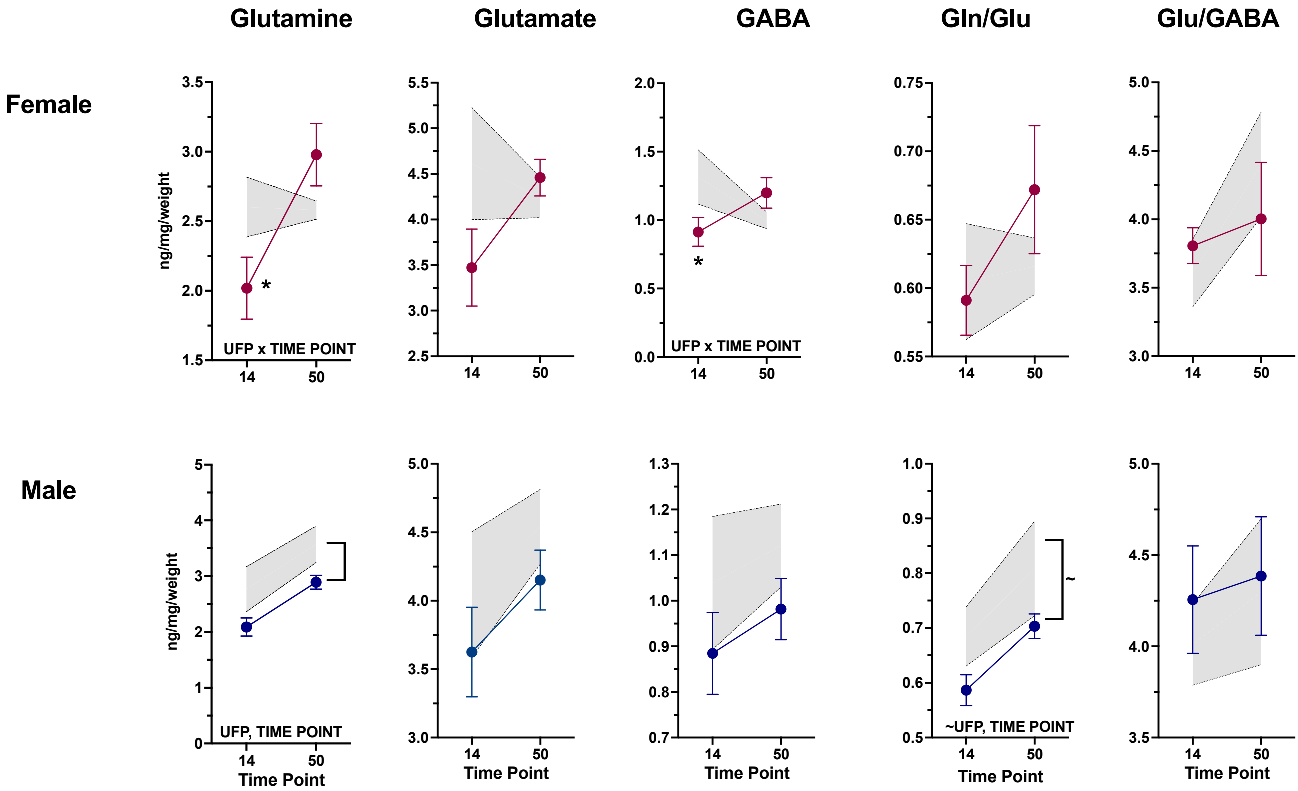

Figure 5. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of striatal glutamatergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFP. Symbols and lines show effects of UFP-treated mice while shaded gray area represents filtered air control. Sample sizes were n = 10–12/sex/treatment group. Time Point = main effect of time point in the analysis of variance; UFP = main effect of UFP exposure in the analysis of variance; UFP × Time Point = interaction effect of Time Point by UFP exposure; ~ = marginally significant, $p \leq 0.10$; * = statistically significant at $p \leq 0.05$; bracket indicates significant difference between UFP and filtered air control.

Striatal dopaminergic function was also influenced by UFP exposures (Figure 7; Table 1), primarily in females. Specifically, this included effects that showed recovery between PND14 and PND50 in terms of reductions in PND14 levels of tyrosine (UFP × Time Point, $F(3, 35) = 2.39$, $p = 0.022$) as well as of >40% in DOPAC (3, 35) = 2.1, $p = 0.043$). In contrast, latent effects of UFP exposure in females were seen in both elevated levels of >70% in NE at PND50 (UFP × Time Point, $F(3, 34) = 2.04$, $p = 0.049$) as well as in reductions of the DA/tyrosine ratio (UFP × Time Point, $F(3, 35) = -2.27$, $p = 0.03$). In contrast, while males showed reductions in levels of tyrosine, DOPAC, and DOPAC/DA, along with increases in the levels of NE and of the DA/tyrosine ratio between PND14 and PND50, UFP effects were limited to a significant reduction in the DOPAC/DA ratio at PND14 that had recovered to filtered air control levels by PND50 (UFP × Time Point, $F(3, 38) = 2.57$, $p = 0.014$).

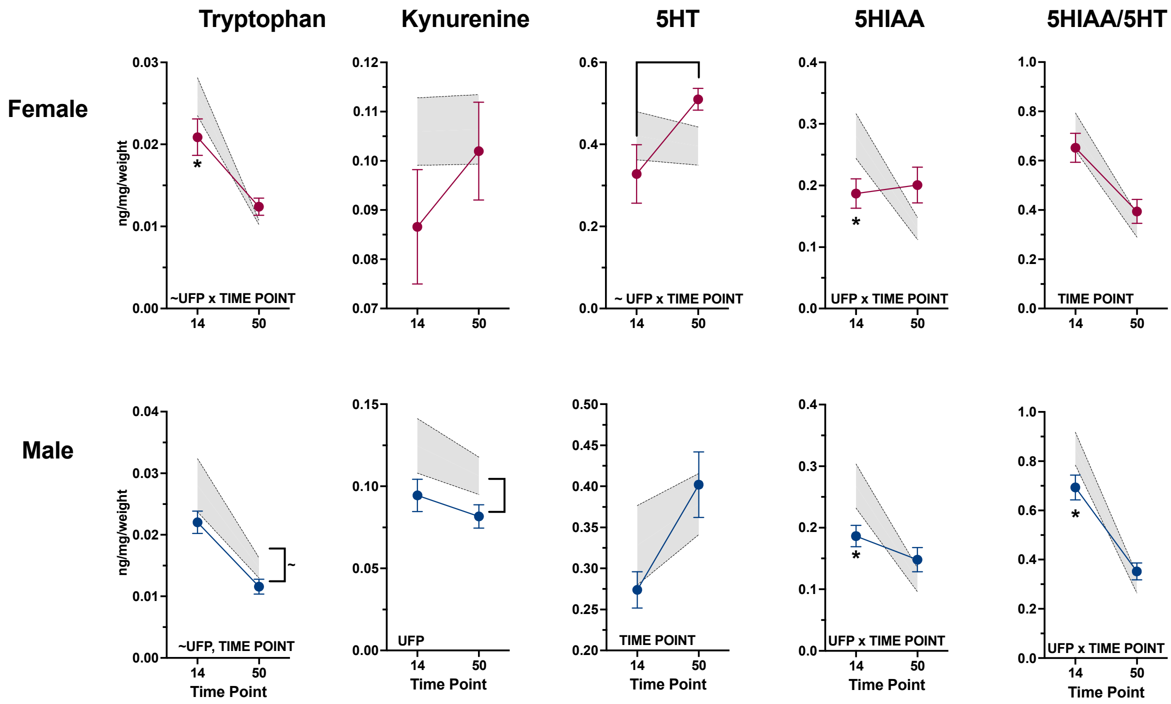

Figure 6. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of striatal serotonergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFP. Symbols and lines show effects of UFP-treated mice while shaded gray area represents filtered air control. Time Point = main effect of time point in the analysis of variance; UFP = main effect of UFP exposure in the analysis of variance; UFP × Time Point = interaction effect of day by UFP exposure; ~ = marginally significant, $p \leq 0.10$; * = statistically significant at $p \leq 0.05$; bracket indicates significant difference between UFP PND14 from UFP PND50 level of 5HT.

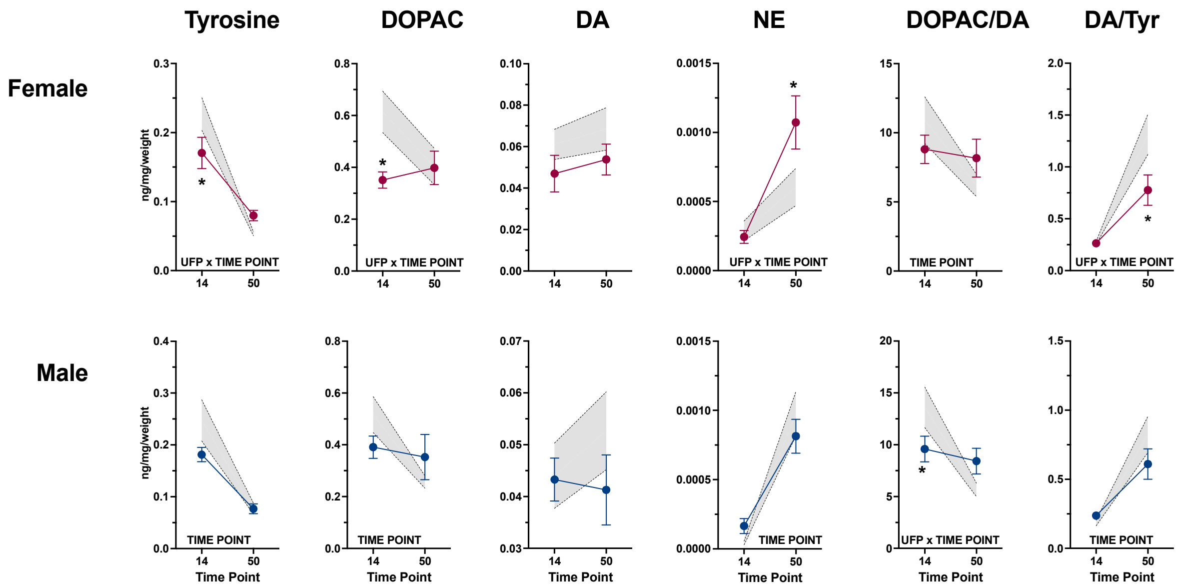

Figure 7. Group mean ± SE levels (ng/mg/tissue weight) at PND14 and PND50 of striatal dopaminergic neurotransmitters in female (**top** row) and male (**bottom** row) mice exposed to concentrated ambient UFP. Sample sizes were n = 10–12/sex/treatment group. Symbols and lines show effects of UFP-treated mice while shaded gray area represents filtered air control. Time Point = main effect of time point in the analysis of variance; UFP × Time Point = interaction effect of day by UFP exposure; * = statistically significant at $p \leq 0.05$.

3.2. Interactions of Fronto-Striatal Neurotransmitter Systems

To examine potential interactive effects within fronto-striatal systems, multivariate correlation analyses were carried out examining correlations between frontal cortex and striatal neurotransmitter levels at both PND14 and PND50 (Figure 8).

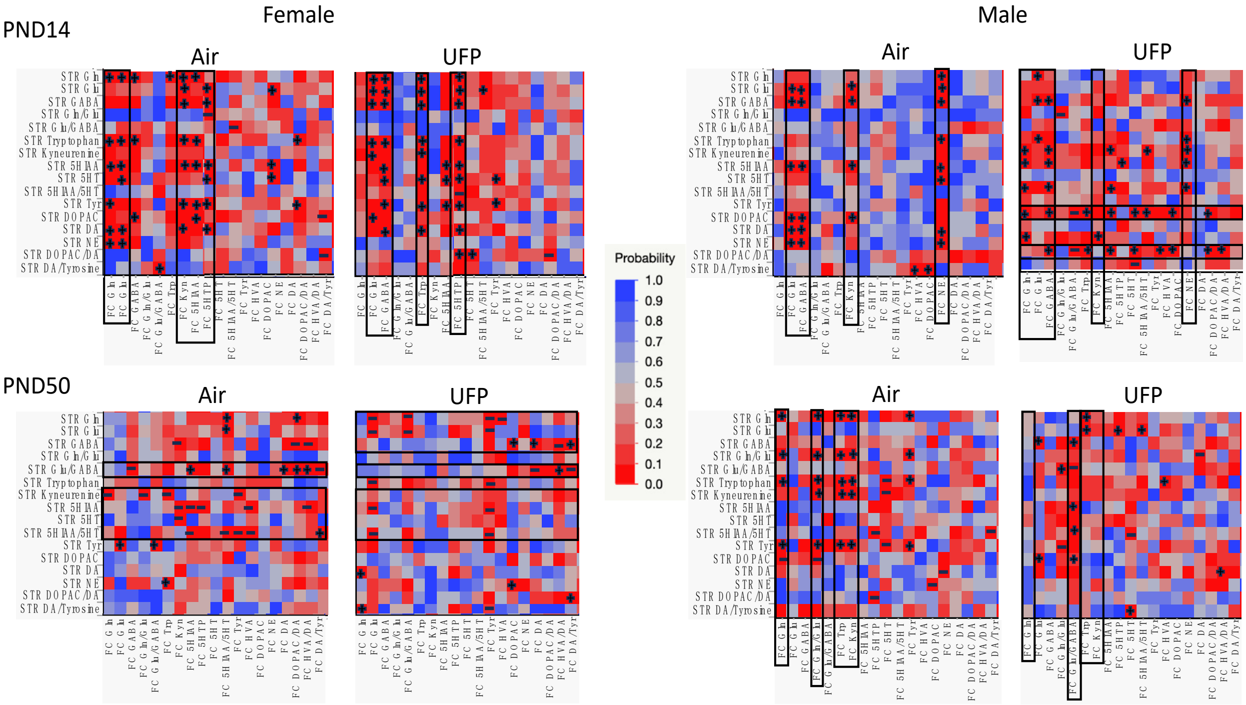

Figure 8. Multivariate correlation *p* values from correlational analyses across neurotransmitter levels in frontal cortex and striatum from PND14 brains (**top** row) and PND50 (**bottom** row) brains of females (**left** columns) and males (**right** columns) exposed to filtered air (**left** side) or concentrated ambient UFPs (**right** side). FC = frontal cortex; STR = striatum; glutamatergic (Gln: glutamine, Glu: glutamate; GABA: gamma aminobutyric acid; Gln/Glu: glutamine/glutamate; Glu/GABA: glutamate/GABA), serotonergic (tryptophan; kyneurenine; 5HT: serotonin; 5HIAA: 5 hydroxyindole acetic acid; 5HIAA/5HT: 5 hydroxyindole acetic acid/serotonin) and dopaminergic (HVA: homovanillic acid; DOPAC: 3,4-dihydroxyphenlyacetic acid; DA: dopamine; NE: norepinephrine; Tyr: tyrosine, HVA/DA: homovanillic acid/dopamine; DOPAC/DA: 3,4-dihydroxyphenlyacetic acid/dopamine; DA/Tyr: dopamine/tyrosine). + = positive correlation; − = negative correlation.

PND14 Fronto-striatal Interactions—As indicated by the positive correlation patterns, frontal cortex glutamatergic neurotransmitters, specifically glutamine and glutamate, as well as frontal cortex serotonergic function (kynurenine, 5HTP, and 5HIAA) were correlated with striatal neurotransmitter levels in all three classes in PND14 air-exposed female brains. However, this pattern was altered in PND14 UFP-exposed females, where a more pronounced effect of frontal cortical GABA control was seen, and where frontal cortical tryptophan levels were likewise highly correlated with striatal neurotransmitter function while correlations with frontal cortical kynurenine were no longer found. While interactive effects of frontal cortical 5HTP were still present following UFP exposures, a notable difference was the lack of an inhibitory control over striatal glutamate turnover levels and the emergence of an inhibitory correlation with striatal serotonin turnover.

In the case of PND14 air-exposed male brains, neurotransmitter interactions were prominent between frontal cortex glutamate and, in this case, GABA and all three classes of striatal neurotransmitters; frontal cortical kynurenine and norepinephrine correlations across striatal neurotransmitter classes were also seen in filtered air male controls. Following UFP exposures, however, some residual control remained with frontal cortical GABA and with norepinephrine, while frontal cortical kynurenine correlations with striatal neurotransmitters were almost totally eliminated. Of note in response to UFP exposures was also an apparent shift to striatal dopaminergic control, with significant correlations of striatal DOPAC and DOPAC/DA with all three classes of frontal cortex neurotransmitters.

PND50 Fronto-striatal Interactions—By PND50, patterns of correlations in filtered air control brains of both sexes differed from those seen at PND14. For filtered air control females, levels of striatal excitatory/inhibitory (glutamate/GABA) and serotonergic functions (kynurenine, 5HT, and 5HIAA/5HT) showed interactions with all three frontal cortical neurotransmitter systems. However, following UFP exposures, this striatal serotonergic control was largely eliminated and replaced by a more prominent control by striatal glutamatergic function, particularly over frontal cortical glutamatergic and dopaminergic function.

In PND50 male filtered air control brains, frontal cortical glutamine and glutamate turnover, as well as tryptophan and kynurenine, were correlated with striatal neurotransmitter function across all three classes. However, following UFP exposures, correlations were eliminated in the case of frontal cortical glutamine and kynurenine, and reduced with glutamate turnover (glutamine/glutamate) as well as with frontal cortical tryptophan, with a shift instead to more control by frontal cortical excitatory/inhibitory (glutamate/GABA) levels.

3.3. Trajectory of Serum Cytokine and Changes

The trajectory of changes in serum cytokines from PND14 to PND50 are shown in Figure 9 and summarized in Table 1. While IL-1a levels declined across this time frame in females, no other effects of either Time Point or UFP exposure were found. While IL-1-a levels also declined in males, persistent reductions were seen in levels of several serum cytokines in UFP-exposed males. Specifically, marked reductions in IL-1b were found of >70% (main effect of UFP, $F(3, 23) = 3.19$, $p = 0.004$). Similarly, serum levels of IL-6 were reduced by 66–80% across this time period (main effect of UFP, $F(3, 23) = 2.7$, $p = 0.013$). In addition, persistent reductions were found in IFN-γ (main effect of UFP, $F(3, 34) = 2.57$, $p = 0.015$) that averaged 40–45%. Concurrently, marginal reductions of TNFa ranging from 35–45% were seen (main effect of UFP, $F(3, 37) = 1.94$, $p = 0.061$). Serum corticosterone levels increased in both sexes between PND14 and PND50, but no significant effects of UFP exposure were found in either case.

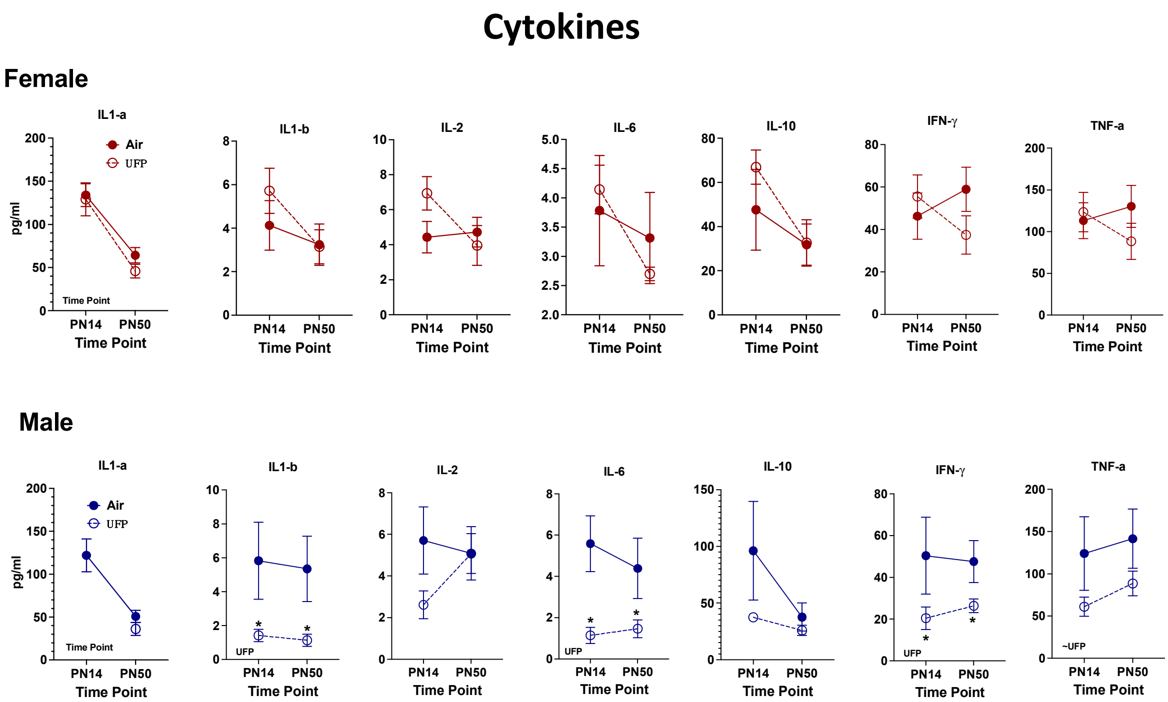

Figure 9. *Cont.*

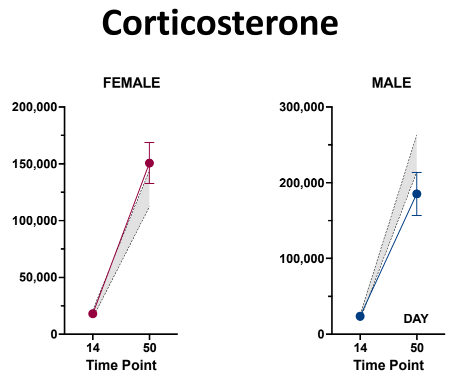

Figure 9. (**Top Two Panels**) Group mean ± SE levels of serum cytokines at PND14 and PND50 in females (**top** row) and males (**middle** row) mice exposed to filtered air or UFPs. (**Bottom Panel**) Group mean ± SE levels of serum corticosterone at PND14 and PND50 in females (**left**) and males (**right**) of mice exposed to filtered air or UFPs. Time Point = main effect of time point in the analysis of variance; UFP = main effect of UFP exposure in the analysis of variance; ~ = marginally significant, $p \leq 0.10$; * = statistically significant at $p \leq 0.05$.

3.4. Interactions of Corticosterone with Frontal Cortex Neurotransmitters

Examination of correlations between serum cytokines and corticosterone with brain neurotransmitters revealed a notable set of correlations between serum corticosterone levels and frontal cortical neurotransmitters in PND14 male brains exposed to UFPs (Figure 10). Despite the absence of UFP-related reductions in serum corticosterone, a significant inverse relation was observed between serum corticosterone with frontal cortical glutamatergic excitotoxicity (glutamate/GABA) levels, as were significant positive relationships between serum corticosterone and both serotonin (5HIAA/5HT) and dopamine (DOPAC/DA) turnover.

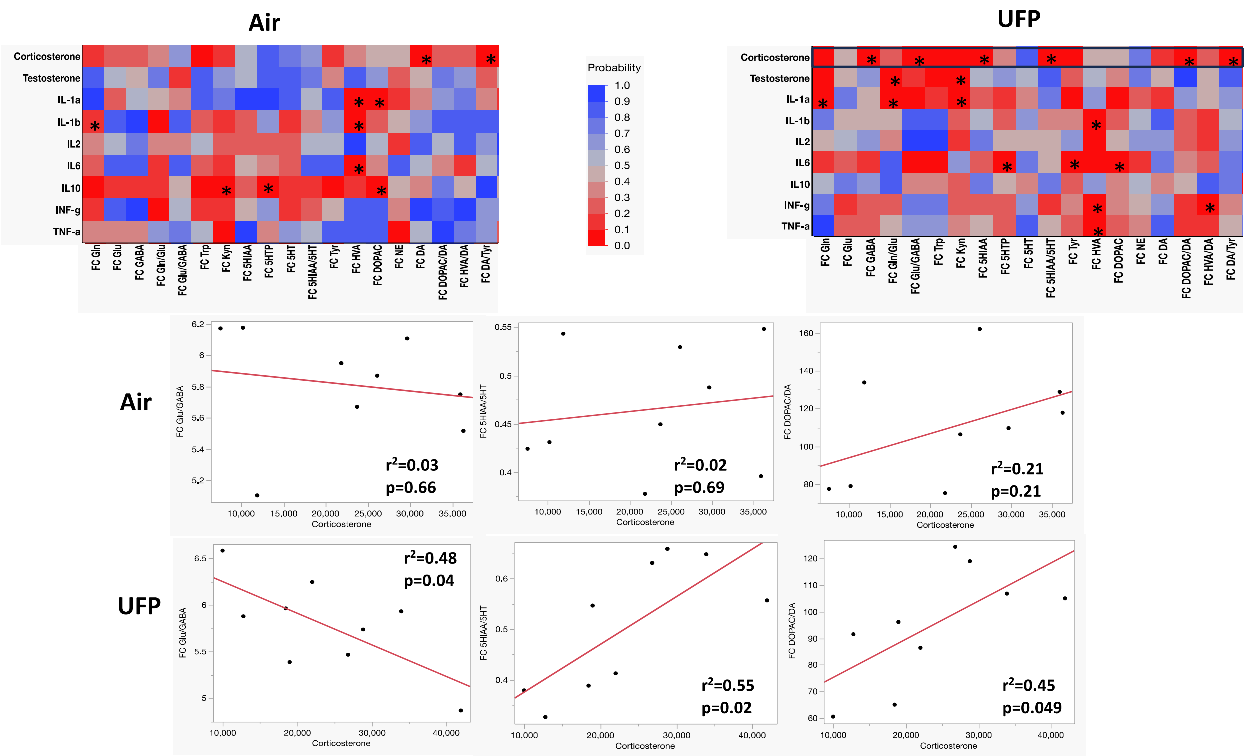

Figure 10. (**Top Panel**) Multivariate correlation *p* values from correlational analyses of serum cytokines and hormones with neurotransmitter levels in frontal cortex from PND14 male brains exposed

to filtered air (**left**) or concentrated ambient UFPs (**right**). (**Bottom Panels**) line of best fit correlations between serum corticosterone and levels of frontal cortical neurotransmitters as indicated. FC = frontal cortex; Gln: glutamine, Glu: glutamate; GABA: gamma aminobutyric acid; Gln/Glu: glutamine/glutamate; Glu/GABA: glutamate/GABA), serotonergic (tryptophan; kyneurenine; 5HT: serotonin; 5HIAA: 5 hydroxyindole acetic acid; 5HIAA/5HT: 5 hydroxyindole acetic acid/serotonin) and dopaminergic (HVA: homovanillic acid; DOPAC: 3,4-dihydroxyphenlyacetic acid; DA: dopamine; NE: norepinephrine; Tyr: tyrosine, HVA/DA: homovanillic acid/dopamine; DOPAC/DA: 3,4-dihydroxyphenlyacetic acid/dopamine; DA/Tyr: dopamine/tyrosine). * = significant correlation, r^2 and p values from correlation analyses.

4. Discussion

A growing body of literature now indicates that early developmental exposures to AP have adverse consequences for brain development and behavior, effects very likely to underlie the corresponding association of AP with several neurodevelopmental and psychiatric disorders, including autism spectrum disorder, attention deficit hyperactivity disorder, and schizophrenia [13,65,66]. The breadth of adverse AP effects suggests that such exposures target features that are shared across neurodevelopmental and psychiatric disorders [17], including alterations in brain neurotransmitter systems [67–71]. Correspondingly, our prior studies have found that gestational and postnatal exposures of mice to UFPs, thought to be the most reactive component of AP [24,52], produce characteristics of neurodevelopmental disorders, including changes in brain neurotransmitter systems in the frontal cortex and striatum.

However, what remains unclear is how AP exposures alter the relationships between frontal cortical and striatal neurotransmitters, i.e., fronto-striatal functions which underly many of the core behavioral aberrations seen in response to developmental AP exposures.

The current study sought to extend the understanding of the impact of developmental UFP exposures specifically on brain fronto-striatal neurotransmitter system functions to further advance understanding of potential mechanisms of behavioral consequences associated with developmental AP exposures. It examined not only the immediate effects of developmental UFP exposures, but also the trajectory of changes to determine potential recovery of effects, persistence of effects, and those with a latent onset out to adolescence. For that purpose, this study examined changes in patterns of correlations between frontal cortex and striatal neurotransmitters as an index of fronto-striatal function, as well as evaluating relationships between serum cytokines and corticosterone, known targets of UFP exposures and interactive modulators of fronto-striatal systems in terms of brain development and function [60,61].

As in prior studies, ambient inhalational exposures to UFPs in mice during the early postnatal period altered brain neurotransmitter systems. Overall, effects were far more prevalent in males than in females (Table 1), and these effects were also more evident in the striatum than the frontal cortex, and included changes in levels of glutamatergic, serotonergic, and dopaminergic neurotransmitters, suggesting an enhanced vulnerability of the male striatum to UFPs. Further, when examined over time, females generally showed recovery from such effects (PND50; Table 1), whereas a greater number of and more persistent changes were found in male brains. Notable among these persistent changes were reductions in striatal glutamate and glutamate turnover, was well as in precursors of serotonergic systems, i.e., tryptophan and kynurenine. In relation to fronto-striatal function, an involvement of striatal dopamine turnover, i.e., striatal DOPAC and DOPAC/DA, emerged in relation to frontal cortical neurotransmitter function, while frontal cortical kynurenine control was lost. In addition, males showed a persisting pattern of peripheral immunosuppression not seen in females as well as a role for serum corticosterone in modulating frontal cortical neurotransmitter turnover, particularly excitotoxicity (GABA, glutamate/GABA), serotonin turnover (5HIAA, 5HIAA/5HT), and dopamine turnover (DOPAC/DA). Collectively, these findings are consistent not only with altered fronto-striatal function, but additionally, the corticosterone correlations with frontal cortical neurotransmitters suggests a broader physiological interaction controlling neurotransmitters. While some effects occurred in females, particularly reductions in striatal neurotransmitter levels, many of the effects were not persistent, suggesting adaptation or compensation. Collectively, the findings are of interest given the male bias in the prevalence of neurodevelopmental disorders [28].

One notable effect in both sexes at PND14 was a UFP-induced loss of frontal cortical kynurenine correlations with striatal neurotransmitters which in males was evident at both PND14 and PND50. In addition, in males, persistent alterations in striatal serotonergic systems were found, with significant reductions in striatal kynurenine levels and marginal reductions in striatal tryptophan levels at both time points. Tryptophan metabolism occurs particularly via the kynurenine pathway to generate kynurenine. Metabolism of kynurenine leads to two intermediates: kynurenic acid, considered neuroprotective based on its ability to block glutamate receptors and scavenge free radicals, while metabolism of kynurenine via kynurenine 3-monooxygenase, an inflammation-mediated enzyme, produces neurotoxic metabolites including quinolinic acid that can activate glutamate receptors [72] and cause lipid peroxidation [73]. Thus, alterations in kynurenine pathway metabolism may be significant, and an additional observation was the persistent reduction in striatal glutamate in males.

The kynurenine pathway has also been implicated in neurodevelopmental disorders. For example, altered kynurenine pathway metabolites have been reported in individuals with autism [74]; however, such findings have not been consistent [75]. In the case of autism, these effects are based on peripheral measures; information on changes in the brain per se does not appear to have been studied. Additionally, kynurenine pathways have been extensively studied in schizophrenia and implicated in its pathophysiology, as the kynurenine pathway can regulate the levels of glutamate in the brain [76]. In those studies in which brain kynurenine levels have been assessed in individuals diagnosed with schizophrenia, however, there has typically been an increase in levels of kynurenine or in the kynurenine/tryptophan ratio [77,78] and only a modest relationship of brain levels to those in serum [79]. Clearly, additional studies to define the full consequences of UFP-induced kynurenine pathway metabolism in the brain and its relationships to other neurotransmitter changes, particularly glutamate, are warranted.

As noted, males also showed persistent reductions in levels of the striatal glutamate precursor glutamine, as well as striatal glutamate turnover. Females showed acute reductions in frontal cortical glutamate and striatal glutamine at PND 14, but these were no longer evident at PND50, where an overshoot of levels of glutamine and of glutamate turnover relative to filtered air controls was observed, suggestive of a compensatory mechanism of elevated function that did not occur in males. Interestingly, a recent study [80] used translational proton magnetic resonance spectroscopy ([1H]MRS) to compare glutamate and GABA levels in adult humans with ASD and found that glutamate concentrations were reduced in the striatum, and, moreover, that these reductions were correlated with the severity of the social behavioral features of autism. Reductions in glutamate, or in particular the hypofunction of NMDA receptors, has been linked to impairments in intracellular calcium homeostasis and neuronal activity as well as synaptic plasticity [81]. In accordance with the lower levels of glutamate and glutamine at PND14 in females, females also showed reduced levels of tyrosine in both the frontal cortex and striatum, with reduced DOPAC seen in the striatum.

In addition, males showed persistent alterations in striatal serotonergic systems, with significant reductions in striatal kynurenine levels and marginal reductions in striatal tryptophan levels at both time points. Brain serotonin levels/function depends upon the availability of tryptophan [82]. At PND14, reductions in striatal tryptophan and kynurenine were accompanied by a reduction in striatal levels of the serotonin metabolite 5HIAA and of serotonin turnover (5HIAA/5HT), with PND14 representing a period of critical brain development in mice, i.e., consistent with third trimester human brain development [23]. The functional significance of changes in levels of these neurotransmitters was corroborated by the evidence showing altered patterns of fronto-striatal correlations. Reductions in tryptophan and 5HIAA were also seen in females at PND14, but the serotonergic system showed evidence of compensation, with a subsequent overshoot at PND50 of 5HT and 5HIAA levels relative to filtered air control in females.

These findings of male-biased serotonergic dysfunction are of particular interest with respect to the links between attention deficit hyperactivity disorder (ADHD) and air pollution in numerous studies [11,83–86], and the ties of ADHD to serotonergic system deficiency [87]. Early studies highlighted the critical role of serotonin in areas of frontal cortex in the mediation of behaviors altered in ADHD, including inattention, impulsivity, and disinhibition. The dorsomedial prefrontal cortex in particular has been reported to be sensitive to low tryptophan levels [88]. Studies in human subjects using dietary tryptophan depletion to reduce brain serotonergic function [89] have reported both impaired instrumental and Pavlovian reversal learning [90], as well as in behavioral paradigms assessing response inhibition [91], particularly response initiation and consequent sensitivity inhibition [92]. While less appears to be known about specific striatal serotonergic system changes in ADHD, studies in humans have reported reductions in striatal serotonin transporter binding [93].

In addition, serotonergic dysfunction, both increases and decreases, have been implicated in autism [94]. While systematic reviews have not supported alterations in peripheral levels of tryptophan/kynurenine in autism spectrum disorder, behavioral studies have shown differential behavioral impacts of tryptophan depletion in individuals diagnosed with autism relative to healthy controls. For example, an early study reported increases in repetitive and self-injurious behavior following acute tryptophan depletion in some autistic individuals [95]. Reductions in serotonin transporter binding have been found in adults with high-functioning autism [51] as well as in children [96], as have reductions in density of serotonin transporters and of specific types of 5HT receptors [97]. In a study in mice, brain serotonin depletion produced deficits in social interaction and communication behaviors [98], features consistent with autism spectrum disorder. Interestingly, studies have also reported reduced serotonin synthesis in males 2–5 yr of age with autism [99]. Collectively, serotonergic and dopaminergic effects might relate to peripheral levels of amino acids, as peripheral sources of amino acids, particularly aromatic amino acids (e.g., tryptophan and tyrosine) are precursors to serotonin and dopamine [100,101]. Studies have reported influences of air pollution exposure on levels of plasma amino acids [102–104].

A further observation from the current study was the persistent immunosuppression produced by UFPs, specifically in serum levels of IL-1β, IL-6, IFN-γ, and TNF-α, again, in males only. These data correspond to findings from our prior studies showing reductions in male hippocampal IL-6, in striatal IL-1β and in midbrain IL-1β and TNFα levels at PND14 following exposures to a concentrated ambient UFP concentration averaging 96 $\mu g/m^3$ [24]. These reductions may reflect serotonergic vulnerability to UFPs, as 5HT receptors are prevalent in immune cells [105]. Whether similar reductions in cytokines in brains also occurred remains to be determined. Moreover, immunosuppression is also a component of neurodevelopmental disorders. Cytokines are also known to play key roles in brain growth, regulation, and function both during development [106,107] and in adulthood [108]. Indeed, pharmacological suppression of proinflammatory cytokine activation of IL-1β, IL-6, TNF-α, and IFN-λ has been shown to significantly inhibit both neurogenesis and oligodendrogenesis in the subventricular zone [109]. While cytokine imbalance is well documented in SCZ, directions of results are often contradictory [19]. Of interest with respect to the current findings are reports of reductions in serum TNF-α levels in chronic schizophrenia patients [110]. In addition, decreased serum levels of IL-2 have been associated with increases in positive syndrome scale scores in schizophrenia [111]. Moreover, current findings in males could suggest a subsequent inability of males to mount immune responses against inflammation, considering that certain of these cytokines, e.g., IL-1 and IL-10, can have major anti-inflammatory properties [112].

In addition, male UFP-exposed PND14 brains revealed a correlation between serum corticosterone levels and frontal cortical neurotransmitters, particularly the turnover of glutamate, serotonin, and dopamine. Interactions of serum corticosterone with brain neurotransmitters have long been recognized [113], and such interactive effects occur during the period of postnatal development used here, as indicated by studies demonstrating impacts of maternal adrenalectomy [114] and maternal metapyrone (corticosterone antagonist) administration [115] on offspring brain neurotransmitter levels. However, correlations in the current study occurred without an accompanying alteration in levels of serum corticosterone in response to UFP exposures. One potential interpretation of such effects at PND14 is a delay in the maturation of the HPA axis, which normally shows a stress hyporesponsive period in rodents with low basal corticosterone levels until approximately PND12 [116]. Clearly, further studies are warranted to assess the basis of the corticosterone-neurotransmitter interactions following UFP exposures.

5. Conclusions

In summary, the current findings demonstrate male-biased persistent changes in brain neurotransmitters, particularly in the striatum, in conjunction with altered patterns of fronto-striatal neurotransmitter correlations with marked immunosuppression following developmental (third trimester equivalent) exposures to inhaled concentrated ambient UFP air pollution. While acute changes were observed in females, these effects were often recovered from by PND50 or showed significantly opposite effects, suggesting overcompensation. Three changes in males suggest an integration across physiological responses to UFP, including (1) the loss of frontal cortical kynurenine control over striatal neurotransmitter function, as kynurenine metabolites can influence glutamate function and thus excitotoxicity, an effect seen in both sexes; (2) persistent immunosuppression that could relate to altered serotonergic function; and (3) the control of striatal neurotransmitter function by peripheral corticosterone levels. Dysfunction of fronto-striatal systems, as well as kynurenine alterations, tend to occur across neurodevelopmental disorders, including ASD, SCZ and ADHD, all of which are also linked to AP exposures [117]. The mechanisms of these interactive effects cannot be discerned from the current study and will require further efforts. In addition, it may be particularly useful to understand mechanisms by which the female brain appears to override the effects of UFP exposures, leading to apparent compensation. The current findings also emphasize the need for more granular assessments of fronto-striatal assessment given the multiplicity of these systems and their often overlapping structures [33]. Moreover, since different fronto-striatal systems mediate specific behavioral functions, the correlations with particular behavioral features would be informative. The findings from the current study also provide biological plausibility for the epidemiologic associations between AP exposure and neurodevelopmental disorders. Given that link, identification of the contaminant components of UFPs that underlie these effects will ultimately be critical not only for elaborating the mechanisms of the effects, but for purposes of public health protection through regulation.

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