Deep Research Report: Models, Measured Processes/Endpoints, and Disease Relevance of

35429626

Target paper: Bahrami M, Simpson SL, Burdette JH, Lyday RG, Quandt SA, Chen H, Arcury TA, Laurienti PJ. *Altered default mode network associated with pesticide exposure in Latinx children from rural farmworker families.* NeuroImage 2022;256:119179. PMID: 35429626 (DOI: 10.1016/j.neuroimage.2022.119179; open access PMC9251855)

Every factual claim about the paper below is traceable to the open-access full text. Items marked [inference] are interpretation, not statements made by the authors.

Summary

This paper is a **cross-sectional resting-state fMRI study** of 78 Latinx 8-year-old children — 48 from rural farmworker (FW) families and 30 from urban non-farmworker (NFW) families — that asks whether probable historic pesticide exposure is associated with the organization of the brain's **default mode network (DMN)**. The authors constructed whole-brain functional networks from a Shen 268-region parcellation, defined edges with Pearson correlations, and applied a **two-part mixed-effects network regression framework** (WFU_MMNET) that separately models the *probability* a connection exists and the *strength* of connections, correcting for multiple comparisons with an adaptive FDR procedure and covarying for sociodemographic and anatomical-distance factors. The headline result is specific and bounded: pesticide exposure is associated with a reorganization of **DMN-specific topology at the connection-probability level only** — higher exposure shifts DMN connections toward being governed more by local **clustering (segregation)** and less by **global efficiency (integration)**.

The effect is graded with exposure. In the primary group contrast (FW vs. NFW within the DMN), the probability–clustering interaction was $\beta = 0.4790$ ($p < 0.0001$) and the probability–global-efficiency interaction was $\beta = -0.4793$ ($p < 0.0001$). In a secondary analysis restricted to the 48 FW children, a continuous measure of parent-reported historic exposure (prenatal through 96 months) reproduced the same directional pattern (clustering $\beta = 0.1444$, $p < 0.0001$; global efficiency $\beta = -0.0705$, $p = 0.0304$). Crucially, **all connection-strength terms and all non-DMN (global) terms were non-significant**, making the finding a narrow, well-isolated signal rather than a diffuse whole-brain effect.

For a disease-mechanism knowledge base, this paper supplies one specific, citable mechanistic edge — *probable pesticide exposure → reorganized DMN connection-probability topology in developing children* — anchored in a vulnerable, understudied population. It provides **direct evidence relevant to organophosphate developmental neurotoxicity** and, through the DMN's established role in attention and higher cognition, to **ADHD and cognitive-deficit risk**. It is **indirectly relevant** to psychiatric disorders characterized by DMN dysfunction (depression, schizophrenia, autism) and **speculatively relevant** to later-life pesticide-linked neurodegeneration (Parkinson disease). The paper's hard limits must be stated plainly: it **diagnoses no disease** in its participants, measures **no cognitive or behavioral outcomes**, uses a **residential-proximity proxy rather than a pesticide biomarker**, and its **cross-sectional design cannot establish causality**.

Key Findings

Finding 1 — The core result: exposure-graded, DMN-specific topology reorganization at the connection-probability level

The paper's central claim is that **pesticide exposure is associated with default mode network-specific topological reorganization**, and that this signal appears specifically at the level of *whether a connection exists* (connection probability), not *how strong* existing connections are, and specifically *within the DMN*, not across the whole brain.

Study system. The cohort comprised **n = 78 children** (48 rural FW, 30 urban NFW), all Latinx, mean age ≈ 8.3–8.4 years. Brain networks were built from the **Shen 268-region functional parcellation**, with edges defined by **Pearson correlation** between regional time series (negative correlations set to zero). The DMN was represented by **37 regions of interest**. Analysis used the **two-part mixed-effects network regression** implemented in WFU_MMNET:

Part I models connection probability with a logistic link; Part II models connection strength. Models were **adaptive-FDR corrected** and covaried for maternal education and race, preschool education, parents' occupation, and inter-ROI anatomical distance plus distance^2.

Primary results (FW vs. NFW contrast, within DMN). The probability–clustering interaction was **β_{r,COI×DMN×Clust} = 0.4790 (p < 0.0001)**, with a contrast sum **β_{r,COI×Clust} + β_{r,COI×DMN×Clust} = 0.5226 (p < 0.0001)** indicating that FW children's DMN connections are *more positively* governed by clustering. The probability–global-efficiency interaction was **β_{r,COI×DMN×Eglob} = −0.4793 (p < 0.0001)**, contrast sum = **−0.5058 (p < 0.0001)**, indicating FW children's DMN connections are *more negatively* related to global efficiency.

Secondary results (continuous historic exposure, FW only, prenatal–96 months). The same directional pattern held: probability–clustering **β = 0.1444 (p < 0.0001)**, contrast = 0.1284 (p = 0.0003); probability–efficiency **β = −0.0705 (p = 0.0304)**, contrast = −0.0759 (p = 0.0466). Low-exposure FW children resembled the NFW group; high-exposure FW children resembled the FW group as a whole.

Specificity / negative controls. Every **connection-strength** term was non-significant (p = 0.36–0.99), and every **non-DMN global** term was non-significant. This is what makes the finding interpretable: the effect is confined to DMN connection probability.

Directional interpretation. Higher exposure → DMN connection probability increasingly governed by **clustering (local segregation)** and decreasingly by **global efficiency (long-range integration)** — a shift toward a more segregated, less integrated DMN.

The authors' own verbatim framing captures both the result and its associational character:

> "We found that network topology was differently associated with the connection probability between FW and NFW children in the DMN. Our results also indicated that, among 48 FW children, historic reports of exposure to pesticides from prenatal to 96 months old were significantly associated with DMN topology, as hypothesized." — PMID: 35429626
>
> "the observed associations between network connectivity/topology and historic exposure reports in FW children provide compelling evidence for a contribution of pesticide exposure on altering the DMN network organization in this vulnerable population" — PMID: 35429626

Finding 2 — Convergent prior evidence: organophosphate exposure alters DMN-constituent structure/connectivity, and the same farmworker-network signature appears in adults

Three independent human neuroimaging lines converge on DMN-region vulnerability and contextualize this paper's rationale and result:

1. **Rauh et al. 2012** (PMID: 22547821) — structural MRI of 40 children found prenatal **chlorpyrifos** associated with cortical enlargement including the **cuneus/precuneus and mesial superior frontal gyrus** — core DMN midline hubs. Verbatim: *"enlarged superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall of the right hemisphere."*
2. **van den Dries et al. 2020** (Generation R; PMID: 32805249) — in n = 518 preadolescents, prenatal **dimethyl-OP metabolites** were associated with lower fractional anisotropy (B = −1.00, 95% CI −1.80, −0.20 per 10-fold increase) in white-matter tracts interconnecting DMN regions. Verbatim: *"a 10-fold increase in averaged DM metabolite concentrations across pregnancy was associated with lower FA."*
3. **Bahrami et al. 2017** (PMID: 28583619) — the same research group's adult Latino farmworker study found *"brain networks in farmworkers had more clustered and modular structures when compared to non-farmworkers,"* with erythrocyte cholinesterase activity tracking the differences. This mirrors the increased-segregation signature seen in the children's DMN and ties it to the cholinergic molecular anchor.

Together these establish that (a) DMN hub regions are structurally and microstructurally sensitive to prenatal OP exposure, and (b) the increased-segregation network phenotype is reproducible across the lifespan within this research program.

Finding 3 — Disease relevance: direct for OP developmental neurotoxicity/ADHD-cognitive risk, indirect for psychiatric DMN disorders, speculative for Parkinson disease

The paper **diagnoses no disease**: only 3 of 78 children had any parent-reported learning disability, and no cognitive outcomes were measured. Disease relevance is therefore **mechanistic/exposure-pathway based**, graded as follows:

Disease / disorder	Relevance	Mechanistic basis	Key citation(s)
Chronic OP developmental neurotoxicity	**Direct**	Prenatal OP exposure → lower mental development, attention problems	PMID: 24291036, PMID: 26896854
ADHD / attention & learning phenotypes	**Indirect→Direct**	DMN implicated in ADHD; OP/pyrethroid exposure linked to ADHD	PMID: 18824195, PMID: 20478945
Psychiatric DMN disorders (depression, schizophrenia, autism)	**Indirect**	DMN segregation/ integration imbalance is a shared feature	PMID: 18824195
Parkinson disease / later-life neurodegeneration	**Speculative** (for pediatric sample)	Pesticide exposure ~2-fold PD risk; developmental OP perturbs PD-risk gene transcription	PMID: 23713084, PMID: 21968025

Supporting verbatim evidence:

- *"Most of the studies evaluating prenatal exposure observed a negative effect on mental development and an increase in attention problems in preschool and school children."* — PMID: 24291036
- *"We relate DMN dysfunction to dementia, schizophrenia, epilepsy, anxiety and depression, autism and attention deficit/hyperactivity disorder"* — PMID: 18824195
- *"Exposure to paraquat or maneb/mancozeb was associated with about a 2-fold increase in risk."* — PMID: 23713084
- *"Epidemiologic studies support a connection between organophosphate pesticide exposures and subsequent risk of Parkinson's disease"* — PMID: 21968025

The paper itself does not diagnose any disease in its participants — this must be emphasized in any knowledge-base encoding.

Finding 4 — Ontology mapping (verified) and the acetylcholinesterase molecular-initiating-event anchor

To represent this paper in a structured knowledge base, the following CURIEs were **verified via EBI OLS4**:

Entity	Term	CURIE	Status
Precuneus (DMN hub)	precuneus cortex	UBERON:0006093	verified
Posterior cingulate cortex	PCC	UBERON:0022353	verified
Medial prefrontal cortex	mPFC	UBERON:4450000	verified
Inferior parietal cortex	IPC	UBERON:0006088	verified
Default mode network	(no UBERON class)	MeSH:D000082702	verified
Exposure to pesticide	—	ECTO:0000530	verified
Exposure to organophosphorus compound	—	ECTO:9000284	verified
Specific learning disability	—	HP:0001328	verified
Neurodevelopmental abnormality	—	HP:0012759	verified
ADHD	—	HP:0007018	verified
Autism	—	HP:0000717	verified
Molecular initiating event	acetylcholinesterase inhibitor	CHEBI:38462	verified

Flagged correction: earlier iteration-1 guesses (ECTO:9000078, ECTO:9000541, UBERON:0002976, UBERON:0022352) were **incorrect** and are superseded by the verified IDs above.

The molecular-initiating-event anchor is **acetylcholinesterase inhibition**, the canonical OP mechanism, broadened by evidence that OP esters also act through **non-cholinergic pathways** (cAMP, glutamate/GABA, endocrine). Verbatim: *"organophosphate esters can alter neurodevelopmental processes by interfering with noncholinergic pathways at environmentally relevant doses"* (PMID: 34612677). Lower-level mechanistic models (absent from the paper, present in related work) include **zebrafish** OP developmental neurotoxicity — chlorpyrifos →

AChE inhibition + down-regulated *mbp/syn2a/a1-tubulin* + locomotor deficits (PMID: 32730898, PMID: 29605586, PMID: 27018022). Verbatim zebrafish anchor: *"The STC test accurately detected the effect of 8 out of 11 neuroactive substances (chlorpyrifos, chlorpyrifos-oxon, diazinon..."* (PMID: 32730898).

Finding 5 — The residential-proximity exposure proxy is externally validated against autism, ADHD, and IQ loss

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defines exposure as **parent-reported months living next to agricultural fields** — a residential-proximity proxy. Independent studies using the same proxy class or OP biomarkers link this exposure to downstream neurodevelopmental disease, strengthening the exposure arm of the inferred pathway:

Study	Cohort	Exposure measure	Outcome	Effect
Shelton 2014 (PMID: 24954055)	CHARGE	Residential proximity to OP application	ASD	~60% ↑ risk; 2nd-trimester chlorpyrifos OR = 3.3 (1.5–7.4)
Gunier 2017 (PMID: 28557711)	—	Prenatal proximity to OP use	IQ	−2.2 Full-Scale IQ points (−3.9, −0.5)
Sagiv 2018 (PMID: 29701446)	CHAMACOS	Prenatal urinary DAP	Social behavior	+2.7 SRS-2 T-score points per 10-fold DAP (age 14)
Bouchard 2010 (PMID: 20478945)	NHANES	Urinary DMAP	ADHD	OR = 1.55 (1.14–2.10)
Wagner-Schuman 2015 (PMID: 26017680)	NHANES	Pyrethroid 3-PBA > LOD	ADHD	OR = 2.42 (1.06–5.57)

Verbatim anchors: - *"Proximity to organophosphates at some point during gestation was associated with a 60% increased risk for ASD, higher for third-trimester exposures"* — PMID: 24954055 - *"We observed a decrease of 2.2 points [95% confidence interval (CI): −3.9, −0.5] in Full-Scale IQ"* — PMID: 28557711 - *"A 10-fold increase in DMAP concentration was associated with an odds ratio of 1.55"* — PMID: 20478945

Study Models / Systems

Models used *in this paper*

Component	Description	Key limitations
Human cohort design	78 Latinx children: 48 rural FW vs. 30 urban NFW; age ≈ 8.3–8.4 y; recruited from the PACE5 study of farmworker families	Cross-sectional; FW vs. NFW confounded by **urban/rural** and **socioeconomic** differences; modest n (esp. 30 NFW); single age snapshot
Exposure-assessment model	"Probable historic pesticide exposure" = **parent-reported months living adjacent to agricultural fields**, prenatal → 96 months; a residential-proximity proxy	**Proxy, not a biomarker**; parent recall bias; no chemical speciation; no dose/intensity; collinear with rural residence
Imaging acquisition	Resting-state fMRI	Standard rs-fMRI confounds (motion, physiological noise); no task validation of DMN function
Network construction	Shen 268-region parcellation; Pearson-correlation edges (negatives zeroed); DMN = 37 ROIs	Parcellation/thresholding choices affect topology; zeroing negatives discards anticorrelation information
Statistical model	Two-part mixed-effects network regression (WFU_MMNET): Part I = connection probability (logistic); Part II = strength; adaptive-FDR; covariates: maternal education/race, preschool education, parents' occupation, distance + distance^2	Associational; residual confounding; covariate set cannot fully separate pesticide from poverty/rurality

Models in the wider literature (NOT in this paper)

- **Human birth cohorts:** CHAMACOS (PMID: 29701446), Columbia CCCEH (Rauh, PMID: 22547821), Generation R (PMID: 32805249), CHARGE (PMID: 24954055), ECHO, Rhea — these

use **urinary DAP biomarkers** or **pesticide-use-registry proximity**, measures this paper's proxy approximates.

- **Rodent:** chlorpyrifos/diazinon/parathion gestational and neonatal exposure (e.g., PMID: 18941570, PMID: 20026089).
- **Zebrafish:** chlorpyrifos and OP flame retardants → locomotor and transcriptional neurodevelopmental deficits (PMID: 32730898, PMID: 29605586, PMID: 27018022).
- **In vitro:** PC12 and neuronal cultures revealing cAMP-cascade convergence (PMID: 20026089, PMID: 21968025).

Biological Processes and Endpoints Measured

Endpoint (in paper)	Biological process it reads out	Ontology anchor (verified)	Direction & strength as reported
DMN connection probability	Existence of functional coupling between DMN regions	DMN = MeSH:D000082702; hubs UBERON:0006093 (precuneus), UBERON:0022353 (PCC), UBERON:4450000 (mPFC), UBERON:0006088 (IPC)	Primary effect — reorganized with exposure
Clustering governing probability	Local **functional segregation**	—	↑ with exposure: β = 0.4790 ($p<0.0001$) group; 0.1444 ($p<0.0001$) continuous
Global efficiency governing probability	Long-range **functional integration**	—	↓ with exposure: β = −0.4793 ($p<0.0001$) group; −0.0705 ($p=0.0304$) continuous
Connection strength	Magnitude of functional coupling	—	**No significant effects** ($p = 0.36$–0.99)
Non-DMN (global) topology	Whole-brain network organization	—	**No significant effects** (negative control)
Exposure measure	Probable historic pesticide/OP exposure	ECTO:0000530 (pesticide), ECTO:9000284 (organophosphorus)	Graded dose-response within FW group

No cognitive, behavioral, or exposure-biomarker endpoints were measured in the paper. The molecular-initiating event (not measured here) is **acetylcholinesterase inhibition** (CHEBI:38462). **[inference]** The CURIEs above are proposed mappings; the DMN has no UBERON class, so MeSH D000082702 is used.

Mechanistic Model / Interpretation

The findings assemble into a candidate **Adverse Outcome Pathway (AOP)** in which this paper supplies one specific, empirically supported edge (the DMN-reorganization step):

```
Pesticide exposure            MOLECULAR INITIATING EVENT        NEURODEVELOPMENTAL          NE
(residential proximity,  -->  Acetylcholinesterase inhibition   PERTURBATION          -->  KEY
 prenatal-96 mo)              (± non-cholinergic: cAMP,     -->  (altered maturation         F
 [ECTO:0000530 /              glutamate/GABA, endocrine)         of late-maturing
  ECTO:9000284]               [CHEBI:38462]                      DMN hubs)

 -- validated externally --   -- rodent/zebrafish/in vitro --    -- Rauh, Generation R --   <
```

The **direction of the network change** — more clustering, less global efficiency — denotes a DMN that is more locally segregated and less globally integrated. Because DMN hubs (precuneus/PCC, mPFC, IPC) are **late-maturing** and support self-referential and higher-order cognition, a developmentally-timed shift toward segregation is a biologically plausible substrate for the attention and cognitive phenotypes repeatedly linked to OP exposure in the epidemiological literature (Findings 3 and 5) **[inference]**. The adult farmworker replication of the increased-segregation signature (PMID: 28583619), together with its link to erythrocyte cholinesterase activity, strengthens the mechanistic plausibility of the cholinergic anchor.

Importantly, the knowledge-base representation should encode this as an **association edge with a proxy exposure node**, not a causal/diagnostic edge. The paper supports the middle of the AOP; the molecular-initiating event and the clinical outcome are imported from other model systems and cohorts.

Evidence Base

PMID	Role	How it supports / challenges
35429626	**Target paper**	Establishes exposure-graded DMN connection-probability reorganization (↑ clustering, ↓ efficiency)
22547821	Supports	Prenatal chlorpyrifos alters precuneus/cuneus and mPFC — DMN hubs
32805249	Supports	Large cohort: prenatal OP metabolites → lower white-matter FA in DMN-connecting tracts
28583619	Supports	Same group: adult farmworkers show increased clustering/modularity tied to cholinesterase
24291036	Supports	Prenatal OP → poorer mental development, attention problems
26896854	Supports	Systematic review: prenatal OP → neurodevelopmental disturbances; pesticide → PD risk
18824195	Supports	DMN dysfunction common across ADHD, autism, depression, schizophrenia
23713084	Supports (speculative arm)	Pesticide exposure → ~2-fold Parkinson disease risk
21968025	Supports (speculative arm)	Developmental OP exposure perturbs PD-risk gene transcription
34612677	Supports (mechanism)	Non-cholinergic OP neurodevelopmental mechanisms
32730898, 29605586, 27018022	Supports (lower-level models)	Zebrafish OP neurotoxicity: AChE inhibition, marker down-regulation, locomotor deficits
24954055, 28557711, 29701446, 20478945, 26017680	Supports (exposure proxy validity + outcomes)	Proximity/biomarker proxies linked to ASD, IQ loss, ADHD

Limitations and Knowledge Gaps

1. **Cross-sectional design** — cannot establish causality or temporal ordering; no longitudinal trajectory.
2. **Proxy exposure** — parent-reported residential proximity, not a measured pesticide biomarker; no chemical speciation, no intensity/dose; subject to recall bias.
3. **Confounding by rurality and SES** — FW vs. NFW differ in urban/rural residence and socioeconomic status; covariate adjustment cannot fully disentangle pesticide exposure from correlated deprivation and environmental factors.
4. **No clinical or cognitive outcomes** — the paper measures network topology only; it **diagnoses no disease** and cannot link the DMN change to any behavioral phenotype in these children (only 3/78 had any parent-reported learning disability).
5. **Modest sample** — 78 total (30 NFW) limits power and generalizability.
6. **Analytic choices** — Shen-268 parcellation, correlation thresholding, and negative-edge zeroing all influence topology; robustness to alternative pipelines is untested here.
7. **Specificity but not localization** — the effect is DMN-specific and probability-specific, but the paper does not identify which individual DMN edges/hubs drive it.

Proposed Follow-up Experiments / Actions

1. **Longitudinal re-imaging** of the PACE5 FW cohort to test whether the DMN segregation shift persists, worsens, or recovers, and whether it predicts later cognitive/attention outcomes.
2. **Add pesticide biomarkers** (urinary DAP metabolites, erythrocyte cholinesterase activity) to convert the proximity proxy into a quantified, speciated exposure and test dose-response at the molecular level.
3. **Couple imaging to cognition** — administer standardized attention/executive and IQ batteries (SRS-2, Conners, WISC) to directly connect DMN topology to clinically meaningful phenotypes.

4. **Edge-level localization** — identify which DMN hubs (precuneus/PCC vs. mPFC vs. IPC) drive the connection-probability effect to sharpen the UBERON-level knowledge-base annotation.
5. **Better control groups** — recruit rural non-farmworker and low-exposure rural children to decouple pesticide exposure from rurality/SES.
6. **Cross-species anchoring** — align the human DMN-segregation readout with zebrafish/rodent AChE-inhibition and connectivity endpoints to formalize the AOP from MIE to network key event.
7. **Knowledge-base encoding** — represent this as an *association* edge: `exposure to organophosphorus compound (ECTO:9000284) → altered DMN (MeSH:D000082702) connection-probability topology`, with the MIE node `acetylcholinesterase inhibitor (CHEBI:38462)` imported from related models and an explicit "no disease diagnosed" flag.

What this paper can and cannot support as evidence

Can support: a specific, exposure-graded **association** between probable historic pesticide exposure and **DMN-specific connection-probability topology** (↑ clustering/segregation, ↓ global efficiency/integration) in developing Latinx children — a mechanistic key-event edge for an OP developmental-neurotoxicity knowledge base.

Cannot support: any disease diagnosis, any causal claim, any cognitive/behavioral outcome, or any molecular measurement — these must be imported from other cohorts and model systems.

Usable verbatim evidence snippets (from the paper): - *"We found that network topology was differently associated with the connection probability between FW and NFW children in the DMN."* - *"among 48 FW children, historic reports of exposure to pesticides from prenatal to 96 months old were significantly associated with DMN topology, as hypothesized."* - *"the observed associations between network connectivity/topology and historic exposure reports in FW children provide compelling evidence for a contribution of pesticide exposure on altering the DMN network organization in this vulnerable population."*
