PARENTS AND CHILDREN: EXPOSURE-EFFECT GRADIENT IN TWO GENERATIONS OF EXPOSURE TO PESTICIDES IN ISRAELI KIBBUTZIM

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ARE THE NEUROTOXIC EFFECTS OF LOW-LEVEL LONG-TERM EXPOSURE TO ORGANOPHOSPHATES PERMANENT?

Approach to addressing this question:

a. Past (1980's): Epidemiologic studies on effects of everyday low-level exposures in workers and residents

b. Recent: Re- examination of the same adult cohort with the same and newer methods

c. Current: Examination of the offspring with same and newer methods

The Hula Valley has been extensively cultivated since its swamps were drained in 1957

OP have been widely used for pest control in fields and orchards in Hula

The neurotoxic effects were studied in the 1980's
In kibbutzim residents – 214 individuals in 3 cohorts:

- **Agricultural workers**
- **Workers in the kibbutzim but not in agriculture**
- **Residents working elsewhere with no occupational or drift exposures**

Richter, ED. *et al* (1992) *Isr. J. Med. Sci.* 28:584-597

The Jordan Rift Valley

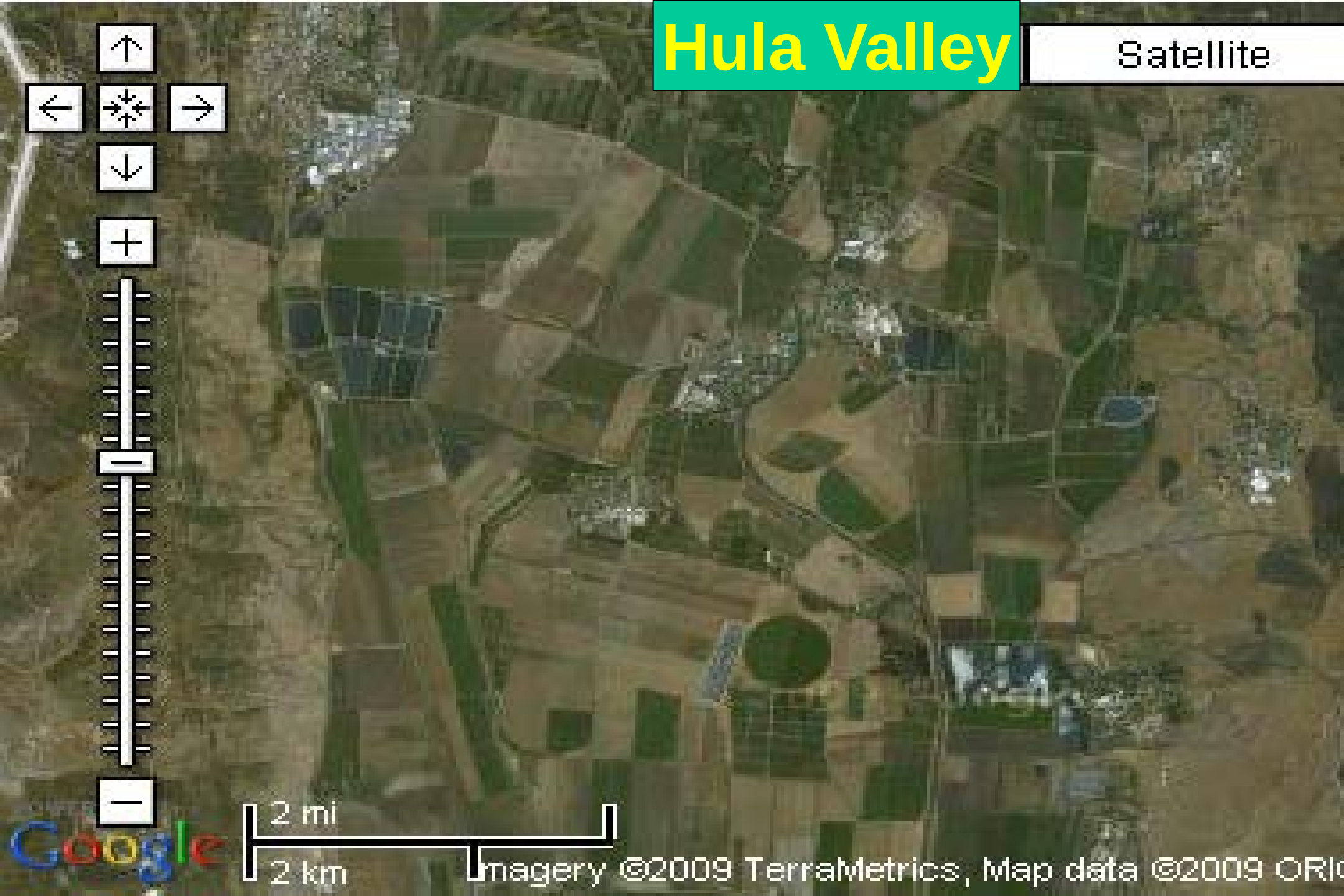
Hula Valley

Sea of Galilee

Beit Shean Valley

Jerusalem

Dead Sea


Hula Valley
Satellite
2 mi
2 km
Google
Imagery ©2009 TerraMetrics, Map data ©2009 ORI

Exposure assessment:

- Annual reports: sales of OP's
- Annual Reports of Water Quality: Jordan river and Sea of Galilee 1998-2010
- Monitoring: Atmospheric levels, transport and degradation products of OP's
- Concurrent Urine OP metabolites

RESEARCH OBJECTIVES AND GROUP STUDIED:

Assessment of neurobehavioral status, cognitive skills and task performance

8-12 years-old schoolchildren in kibbutzim "second generation" in families with 30-50 y in exposed settings

Schoolchildren (N=96) studied: two sub-groups:

- Children (N=51) who reside and attend school in Hula valley.
- Children (N=45) residing in hills around Hula valley and attend school in valley.

Comparison group (N=40) included age- and gender-matched children residing in a different kibbutz in Jordan Rift Valley in which use of pesticides has been minimal ("organic agriculture") for decades.

The Jordan Rift Valley

Hula Valley

Sea of Galilee

Beit Shean Valley

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Cognitive Tests

- **Trail Making Tests A and B** for screening, attention and graphomotor ability
- **Digit Span Test (forward and backward)** for auditory memory involving attention (WISC-III)
- **Digit Symbol Test** for eye-hand coordination in new learning processes (WISC-III)
- **Arithmetic Test** (WISC-III)
- **Bender–Gestalt Test** for visual-motor Gestalt
- **Digit Cancellation Test** as a measure of short-term memory and reaction time
- **Diamond Test** for screening and attention ability
- **Rapid Automatized Naming** for reading competence
- **Purdue Pegboard** for manual dexterity

Children: 2 models of analysis

- **A full model**: all the examined **136** children

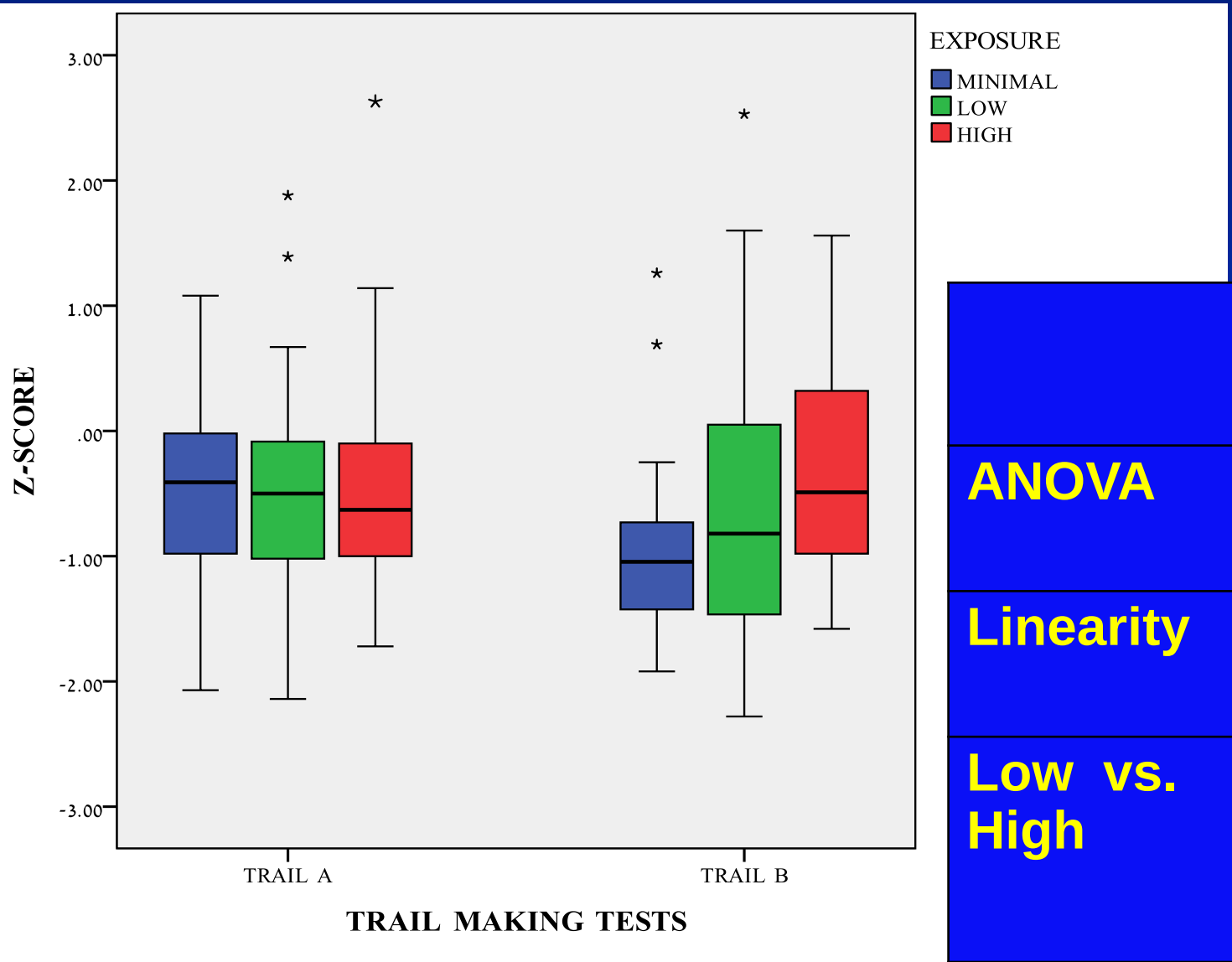
- **A family model**: only the older participating child in each family - **100** children in 100 families

FAMILY MODEL (N = 100): CHARACTERISTICS

	VALLEY HIGH EXPOSURE	HILLS LOW EXPOSURE	COMPARISON MINIMAL EXPOSURE	P-value
Number	35	38	27	
GENDER F M	14 (40%) 21 (60%)	22 (57%) 16 (43%)	13 (48%) 14 (52%)	0.31
Parents' Marital Status: Married Divorced Other	 33 1 1	 33 5 0	 27 0 0	0.10
Place of Birth Israel abroad	 35 0	 38 0	 27 0	
Father's Education Years Mean (S.D.)	14.74 (2.47)	13.89 (2.24)	16.04 (1.93)	0.00
Mother's Education Years Mean (S.D.)	15.09 (2.30)	15.28 (3.40)	16.04 (2.00)	0.34

FAMILY MODEL: TRAIL MAKING TESTS A and B

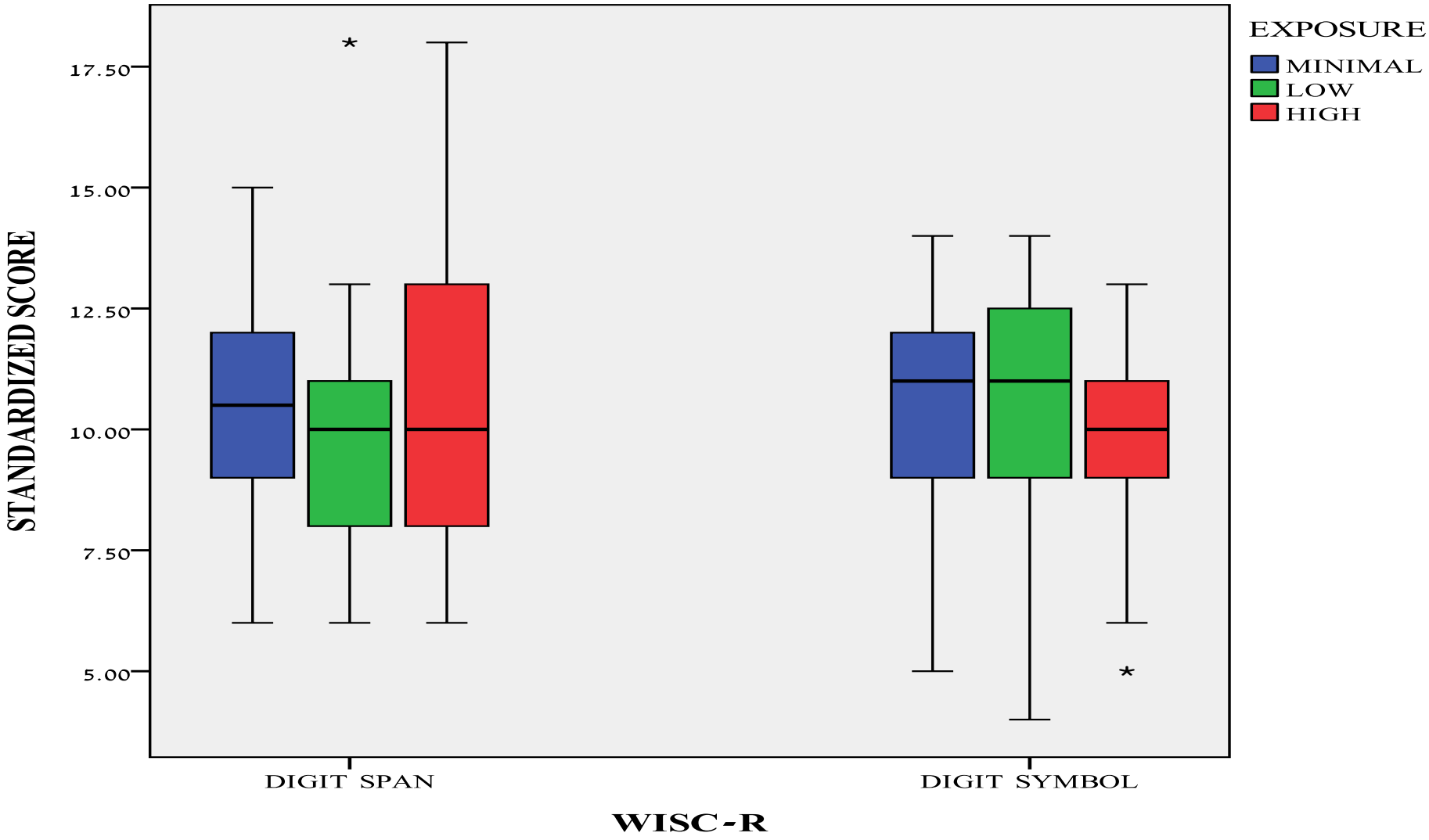
for screening ability, attention and graphomotor ability



	TRAIL A	TRAIL B
ANOVA	0.85	0.05
Linearity	0.91	0.01
Low vs. High	0.99	0.03

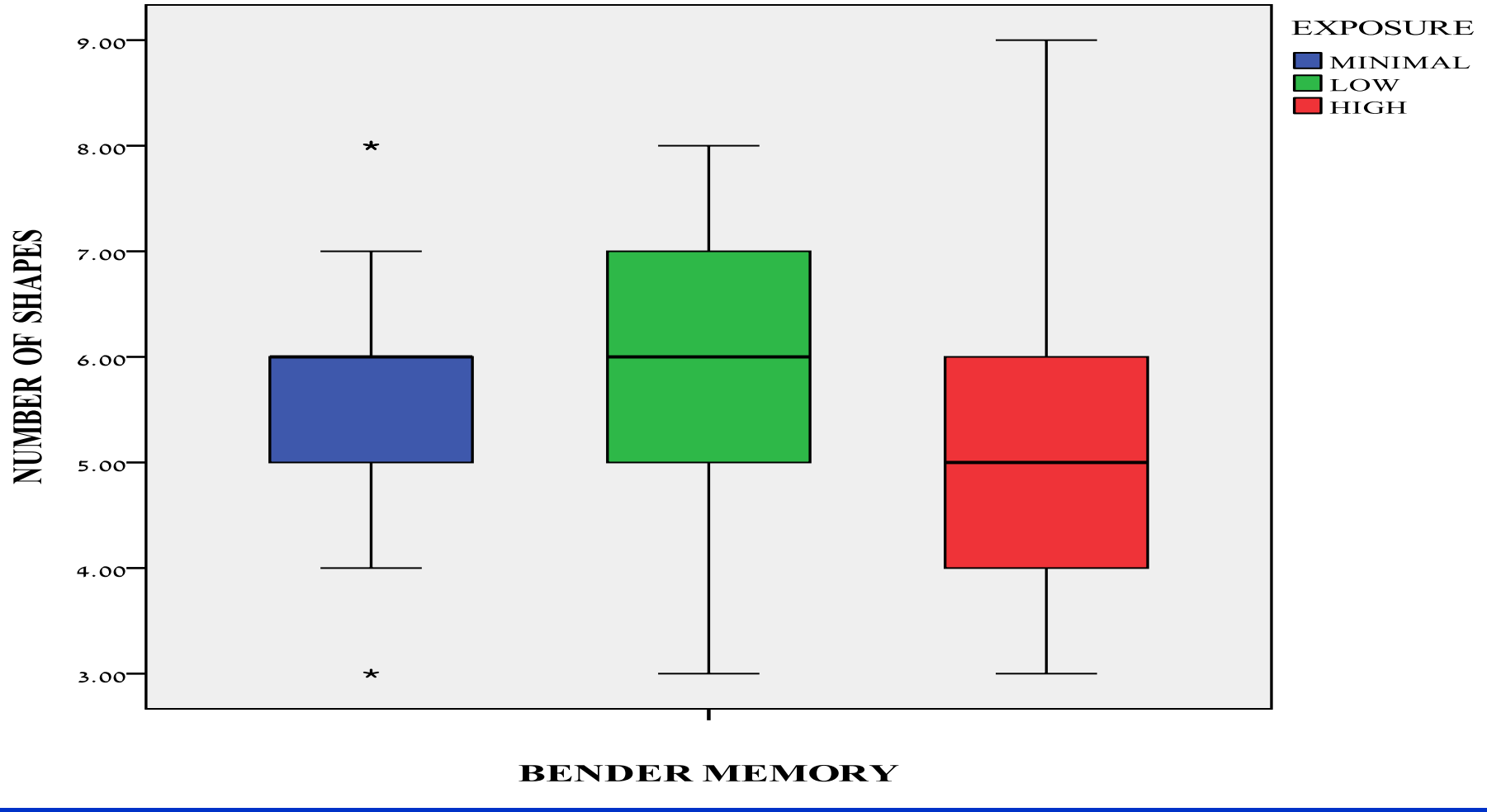
DIGIT SPAN
for auditory memory

DIGIT SYMBOL
for eye-hand coordination



(Digit Symbol: Kruskal-Wallis: p=0.05, Linearity: p=0.08)

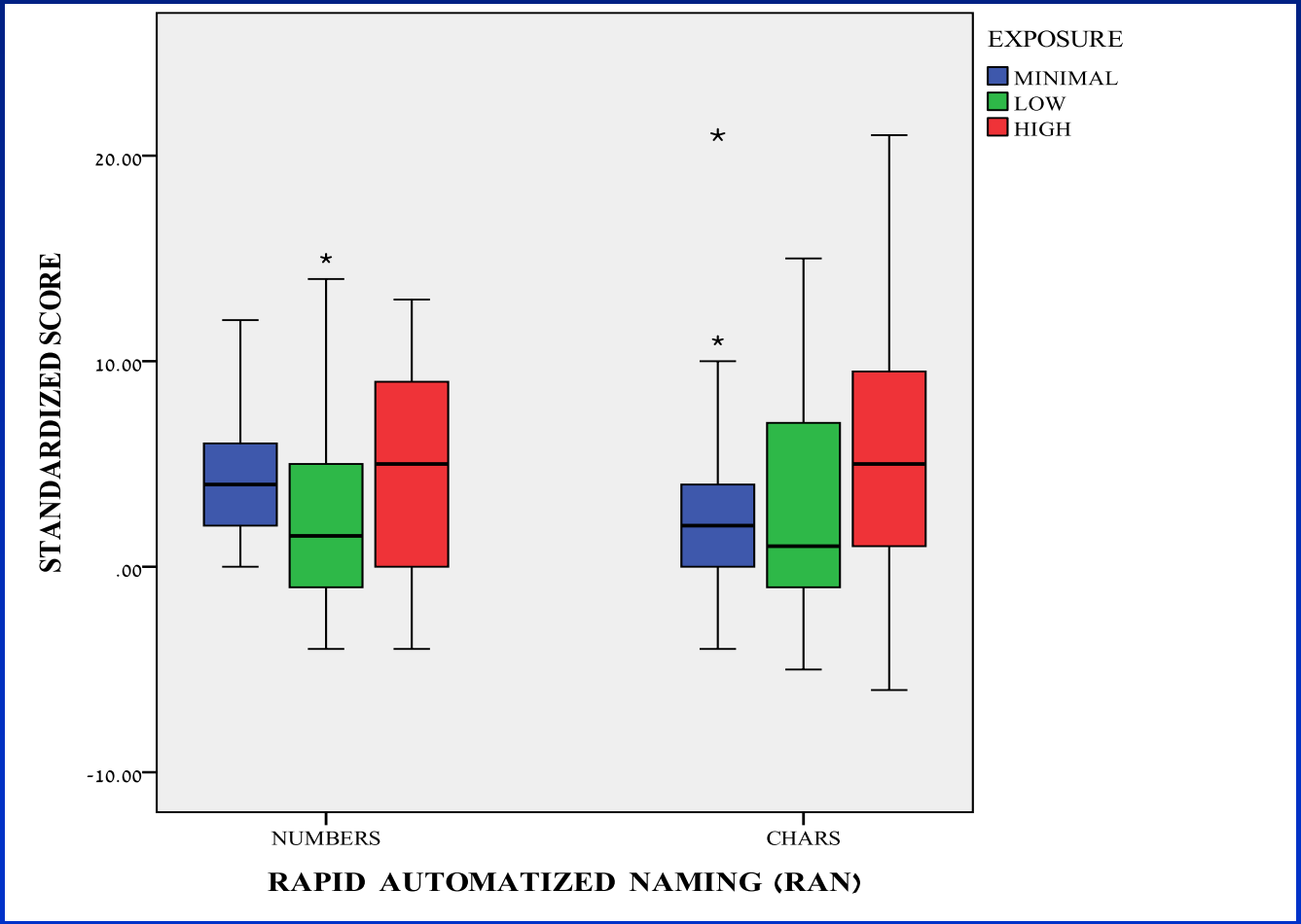
BENDER-GESTALT for perceptual motor skills



Valley Group (highly exposed): 50% of the schoolchildren are below normal limits

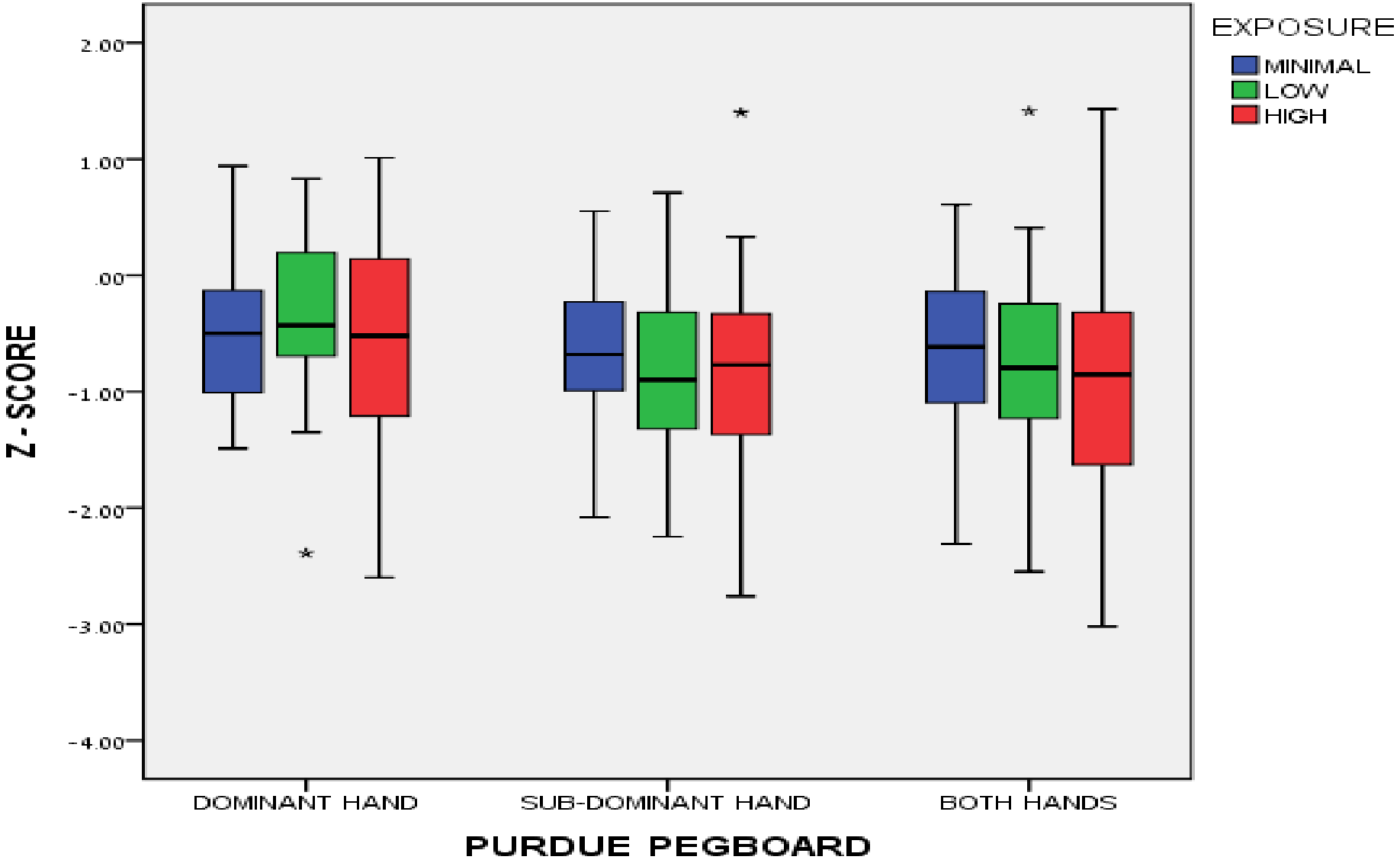
RAPID AUTOMATIZED NAMING

for reading competence



(RAN CHARACTERS: Kruskal-Wallis: p=0.07, Linearity: p=0.09)

PURDUE PEGBOARD for manual dexterity
FAMILY MODEL



Cognitive Indicative Tests:

- For comparison between past and present studies in same cohort, we used older tests
- In these tests, threshold of task accomplishment is relatively low
- Tests are less demanding than currently used Cognitive Ability Selection Tests

Anatomical Selectivity of OP-induced Effects

- **Findings:** dose-response gradient between OP exposure and changes in cognitive skills in children with background exposures

- **Findings:** altered executive skills, first and foremost those involving multi-tasking and mental rotation

- **Interpretation:** impairment of both frontal lobes and associated pathways?

ADHD questionnaires

Respondents in original adult cohort :

at least one child had been diagnosed with Attention Deficit/Hyperactivity Disorder (ADD/ADHD):

- **Hula Valley : 48 %**
- **Hills: 50 %**

ADD/ADHD affects 5%-7% of the children in Israel

HEALTH OUTCOMES vs. DISTANCE FROM SPRAYED FIELDS

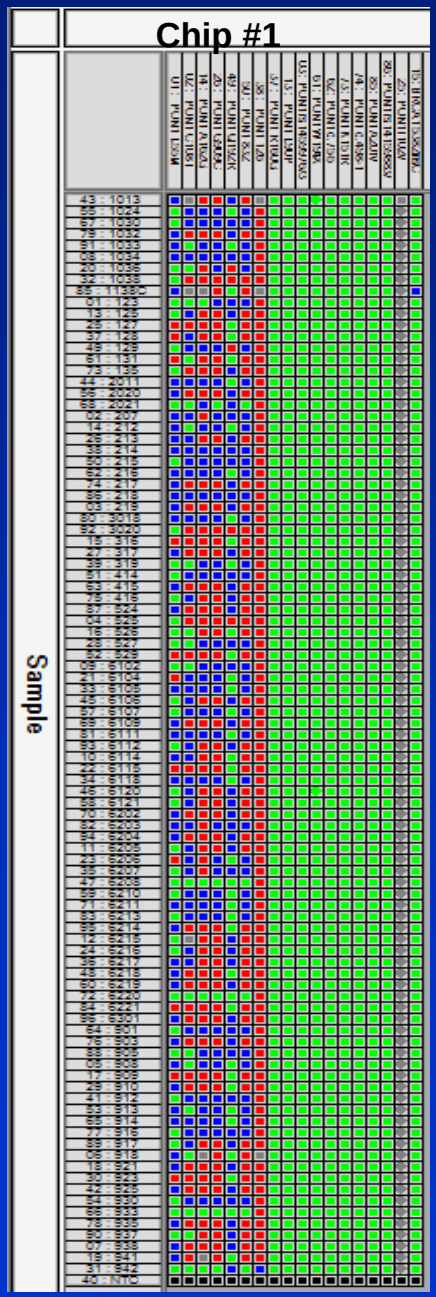
	Distance: 0-50 m Vs. >50 m	Distance: 0-100 m Vs. >100m
DD/ADHD OR (CI) Fisher's exact test Yes/Total (%) close vs. far	1.88 (0.51 ; 6.94) 0.26 5/11(45) vs. 19/62 (30)	1.15 (0.36 ; 3.60) 0.51 6/17(35) vs. 18/56(32)
ASTHMA OR (CI) Fisher's exact test Yes/Total (%) Near vs. Far	2.20 (0.59 ; 8.18) 0.19 5/11(45) vs. 17/62(27)	0.95 (0.29 ; 3.13) 0.59 5/17(29) vs. 17/56 (30)

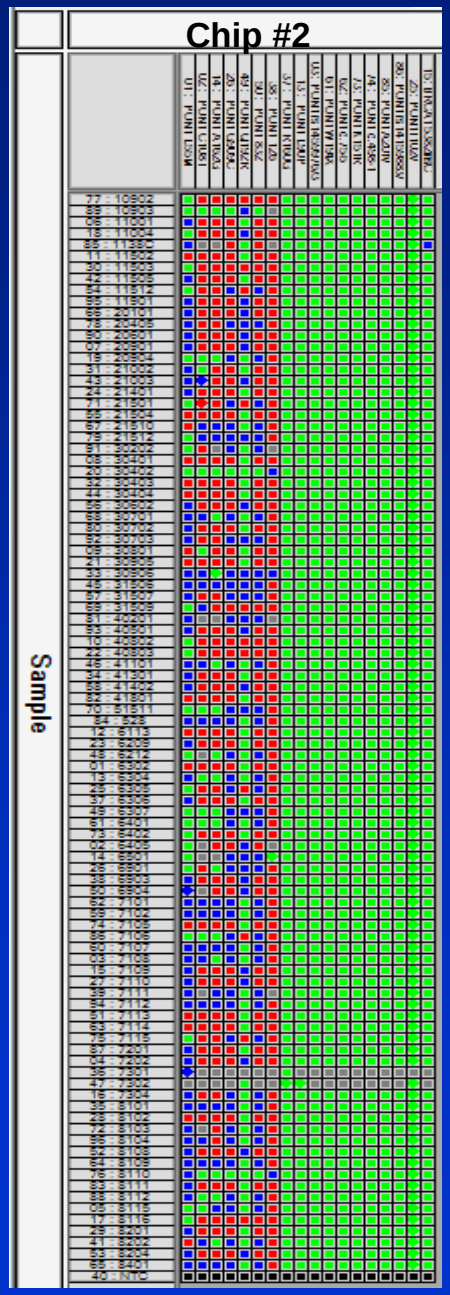
Current paradigm: a genetic factor is primarily responsible for ADHD.

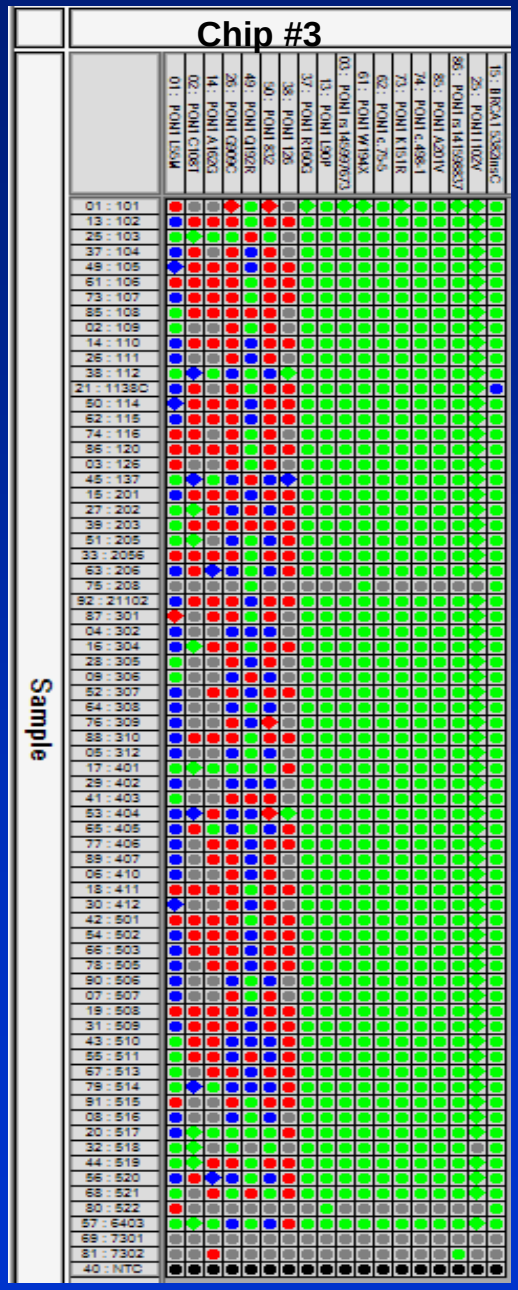
Need for:

PON-1 gene polymorphisms might reflect genetic susceptibility of children to effects of long-term low-level exposure to OP's.

Fluidigm Arrays raw results



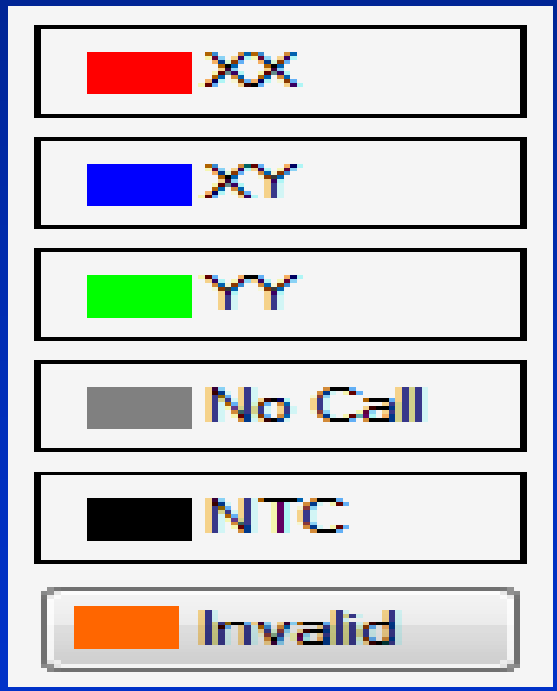




Rows: SNP Assays

Lines: Samples

Genotypes:



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