# Environmental contributors to neurodegeneration: Why not measure everything?
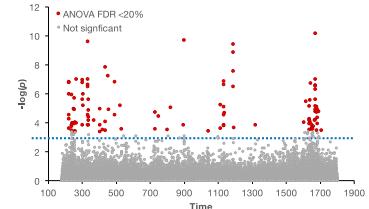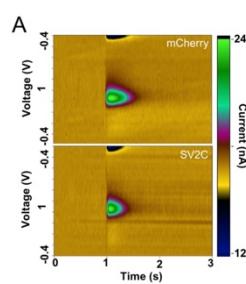
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@exposome
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COLUMBIA | MAILMAN SCHOOL OF PUBLIC HEALTH

age

pesticides

genes

head trauma

smoking

caffeine

exercise
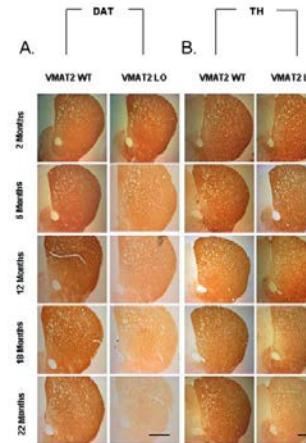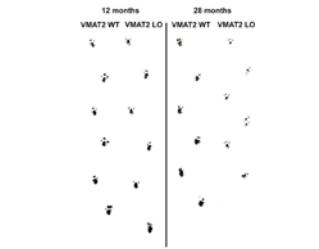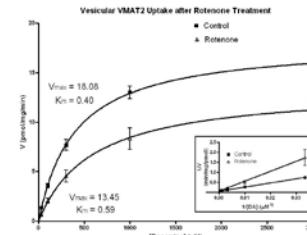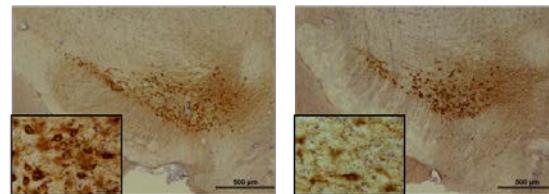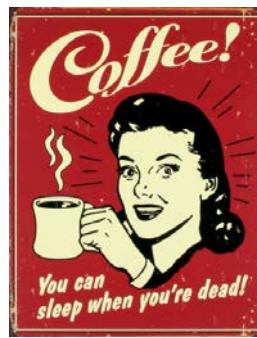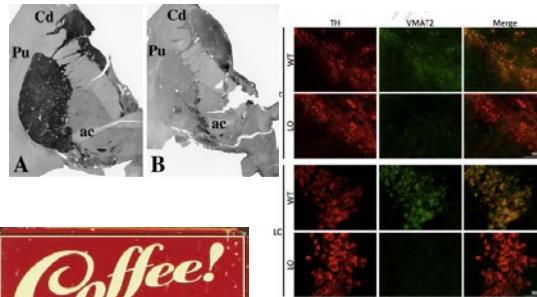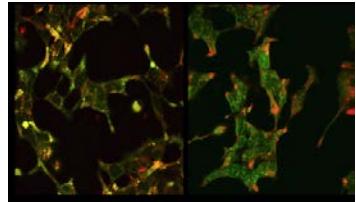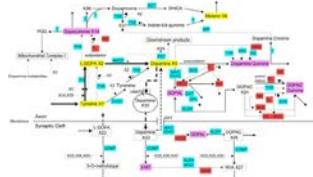
PESTICIDES

RODENTICIDES
Zinc Phosphide
Fluoroacetate Derivatives
α-naphthyl thiourea
Anticoagulants

FUMIGANTS
Phophine
Ethylene dibromide/
dibromochloropropane

HERBICIDES

Bipyridyls
- *Paraquat*
  Diquat
Chloroacetanilides
- *Alachlor*
Chlorophenoxy Compounds
- *2,4-dichlorophenoxyacetate*
Phosphomethyl amino acids
- *Glyphosate*

FUNGICIDES
Hexachlorobenze
Pentachlorophenol
Phthalamides
  - *Captan, Folpet*
Dithiocarbamates
  - *Maneb, Ziram*

INSECTICIDES

Organochlorines

- Cylclodienes
  -*Dieldrin, Heptachlor*
- Dichlorodiphenylethanes
  -*DDT, methoxychlor*
- Cyclohexanes
  - *Lindane, β-HCH*

Anticholinesterases

- Organophosphates
  - *Parathion,*
  Chlorpyrifos
- Carbamates
  - Aldicarb, Methomyl

Pyrethroids

- Type I
  - *Phenothrin*
- Type II
  - *Cypermethrin,*
  Deltamethrin

Avermectins
- *Ivermectin*

Botanicals

- Nicotine
- Rotenoids
  - *Rotenone,*
  Deguelin

Other

- Nitromethylene
- Chlor-onicotinyl
- Phenylpyrazole

Paraquat, rotenone, and MPTP are different
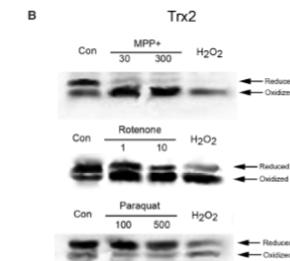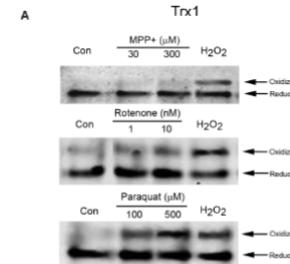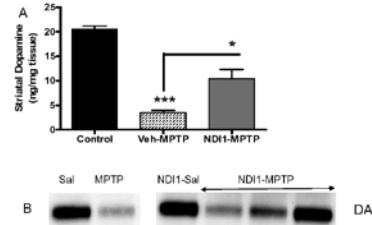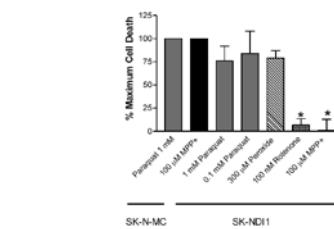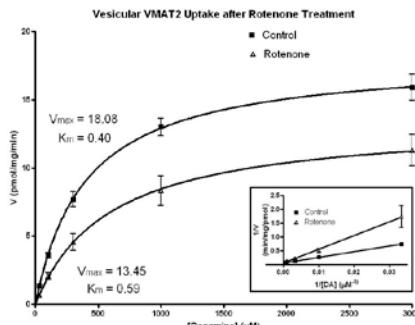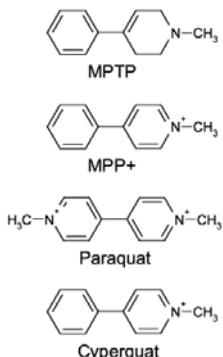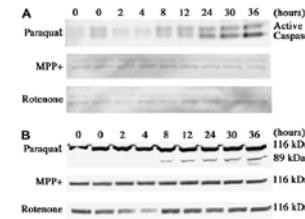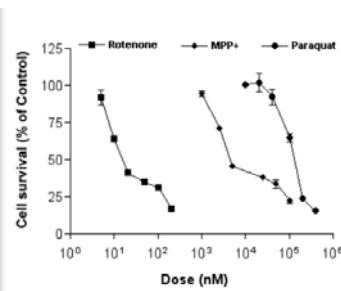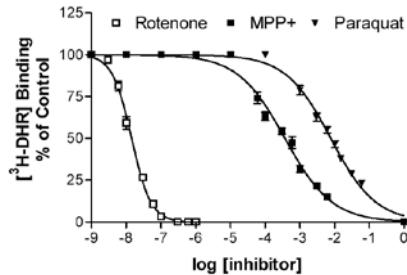
Increased vesicular monoamine transporter enhances dopamine release and opposes Parkinson disease-related neurodegeneration in vivo

Kelly M. Lohr[a,1], Alison I. Bernstein[a,1], Kristen A. Stout[a], Amy R. Dunn[a], Carlos R. Lazo[a], Shawn P. Alter[a], Minzheng Wang[a], Yingjie Li[a], Xueliang Fan[b], Ellen J. Hess[b,c], Hong Yi[d], Laura M. Vecchio[e], David S. Goldstein[f], Thomas S. Guillot[a], Ali Salahpour[e], and Gary W. Miller[a,b,c,g,2]

[a]Department of Environmental Health, Rollins School of Public Health, [b]Department of Pharmacology, [c]Department of Neurology, and [d]Robert P. Apkarian Integrated Electron Microscopy Core, and [g]Center for Neurodegenerative Diseases, Emory University, Atlanta, GA 30322; [e]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada M5S 1A8; and [f]National Institute of Neurological Disorders and Stroke, Bethesda, MD 20824

Synaptic vesicle glycoprotein 2C (SV2C) modulates dopamine release and is disrupted in Parkinson disease

Amy R. Dunn[a], Kristen A. Stout[a], Minagi Ozawa[a], Kelly M. Lohr[a], Carlie A. Hoffman[a], Alison I. Bernstein[a], Yingjie Li[a,b], Minzheng Wang[a], Carmelo Sgobio[c], Namratha Sastry[c], Huaibin Cai[c], W. Michael Caudle[a], and Gary W. Miller[a,b,d,e,1]

[a]Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA 30322; [b]Center for Neurodegenerative Diseases, Emory University School of Medicine, Atlanta, GA 30322; [c]Transgenics Section, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892; [d]Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322; and [e]Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322
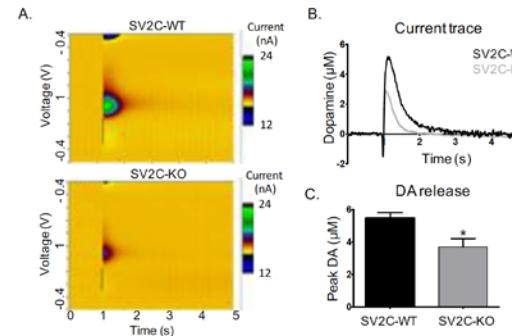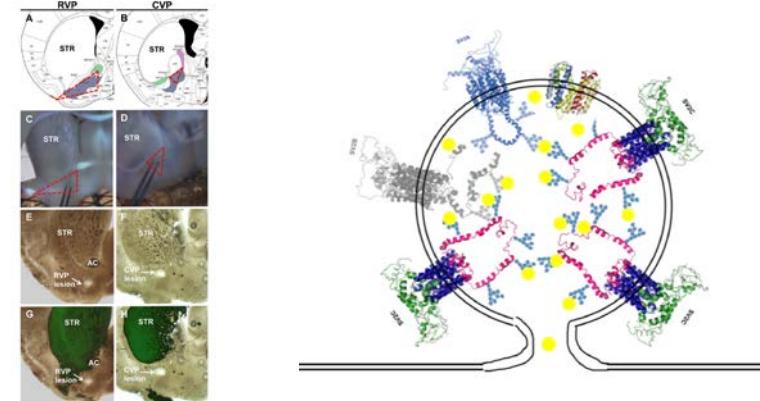
Vesicular Monoamine Transporter 2 (VMAT2) Level Regulates MPTP Vulnerability and Clearance of Excess Dopamine in Mouse Striatal Terminals
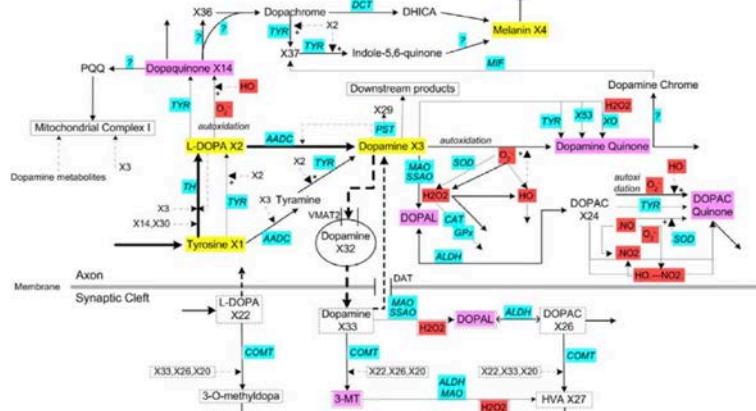
An imbalanced equation
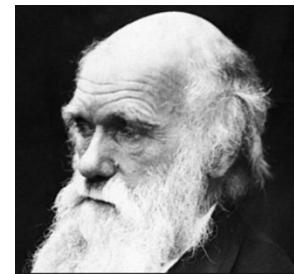
$$G \times E = P$$

Geneticists talk about the missing heritability, but I am interested in the missing everything else.

The Exposome: a Wild idea

**Complementing the Genome with an "Exposome":
The Outstanding Challenge of Environmental
Exposure Measurement in Molecular Epidemiology**

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health
and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

Rappaport and Smith, 2010

Characterizing the exposome. The exposome represents the combined exposures from all sources that reach the internal chemical environment. Toxicologically important classes of exposome chemicals are shown. Signatures and biomarkers can detect these agents in blood or serum.

ESEHD, NAS, 2010

Defined the "*Exposome*" as all exposures from
conception onwards, including those from
lifestyle, diet and the environment (2005)

Exposome: the cumulative measure of the environmental
influences and corresponding biological responses throughout
the lifespan (Miller and Jones, 2014)

External factors → internal signals

Ecosystems
Food outlets, alcohol outlets
Built environment and
  urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress
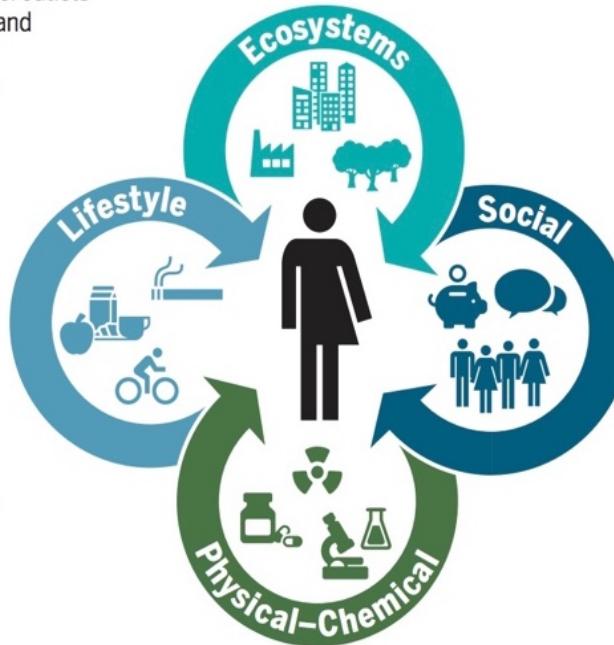
Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g,
  factories, ports
Outdoor and indoor air
  pollution
Agricultural activities,
  livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Vermeulen, Schymanski, Barabasi, Miller, 2020

A combined LC and GC high-resolution exposomics and metabolomics platform

Capturing <u>exogenous</u> chemicals and <u>endogenous</u> metabolites

ESI LC-MS

Ultra-high resolution MS
LTQ-FT
LTQ-Velos Orbitrap
Q-Exactive HF
Thermo Fusion

Data extraction

Data Table
m/z, RT, Intensity
Quality metrics

Biostatistics
Bioinformatics

MWAS

PLS-DA

Metabolites of interest

Unequivocal Identification

MSⁿ; UHRAM MS;
1-D, 2-D NMR; ion
Mobility; Chemical
Reactivity, etc

Metabolite forensics

Network and pathway analysis: *Mummichog*, MetabNet, others

T Yu et al 2009 Bioinformatics 25:1930-6
JM Johnson et al 2010 Analyst 135: 2864-2870
Q Soltow et al 2013 Metabolomics 9:S132–S143
T Yu et al 2013 J Proteome Res 12:1419-27
S Li et al 2013 Plos Comp Biol 9:e1003123
K Uppal et al 2013 BMC Bioinformatics 14:15
K Uppal et al 2015 Frontiers Bioeng Biotech 3:87

DP Jones 2016 *Tox Reports* **3**: 29-45

Gas-phase analysis | Overlap | Liquid-phase analysis

Semi-volatiles
Volatiles
Eicosanoids
Esters
Perfumes
Terpenes
Waxes
Caratenoids
Flavenoids
Chlorinated pollutants
Brominated flame retardants
PAHs

Alcohols
Alkaloids
Amino acids
Catecholamines
Fatty acids
Phenolics
Polar Organics
Prostaglandins
Steroids
ON pesticides
Plasticizers
Flame retardants

Non-volatiles
Semi-volatiles
Organic acids
Organic Amines
Nucleosides
Ionic Species
Nucleotides
Polyamines
Pollutant metabolites
Drug metabolites
Lipids
Water soluble vitamins

Less polar — **More polar**

Exposomics
Environmental exposures

Metabolomics
Biological response

Knowns, unknowns, and soon-to-be knowns

Metabolic, halogenated environmental chemical, dietary constituent, Alzheimer's medication

Table 2. Non-medication plasma metabolite features reproducibly associated with AD from MWAS

| Feature			Study 1		Study 2		Meta-analysis		
m/z[a]	RT[a]	Metabolite	Est (SE)	p	Est (SE)	p	Est (SE)	p	FDR
129.0661	89	Glutamine	0.22 (0.11)	0.04	0.31 (0.13)	0.02	0.25 (0.08)	0.002	0.07
246.9550	127	Unknown	0.41 (0.17)	0.02	0.38 (0.21)	0.07	0.40 (0.14)	0.003	0.08
349.1515	80	Piperine	-0.59 (0.31)	0.06	-0.89 (0.49)	0.07	-0.68 (0.27)	0.01	0.18
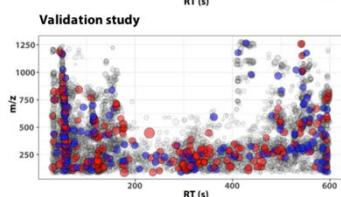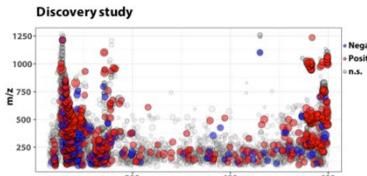
*Adduct of rivastigmine strongest feature associated with AD

Niedzwiecki et al., 2019 Annals of Clinical and Translational Neurology

# WHICAP study of Alzheimer's disease, Richard Mayeux, PI

Table 2. Number of blood samples	SA1		SA 2a	All Aims
	Controls	Incident AD	Prevalent AD	Metabolomes
2 +	724	247	375	3,692
3 (or more) ++	760	529	260	4,647
Totals	1484	776	635	8,339

Vardarajan et al. Differences in Plasma Metabolites Related to Alzheimer's Disease, APOE-ε4 status and Ethnicity. medRxiv posted 1/20/2020. Published in Alzheimer's and Dementia. May 6;6(1):e12025, 2020

Pathways altered in cases across different ethnicities

Size of bubble represents number of significant hits
Enrichment is calculated as (Total Hits/Pathway size)

Vardarajan et al. Differences in Plasma Metabolites Related to Alzheimer's Disease, APOE-ε4 status and Ethnicity. medRxiv posted 1/20/2020. Published in Alzheimer's and Dementia. May 6;6(1):e12025, 2020

The exposomic workflow is amenable to *C. elegans* (~500 worms)-pro-aggregating tau
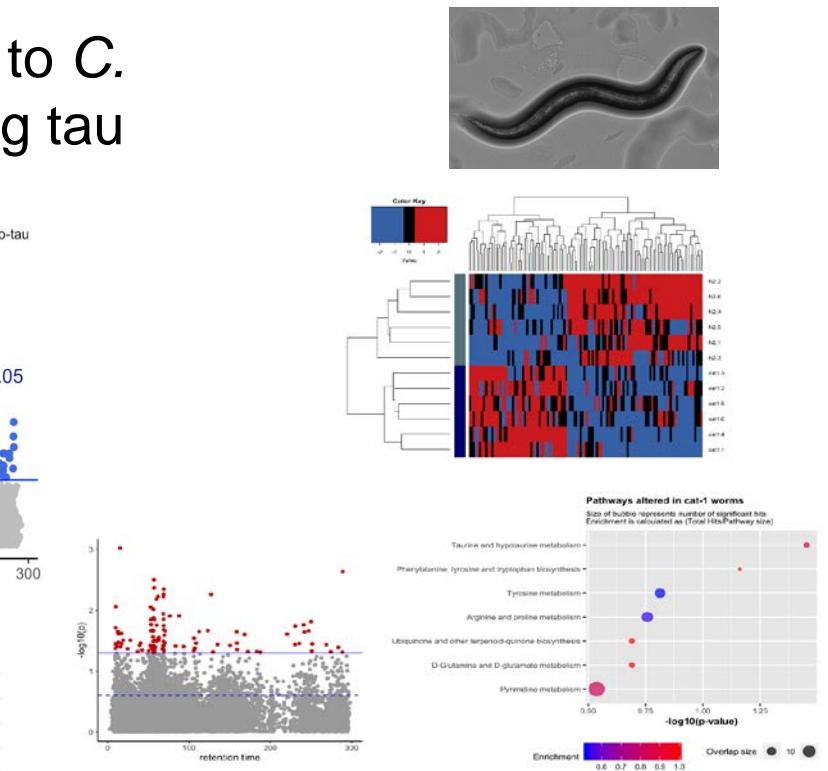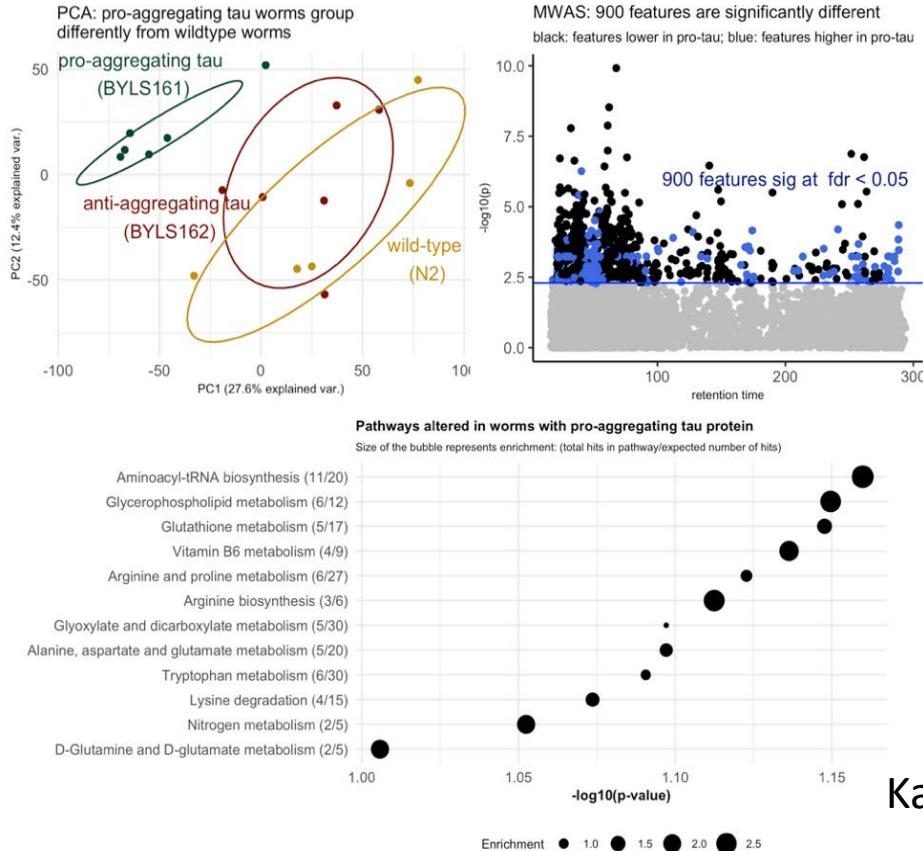
Kalia and Miller, unpublished observations

Mor, Kalia, Miller, Murphy (Preprint, bioRxiv 2/22/20, currently under review)
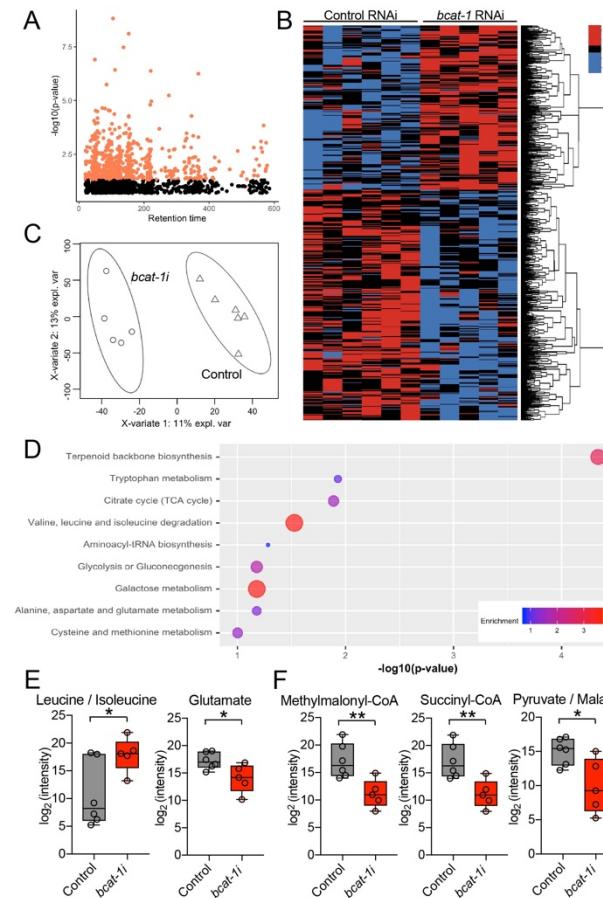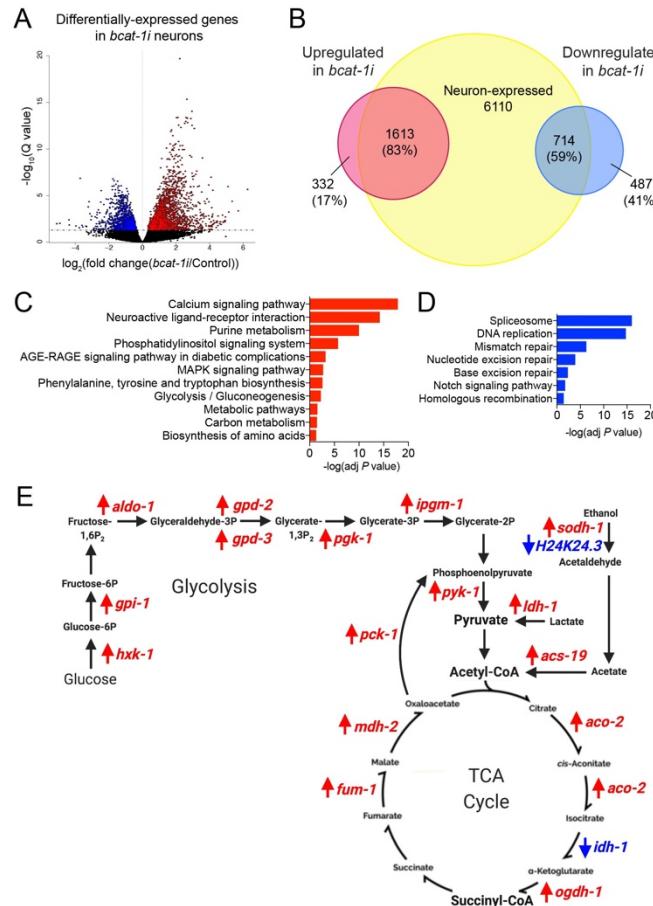
Conclusions

High-resolution mass spectrometry (HRMS) has become the *de facto* machinery for **exposome research** (in biological and environmental matrices**:** plasma, tissue, urine, water, dust, air, passive samplers)

HRMS provides the field with a tool that facilitates a systematic, comprehensive, and unbiased approach to study environmental contributors to neurodegenerative disease (or neuropsychiatric or neurodevelopmental conditions)

The exposome and health: Where chemistry meets biology

Roel Vermeulen[1,2]*, Emma L. Schymanski[3], Albert-Laszlo Barabási[4,5,6], Gary W. Miller[7]*

Despite extensive evidence showing that exposure to specific chemicals can lead to disease, current research approaches and regulatory policies fail to address the chemical complexity of our world. To safeguard current and future generations from the increasing number of chemicals polluting our environment, a systematic and agnostic approach is needed. The "exposome" concept strives to capture the diversity and range of exposures to synthetic chemicals, dietary constituents, psychosocial stressors, and physical factors, as well as their corresponding biological responses. Technological advances such as high-resolution mass spectrometry and network science have allowed us to take the first steps toward a comprehensive assessment of the exposome. Given the increased recognition of the dominant role that nongenetic factors play in disease, an effort to characterize the exposome at a scale comparable to that of the human genome is warranted.
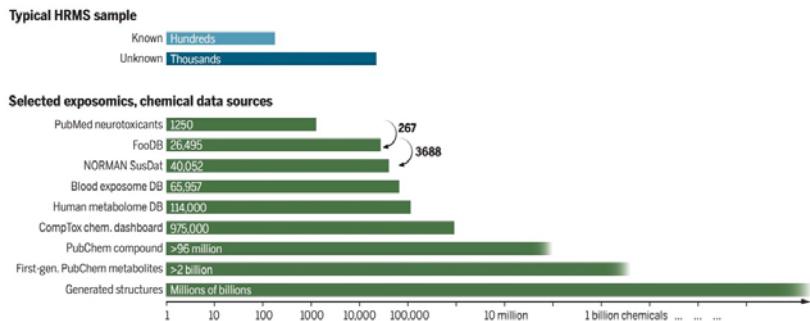

Fig. 2. Chemical complexity of HRMS and the exposome. Top: Known versus unknown features in a typical HRMS measurement [data from (7)]. Bottom: Selected data sources relevant to the chemical exposome (10–14, 19). Arrows show the overlap of potential neurotoxicants in FooDB (http://foodb.ca/) and FooDB components in NORMAN SusDat (www.norman-network.com/nds/susdat/) (prioritized chemicals of environmental interest).

Science. 367: 392-396, 2020

July 23-24, 2020
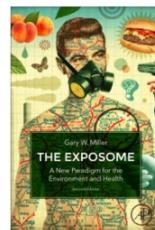
The Exposome

2nd Edition

A New Paradigm for the Environment and Health

☆☆☆☆☆ Write a review

Author: Gary W. Miller

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