In-Utero and Postnatal Exposure to 2,3,7,8 TCDD in Times Beach, Missouri: 2. Impact on Neurophysiological Functioning

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ABSTRACT

Fourteen children (7 girls and 7 boys) born between 1977 and 1983 to mothers who resided in the TCDD-contaminated environment of Times Beach, Missouri during and subsequent to pregnancy were tested in 1992 using neurometric testing to evaluate brain function relative to an age and sex matched population. The TCDD exposed children exhibited neurophysiological dysfunction principally in the bilateral frontal lobe regions relative to unexposed children, with females exhibiting more dysfunction than males.

INTRODUCTION. Exposure to 2,3,7,8-TCDD as well as related dioxins, polychlorinated biphenyls and dibenzofurans *in utero* and postnatally have previously been related to impaired mental functioning in later infant and child mental development.[4,5,8,13-15] Resultant adverse developmental effects have included hyper- and hypoactivity as well as impaired attention, memory, learning, and motor development.[2-5,8,9,11,14] While previous studies employed a variety of neuropsychological test batteries, none have used neuroimaging or comprehensive neurofunctional instruments to identify neurophysiological concomitants of behavioral and cognitive deficits following a child's *in utero* or postnatal exposure to TCDD and related compounds. In order to evaluate neurophysiological concomitants to TCDD, neurometric testing[6] was used to compare brain function of exposed children to an age and sex matched normal population.

METHODS

Subjects: Seven girls (mean age 11.3 yr) and 7 boys (mean age 10.7 yr) born between 1977 and 1983 to mothers who resided in the TCDD-contaminated environment of Times Beach, Missouri, during and subsequent to pregnancy (c.f. Stockbauer *et al.*[11]) were made available by their parents for several days of exhaustive testing. The children were among the 15 examined for immunological effects by Smoger, *et al.*[10] One boy subsequently reported a head injury and was therefore not included in the present study, while the 14 subjects described herein reported no such history. At the time of testing the children were between 9 and 14 years of age.

Procedures: Subjects were seated comfortably in a darkened room and fitted with a stretchable cap (Electro-Cap, Dallas, TX) which contained tin alloy electrodes in the 19 standard locations (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, C3, Cz, C4, T5, P3, Pz, P4, T6, O1, Oz, O2) of the International 10-20 System. Eye movement (EOG) was monitored with a bipolar derivation above and below one of the eyes. All electrophysiological data were amplified, stored, and analyzed using a Cadwell Spectrum-32 system (Kennewick, WA). This acquisition/analytic system is designed with a normative data base and neurometric data acquisition and analysis procedures.[1,6] At least 15 minutes of closed eyes EEG activity were digitized and filtered to fit a broad band of 0.5 to 70 Hz. A Fast Fourier Transform (FFT) was used on 2.5 second intervals of artifact free data until a minimum of one minute of artifact free EEG data were analyzed. From a linked ears referenced monopolar montage, the FFT was used to define four EEG frequency bands as: δ (1.5 to 3.5 Hz), θ (3.5 to 7.5 Hz), α (7.5 to 12.5 Hz), and β (12.5 to 25.0 Hz). The following EEG measures were then derived for each frequency band: absolute power (μV^2), relative power (%), mean frequency (Hz), interhemispheric and intrahemispheric amplitude asymmetries, and interhemispheric and intrahemispheric coherence. These measures were Z-transformed by using a log transformation to approximate a Gaussian distribution for each measure. Measures were then fitted to age regression equations to correct for effects due to cortical maturation.[1] All Z-scored measures which exceeded ± 1.96 were recoded as abnormal "hits" (1) and all others were recoded as normal range values (0). Collapsing measures across frequency bands, the following summarized means of regional percentage of abnormal hits were tallied as follows: left frontal [(Fp1+F3+F7)/3], right frontal [(Fp2+F4+F8)/3] , left centro-temporal [(C3+T3)/2], right fronto-temporal [(T4+C4)/2], left posterior [(T5+P3+O1)/3], right posterior [(T6+P4+O2)/3], and midline [(Fpz+Fz+Cz+Pz+Oz)/5]. Descriptive statistical analyses were then applied to these regional mean Z-scores and to the mean number of abnormal "hits". T-tests were used to compare means between regions and a one-way ANOVA was used to compare possible sex differences in these measures.

RESULTS

Overall Group Results. In Figure 1 the distribution of the mean percent of neurometric abnormalities by summarized cortical regions is shown. Values in excess of 5% are beyond chance. To illustrate the degree of deviation from normal, absolute values of the means of the absolute and relative power measures were calculated for these same regions and are shown in Figure 2.

Figure 1
Mean % of Neurometric "Hits" by Cortical Region

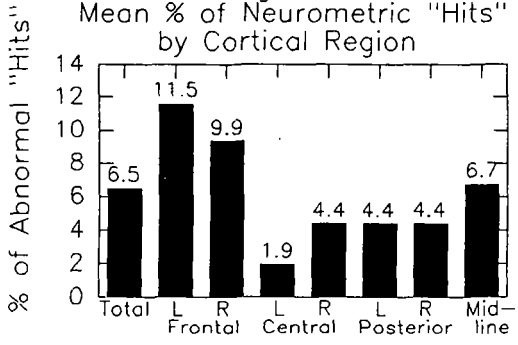
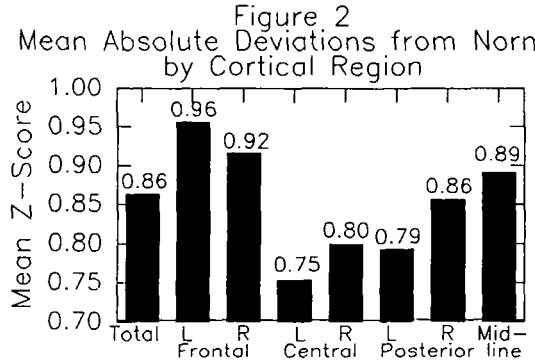


Figure 2
Mean Absolute Deviations from Normal by Cortical Region



T-tests of these means show significantly more deviations from normal across measures in the left frontal region than the bilateral central/temporal and bilateral posterior regions ($p < .05$), while the right frontal region is significantly greater than the bilateral central-temporal and left posterior. The right frontal is also greater than the right posterior, but the difference is not significant. There was no significant difference between the left and right frontal regions. The percent "hits" in Figure 1 shows a trend of differences similar to those in Figure 2. The frontal regions thus show more statistically deviant measures per region than other regions, and the absolute values of these deviations from normal are also greater than those of other regions.

Analyses of Sex Differences. Assessment for a sex effect was then made. When the means of the absolute deviations of collapsed measures for each region were analyzed by ANOVA, several significant differences were noted and are summarized in Table 1.

Table 1

Means, Standard Deviations, and ANOVA Results for the Absolute Mean Z-scores of All Neurometric Measures Collapsed into Defined Regions by Gender (* = statistically significant)

	Males (N= 7)		Females (N=7)			
Cortical Region	Mean	Std. Dev.	Mean.	Std. Dev.	F	Prob.
Left Frontal	0.80	0.13	1.11	0.14	17.73	.001*
Right Frontal	0.74	0.10	1.09	0.12	36.41	.000*
Left Central/Temp	0.76	0.18	0.74	0.16	0.04	.833
Right Central/Temp	0.76	0.12	0.84	0.17	1.04	.327
Left Posterior	0.69	0.16	0.89	0.15	5.88	.031*
Right Posterior	0.78	0.10	0.93	0.11	6.41	.026*
Midline	0.81	0.10	0.97	0.11	8.97	.011*
Overall	0.77	0.08	0.96	0.11	13.39	.003*

Table 1 shows consistent significant differences in which females in this sample have greater absolute deviations from normal than males in all regions except bilateral centro-temporal. The percentages of abnormal hits show statistically significant differences only in the right frontal region (females, mean = 14.65; males, mean = 4.02, $p < 0.05$) and total number of abnormalities (females, mean = 8.79; males, mean = 4.44, $p < 0.05$).

DISCUSSION. The results show clearly defined excessively abnormal brain measures. Region summary measures indicate the bilateral frontal areas are the most significantly impaired both from the standpoint of the number of abnormal "hits" and the absolute mean deviation of the scores. It is generally believed that abnormal frontal region function affects intellectual processes indirectly by altering states of arousal, motivation, affective states, and attention.[7] This study indicates that exposure to TCDD *in utero* and post-natally induces neurophysiological dysfunction in the bilateral frontal lobes with the left hemipshere more deviant than the right.

Of interest are the findings of sex differences in the cortical regions. Thatcher *et al.*[12] have shown that neurofunctional development of human females measured neurometrically is different from that of males early in life, and it is possible that the hormone-like activities of TCDD have a greater effect on the developing female. While few studies have examined such sex

differences, those that did have found that females were more adversely affected in their development[5].

References

1. Ahn, H., Prichep, L., John, E.R., *et al.* Developmental equations reflect brain dysfunctions. *Science* 1980; 210:1259-62.
2. Bowman, R.E., Schantz, S.L., Gross, M.L., Ferguson, S.A. Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing. *Chemosphere* 1989; 18: 235-242.
3. Jacobson, S.W., Fein, G. Jacobson, J., *et al.* The effect of intrauterine PCB exposure on visual recognition memory. *Child Development* 1985; 56: 853-860.
4. Jacobson, J., Jacobson, S., Humphrey, H. Effects of *in utero* exposure to PCBs and related contaminants on cognitive functioning in young children. *J.Pediatr.* 1990; 116: 38-45.
5. Jacobson, J. Jacobson, S. & Humphrey, H. Effects of exposure to PCBs and related compounds on growth and activity in children, *Neurotoxicol. and Teratol.* 1990; 12:319-326.
6. John, E.R., Karmel, B.Z., Corning, W.C., *et al.* Neurometrics: Numerical taxonomy identifies different profiles of brain functions within groups of behaviorally similar people. *Science* 1977; 196: 1383-1410.
7. Lezak. M.D. *Neuropsychological Assessment*, 2nd Ed., New York, Oxford University Press. 1983.
8. Rogan, W.J., Gladen, B.C., Hung, K.L., *et al.*, 1988. Congenital poisoning by PCBs and their contaminants in Taiwan. *Science* 241; 334-336. Yu, M.-L., Hsu, C.-C., Gladen, B.C., Rogan, W.J. *In utero* PCB/PCDF exposure: relation of developmental delay to dysmorphology and dose. *Neurotoxicol. Teratol.* 1991; 13: 195-202.
9. Schantz, S. & Bowman, R. Learning in monkeys exposed perinatally to 2,3,7,8-TCDD. *Neurotoxicol. and Teratol.* 1989; 11:13-19.
10. Smoger, G.H., Kahn, P.C., Rodgers, G.C., *et al. In utero* and postnatal exposure to 2,3,7,8-TCDD in Times Beach, Missouri: 1. Immunological effects: lymphocyte phenotype frequencies. This volume.
11. Stockbauer, J., Hoffman, R., Schramm, W., Edmonds, L. Reproductive outcomes of mothers with potential exposure to 2,3,7,8,-TCDD. *Amer. J. of Epidemiol.* 1988; 128: 410-419.
12. Thatcher, R.W., Walker, R.A., & Giudice, S. Human cerebral hemispheres develop at different rates and ages. *Science* 1987; 236: 1110-1113.
13. Tilson, H., Jacobson, J., & Rogan, W. Polychlorinated biphenyls and the developing nervous system: Cross-species comparisons. *Neurotoxicol. and Teratol.* 1990; 12: 239-248.
14. Troster, A., Ruff, R., & Watson, D. Dementia as a neuropsychological consequence of chronic occupational exposure to polychlorinated biphenyls (PCBs). *Arch. Neuropsych.* 1991; 6: 301-318.
15. Webb, K., Ayres, S., Mikes, J., and Evans, R. The diagnosis of dioxin-associated illness. *Amer. J. Prev. Med.* 1986; 2:103-108; Webb, K., Evans, R., Knutsen, A, *et al.* Medical evaluation of subjects with known body levels of 2,3,7,8-TCDD. *J. Toxicol. Environ. Health* 1989; 28: 183-193.