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Developmental exposure to Pb^{2+} induces transgenerational changes to zebrafish brain transcriptome

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ABSTRACT

Lead (Pb^{2+}) is a major public health hazard for urban children, with profound and well-characterized developmental and behavioral implications across the lifespan. The ability of early Pb^{2+} exposure to induce epigenetic changes is well-established, suggesting that Pb^{2+}-induced neurobehavioral deficits may be heritable across generations. Understanding the long-term and multigenerational repercussions of lead exposure is crucial for clarifying both the genotypic alterations behind these behavioral outcomes and the potential mechanism of heritability. To study this, zebrafish (*Danio rerio*) embryos (<2 h post fertilization; EK strain) were exposed for 24 h to waterborne Pb^{2+} at a concentration of 10 μM. This exposed F_0 generation was raised to adulthood and spawned to produce the F_1 generation, which was subsequently spawned to produce the F_2 generation. Previous avoidance conditioning studies determined that a 10 μM Pb^{2+} dose resulted in learning impairments persisting through the F_2 generation. RNA was extracted from control- and 10 μM Pb^{2+}-lineage F_2 brains, (n = 10 for each group), sequenced, and transcript expression was quantified utilizing Quant-Seq. 648 genes were differentially expressed in the brains of F_2 lead-lineage fish versus F_2 control-lineage fish. Pathway analysis revealed altered genes in processes including synaptic function and plasticity, neurogenesis, endocrine homeostasis, and epigenetic modification, all of which are implicated in lead-induced neurobehavioral deficits and/or their inheritance. These data will inform future investigations to elucidate the mechanism of adult-onset and transgenerational health effects of developmental lead exposure.

1. Introduction

Despite increased awareness and management of the common routes of lead (Pb^{2+}) exposure, the persistence of lead-contaminated low-income housing and aging water infrastructure in many susceptible communities, as evidenced in the Flint, Michigan water crisis, puts young children and pregnant/lactating women at risk for long-term health consequences (Carrel et al., 2017; ATSDR, 2019; Campbell et al., 2016). Although both environmental Pb^{2+} and average childhood blood Pb^{2+} levels (BLL) have declined over the past decade (Jain, 2016), approximately 15% of urban children in the United States still exhibit blood Pb^{2+} poisoning (defined by the Center for Disease Control and Prevention as levels ≥5 μg Pb^{2+}/dL; Filippelli et al., 2005), and about 1% of women of childbearing age (15–44 years) have BLL ≥5 μg Pb^{2+}/dL (Jones et al., 2010). Maternal Pb^{2+} exposure during pregnancy can cause fetal Pb^{2+} exposure, adversely affecting child health and behavioral outcomes. In fact, early-life Pb^{2+} exposure remains a major cause of life-long learning and behavioral difficulties, ranging from decreased performance on a variety of cognitive, intelligence, and mental development tests to increases in reported anti-social behaviors and Attention Deficit/Hyperactivity Disorder symptoms (Dietrich et al., 1991, 2001; Jedrychowski et al., 2009).

Pb^{2+} exposure during development can alter nervous system morphology through several mechanisms, including disruption of

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blood-brain barrier establishment (Goldstein, 1990), alterations in synaptic proliferation and pruning (Goldstein, 1992; Jaako-Movits et al., 2005; Costa et al., 2004), interference with thyroid hormone transport into the brain (Zheng et al., 2001) and shifts in neurotransmitter release (Cory-Slechta, 1997), affecting both the glutamatergic system, which is implicated in learning and memory (Lidsky and Schneider, 2003), and the dopaminergic system, which is implicated in executive functioning and attention (Brown et al., 1997). Although the effect of early childhood lead exposure on IQ levels was first observed 40 years ago when the mean BLL was 15 μg Pb^{2+}/dL, studies since then have reported behavioral dysregulation and speech and learning deficits at continually decreasing levels of exposure, suggesting no threshold for the neurological effects of lead (Needleman et al., 1979; Needleman and Landrigan, 2004; White et al., 2007).

Persistence of Pb^{2+}-induced neurobehavioral effects may be attributable to epigenetic modifications to the genome; early Pb^{2+} exposure in primates is associated with later life repression of DNA methylation and histone modification enzymes, and occupationally-exposed humans displayed Pb^{2+}-induced changes in global DNA methylation (Bihaqi et al., 2011; Devóz et al., 2017). Heritable changes in gene expression due to early developmental exposures to contaminants may increase the risk for transgenerational inheritance of phenotypes associated with toxicity (Bernal and Jirtle, 2010; Baker et al., 2014). Although transgenerational effects of Pb^{2+} exposure have yet to be well characterized, some evidence supports the heritability of these epigenetic effects, including altered DNA methylation patterns in the grandchildren of pregnant mothers exposed to Pb^{2+} (Sen et al., 2015). Heritable behavioral effects have been reported in one other animal model, to our knowledge; early-life exposure to a mixture of lead and BDE-209 resulted in transgenerational neurobehavioral toxicity in zebrafish (Chen et al., 2017). The inheritance of neurobehavioral health deficits well past the original Pb^{2+} exposure has concerning implications, suggesting the need for a deeper understanding of the mechanism underlying these effects. To study this, zebrafish exposed to 10 μM Pb^{2+} during embryonic development were raised to the F_2 generation and assessed with an avoidance conditioning paradigm, establishing a transgenerational pattern of neurobehavioral impairment in the exposed fish line (Xu et al., 2016).

In this study, we performed Quant-Seq gene expression analysis on the brains of F_2 generation fish to determine the presence of transgenerational changes in gene expression due to ancestral Pb^{2+} exposure. To our knowledge, this study was the first use of zebrafish to model the transgenerational effects of Pb^{2+} exposure; others, however, have well established that F_0 lead exposure in zebrafish results in neurological impairment as indicated by behavioral, neuromorphological, and transcriptomic analysis (Chen et al., 2012; Lee et al., 2018; Zhang et al., 2011). Zebrafish are increasingly used to model the consequences of toxicant exposure during nervous system development, since they share overall brain structural homology, basic behavioral neural circuits, and neurodevelopmental gene networks with humans, coupled with the advantages of high fecundity, rapid neurodevelopment, and external fertilization (Lee and Freeman, 2014a, b; Teame et al., 2019; Sakai et al., 2018; d'Amora and Giordani, 2018; Horzmann and Freeman, 2018). Considering that zebrafish also have a relatively rapid generation time (3–4 months), multiple generations can be conveniently screened for an inherited disease phenotype. By utilizing this model, we can characterize any transgenerational effects observed due to F_0 generation Pb^{2+} exposure during embryonic development, and gain insight into the mechanism of persistent Pb^{2+}-induced neurobehavioral disease.

2. Methods

Animal husbandry. Zebrafish (EK strain) were kept at 26–28 °C with a standard 14 h:10 h light:dark cycle as described by Westerfield (2000). Husbandry was performed as previously described in Xu et al. (2016). Zebrafish were raised in a flow-through system at the Aquatic Animal Facility of the University of Wisconsin-Milwaukee Children's Environmental Health Sciences Center. Larval fish were fed vinegar eels twice daily from 5 days post-hatch until they grew large enough to ingest *Artemia nauplii*. Adult fish were fed Aquarian™ flakes and *Artemia nauplii*, each once per day. The protocol for zebrafish use and maintenance was approved by the Institutional Animal Care and Use Committee at University of Wisconsin-Milwaukee, which follows the National Institutes of Health Guide to the Care and Use of Laboratory Animals.

Lead exposure. Lead ($Pb(NO_3)_2$) exposure was performed as previously described in Xu et al. (2016). The F_0 generation was exposed as embryos [<2 h post fertilization (hpf)] to 0 or 10 μM Pb^{2+} in glass dishes with 100 ml E2 medium for a period of 24 h. Embryos were then rinsed and maintained in Pb^{2+}-free E2 medium. No significant developmental toxicity was observed in Pb^{2+}-exposed F_0 fish compared to controls, as measured by mortality and presence of developmental malformations. This exposed generation was mass-spawned to produce the F_1 generation, which was then mass-spawned to produce the F_2 generation. Only the F_0 generation was directly exposed to Pb^{2+}. To note, this generational schema presents a departure from that of the Xu et al. (2016) paper, in which the directly-exposed generation is referred to as the F_1 generation. Here, we refer to the directly-exposed generation as the F_0 generation for consistency with other transgenerational animal models.

RNA Isolation. At 10 months post fertilization, brains from 5 female fish and 5 male fish from both control (n = 10) and 10 μM Pb^{2+} (n = 10) groups from the F_2 generation were extracted, formalin-fixed, and stored at −80 °C. Brains were homogenized and RNA was isolated using RecoverAll™ Total Nucleic Acid Isolation Kit (Life Technologies, Carlsbad, CA), designed to extract nucleic acids from formalin-fixed samples. The Qubit® 2.0 Fluorometer and Qubit® RNA High Sensitivity Assay Kit (Invitrogen, Carlsbad, CA) were used to measure RNA concentrations (Supplemental Table S1).

QuantSeq. 3′ mRNA-seq libraries were prepared from isolated RNA using QuantSeq 3' mRNA-Seq Library Prep Kit FWD for Illumina (Lexogen, Vienna, Austria), which has shown robust correlation between fresh frozen and formalin-fixed transcriptomic profiles (Turnbull et al., 2018). Samples were normalized to 15 ng/μL (total input of 75 ng in 5 μL) and amplified at 18 cycles. Libraries were quantified using a Qubit® 2.0 Fluorometer and Qubit® dsDNA Broad Range Assay Kit (Invitrogen, Carlsbad, CA), and run on an Agilent TapeStation 2200 (Agilent Technologies, Santa Clara, CA) for quality control. The samples were sequenced on a HiSeq 2500 (Illumina, San Diego, CA) in rapid mode (single-end 50 bp reads). Reads were aligned to *D. rerio* (Build danRer10, selected due to supporting documentation) using the alignment tool STAR (Spliced Transcripts Alignment to a Reference; Dobin et al., 2013). Differential gene expression between the control and exposure lineage zebrafish was evaluated using edgeR (available through Bioconductor; Robinson et al., 2009). Female and male brains were analyzed both separately and combined for gene expression and pathway analysis. Genes with significant changes in expression, as defined by absolute log2 fold change value ≥ 1 and p-value < .05 (Supplemental Table S2), were uploaded into Ingenuity Pathway Analysis software (IPA; QIAGEN Bioinformatics, Redwood City, CA) for analysis using RefSeq IDs as identifiers. For the combined

samples, 437 molecules were available for analysis; when female and male brains were analyzed separately, 197 molecules were available for females, and 297 were available for males (full IPA disease and biological functions output in Supplemental Table S3).

qRT-PCR. TaqMan® Gene Expression Assays (Applied Biosystems™, Foster City, CA) were used to validate a representative group of six genes found to be differentially expressed in the QuantSeq analysis. At 50 ng/μL, 10 μL of RNA were reverse-transcribed using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems™, Foster City, CA), resulting in 20 μL of 25 ng/μL cDNA. Using the TaqMan® PreAmp Master Mix Kit (Applied Biosystems™, Foster City, CA), 10 μL of cDNA were pre-amplified for 14 cycles in a reaction volume of 50 μL. Predesigned TaqMan® Gene Expression Assay probes providing best coverage according to the ThermoFisher database were used for pre-amplification and qRT-PCR reactions *[isca1* (Dr03135587_m1), *epcam* (Dr03447764_s1), *klhl41b* (Dr03106263_m1), *fkbp5* (Dr03114487_m1), *pnp5a* (Dr03439861_m1), and *itm2cb* (Dr03106604_m1)]. For qRT-PCR, TaqMan® Universal PCR Master Mix (Applied Biosystems™, Foster City, CA) was used in 20 μL reactions with 2 μL pre-amplified cDNA. The QuantStudio® 5 Real-Time PCR System (Applied Biosystems™, Foster City, CA) was used to analyze qRT-PCR. Reactions were plated with a PIPETMAX 268 liquid handling platform (Gilson®, Middleton, WI) in triplicate on 384-well plates. Thermal cycling parameters were determined using manufacturers' protocol. All qRT-PCR protocols and TaqMan® Gene Expression Assays are MIQE-compliant. $2^{-\Delta\Delta Ct}$ (cycle threshold) methods were used to analyze qRT-PCR data. All transcripts were normalized to the reference gene *actb1* (β-actin), which showed no alteration due to Pb^{2+}. Student's t-test in Microsoft Excel was used to determine significant differences between control and experimental data, as indicated by p-value <.05 (see Supplemental Table S4).

3. Results

3.1. Quant-Seq

Transcript expression quantification revealed 648 differentially expressed genes in the brains of F_2 descendants of control versus lead-exposed zebrafish when assessing combined females and males (Fig. 1A, see Supplemental Table S2 for all differentially expressed transcripts). Of these genes, 52% were downregulated, with 48% upregulated. In female fish alone, we found 338 differentially expressed genes, with 66% upregulated and 34% downregulated (Fig. 1B), while in males, 411 genes were differentially expressed between exposed- and control-lineage fish, with 40% upregulated and 60% downregulated (Fig. 1C). Differentially expressed genes were assessed with IPA software and literature review to determine which biological and disease-linked pathways were enriched in F_2 lead-lineage fish. Overall, enriched pathways involved nervous and endocrine system function, as well as epigenetic modification. Table 1 indicates the log2 fold change and p-value of specific genes involved across nervous system, endocrine system, and epigenetic pathways of interest, as depicted in the heatmap in Fig. 2.

Pathway analysis identified nervous system and embryonic/organismal development as a subset of the top pathways affected across all fish, females alone, and males alone (Table 2; Supplemental Table S3), which corresponds with both the established neurodevelopmental effects of lead exposure and previous findings of neurobehavioral impairment in exposed-lineage F_2 fish (Lidsky and Schneider, 2003; Xu et al., 2016). Across all fish specifically, nervous system development and function as well as neurological disease were two of the top pathways altered, involving 117 (18% of total) and 138 (21% of total) genes, respectively, in processes including nervous system morphology, neuromuscular disease, learning, cognition, and memory (Table 2A). Table 3 indicates the differentially expressed genes implicated in various neurological processes across all samples, females alone, and males alone.

In all F_2 lead-lineage fish, genes involved in learning, memory, and behavior were differentially expressed. The majority of these genes were downregulated, including *mapk1* (mitogen activated protein kinase 1; log2FC = −4.96, $p < .01$), *creb1b* (cAMP responsive element binding protein 1b; −2.23, $p < .05$), *camkk1a* (calcium/calmodulin-dependent protein kinase kinase 1, alpha a; −6.73, $p < .05$), and *egr1* (early growth response 1; −4.55, $p < .05$), as well as the upregulated gene *cebpd* (CCAAT enhancer binding protein delta; 1.71, $p < .05$). Genes implicated in neurotransmission were also commonly downregulated, with the most highly targeted pathways involving synaptic function and plasticity. These genes included *erbb4a* (erb-b2 receptor tyrosine kinase 4a; −5.84, $p < .05$), *ephb2b* (eph receptor B2b; −1.05, $p < .05$), *gsk3b* (glycogen synthase kinase 3 beta; −2.84, $p < .05$), *mtor* (mechanistic target of rapamycin kinase; 2.47, $p < .01$), *synj1* (synaptojanin 1; −5.20, $p < .05$), *nlgn3a* (neuroligin 3a; −6.23, $p < .01$), and *stxbp1a* (syntaxin binding protein 1a; −2.47, $p < .05$). We also observed downregulation of genes primarily implicated in neurogenesis, axonogenesis, and brain development, including *tgif1* (TGFB-induced factor homeobox 1; −1.92, $p < .01$), *tbc1d23* (TBC1 domain family, member 23; −1.13, $p < .05$), *kif5c* (kinesin family member

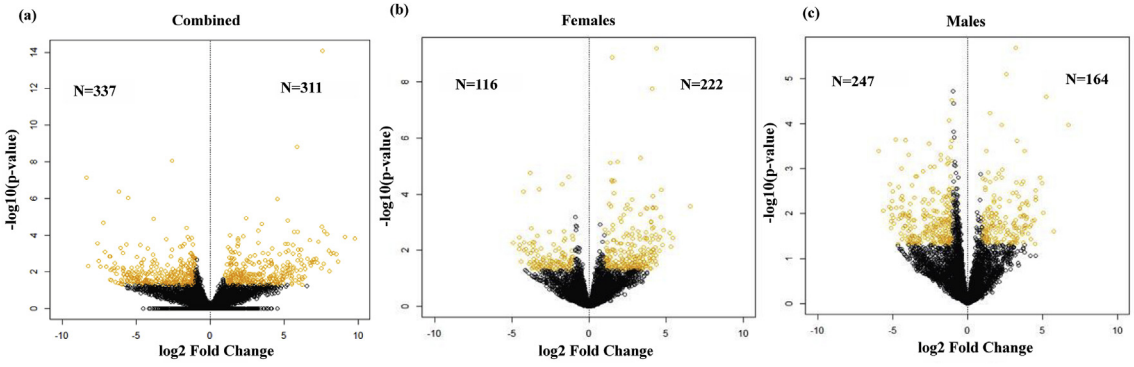

Fig. 1. Differentially expressed genes between F_2 control and lead (10 μM Pb^{2+}) exposed lineage adult zebrafish brains for a) combined males and females, b) females alone, and c) males alone. Volcano plots depict log2 fold change and p-value for each gene (circles). Orange circles indicate genes that are significantly differentially expressed (absolute log2 fold change value ≥ 1 and p-value < 0.05). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
All genes in pathways of interest (nervous system, endocrine system, and epigenetic modification) found to be differentially expressed (absolute log2 fold change value ≥ 1 and p-value $< .05$) between F_2 control and lead (10 μM Pb^{2+}) exposed-lineage adult zebrafish brains. Log2 fold change and p-value reported across combined genders, females alone, and males alone. **FC**, fold change.

Gene Symbol	Full Gene Name	Combined		Female		Male	
		log2 FC	*p*-value	log2 FC	*p*-value	log2 FC	*p*-value
aanat2	arylalkylamine N-acetyltransferase 2	5.29	0.0007	3.27	0.0030	-	-
abhd14a	abhydrolase domain containing 14A	−4.83	0.0150	-	-	-	-
adipor1b	adiponectin receptor 1b	−1.22	0.0425	-	-	-	-
adra2b	adrenoceptor alpha 2B	−4.88	0.0104	-	-	-	-
anos1b	anosmin 1b	1.79	0.0493	-	-	-	-
arr3a	arrestin 3a, retinal (X-arrestin)	3.98	0.0198	-	-	-	-
atp1a1a.4	ATPase Na+/K+ transporting subunit alpha 1a, tandem duplicate 4	7.66	0.0036	3.86	0.0310	-	-
avil	advillin	-	-	4.32	0.0239	-	-
bmi1a	bmi1 polycomb ring finger oncogene 1a	−1.21	0.0272	-	-	-	-
camkk1a	calcium/calmodulin-dependent protein kinase kinase 1, alpha a	−6.73	0.0260	-	-	-	-
cebpd	CCAAT enhancer binding protein delta	1.71	0.0467	-	-	-	-
cenpo	centromere protein O	−5.30	0.0186	-	-	-	-
cga	glycoprotein hormones, alpha polypeptide	6.40	0.0183	-	-	-	-
creb1b	cAMP responsive element binding protein 1b	−2.23	0.0331	−1.79	0.0175	-	-
crx	cone-rod homeobox	5.62	0.0056	3.26	0.0184	-	-
dlg4b	discs, large homolog 4b (Drosophila)	-	-	−1.49	0.0489	-	-
dmap1	DNA methyltransferase 1 associated protein 1	−4.72	0.0192	-	-	-	-
dmrt3a	doublesex and mab-3 related transcription factor 3a	-	-	3.18	0.0190	-	-
dnmt3bb.1	DNA (cytosine-5-)-methyltransferase 3 beta, duplicate b.1	-	-	-	-	−1.96	0.0458
dpy30	dpy-30 histone methyltransferase complex regulatory subunit	-	-	-	-	−1.09	0.0108
dusp1	dual specificity phosphatase 1	2.26	0.0274	-	-	-	-
egln3	egl-9 family hypoxia-inducible factor 3	−2.36	0.0091	-	-	-	-
egr1	early growth response 1	−4.55	0.0425	-	-	-	-
ephb2b	eph receptor B2b	−1.05	0.0431	-	-	−1.07	0.0046
erbb4a	erb-b2 receptor tyrosine kinase 4a	−5.84	0.0463	-	-	-	-
fezf2	FEZ family zinc finger 2	−3.29	0.0076	−2.31	0.0063	-	-
fgf13a	fibroblast growth factor 13a	−2.54	0.0358	-	-	−2.26	0.0123
fkbp5	FKBP prolyl isomerase 5	7.58	<.0001	4.38	<.0001	3.20	<.0001
fshb	follicle stimulating hormone subunit beta	7.16	0.0019	4.20	0.0096	-	-
gdf6a	growth differentiation factor 6a	−5.96	0.0481	-	-	-	-
gdi1	GDP dissociation inhibitor 1	−4.19	0.0005	−2.17	0.0104	−2.02	0.0196
grin1a	glutamate receptor, ionotropic, N-methyl D-aspartate 1a	-	-	3.55	0.0258	−3.70	0.0301
gsk3b	glycogen synthase kinase 3 beta	−2.84	0.0175	-	-	-	-
hdac4	histone deacetylase 4	−3.59	0.0035	−1.70	0.0465	−1.89	0.0328
hdac8	histone deacetylase 8	−1.55	0.0148	-	-	-	-
hypk	huntingtin interacting protein K	−1.65	0.0444	-	-	-	-
isl1l	islet1, like	-	-	−2.96	0.0185	-	-
kbtbd8	kelch repeat and BTB (POZ) domain containing 8	-	-	-	-	−1.37	0.0468
kif5c	kinesin family member 5C	−6.05	0.0432	-	-	-	-
kiss1	KiSS-1 metastasis suppressor	−2.16	0.0200	-	-	-	-
klf7b	Kruppel-like factor 7b	−2.42	0.0096	-	-	−1.48	0.0343
lepr	leptin receptor	−4.35	0.0275	-	-	-	-
lhb	luteinizing hormone subunit beta	5.50	0.0478	-	-	-	-
mapk1	mitogen-activated protein kinase 1	−4.96	0.0016	−2.61	0.0183	−2.36	0.0351
mat1a	methionine adenosyltransferase 1, alpha	-	-	2.34	0.0298	-	-
mecp2	methyl CpG binding protein 2	−4.14	0.0102	-	-	−3.54	0.0044
metrn	meteorin, glial cell differentiation regulator	−1.19	0.0310	-	-	-	-
mettl3	methyltransferase like 3	-	-	−1.24	0.0289	-	-
mettl7a	methyltransferase like 7A	1.49	0.0484	1.19	0.0234	-	-
mmp9	matrix metallopeptidase 9	2.47	0.0285	-	-	-	-
mtor	mechanistic target of rapamycin kinase	2.47	0.0022	1.49	0.0096	-	-
negr1	neuronal growth regulator 1	−1.96	0.0021	-	-	−1.18	0.0099
neurod6a	neuronal differentiation 6a	−1.23	0.0153	−1.02	0.0040	-	-
ngdn	neuroguidin, EIF4E bindng protein	-	-	1.68	0.0339	-	-
nlgn3a	neuroligin 3a	−6.23	0.0058	−2.81	0.0470	-	-
nr1d2a	nuclear receptor subfamily 1, group D, member 2a	2.24	0.0001	1.61	<0.0001	-	-
opn1lw1	opsin 1 (cone pigments), long-wave-sensitive, 1	6.99	0.0028	-	-	3.84	0.0207
per2	period circadian clock 2	1.68	0.0008	1.29	0.0002	-	-
phf8	PHD finger protein 8	−2.84	0.0174	-	-	−2.11	0.0174
pla2g6	phospholipase A2, group VI (cytosolic, calcium-independent)	2.02	0.0086	-	-	1.29	0.0174
prdm12b	PR domain containing 12b	-	-	−1.45	0.0384	-	-
rab33ba	RAB33B, member RAS oncogene family a	-	-	−3.57	0.0198	-	-
slc6a17	solute carrier family 6 member 17	-	-	-	-	−1.38	0.0041
smarcd1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	−1.11	0.0142	-	-	-	-
smyd2b	SET and MYND domain containing 2b	-	-	3.37	0.0142	-	-
sncaip	synuclein, alpha interacting protein	−5.56	0.0153	−3.29	0.0300	-	-
spon1a	spondin 1a	-	-	-	-	−3.63	0.0140
stxbp1a	syntaxin binding protein 1a	−2.47	0.0356	-	-	−2.26	0.0085
syngap1b	synaptic Ras GTPase activating protein 1b	-	-	-	-	−3.83	0.0060
synj1	synaptojanin 1	−5.20	0.0310	-	-	−4.97	0.0125
sypa	synaptophysin a	-	-	-	-	−2.84	0.0335

Table 1 (*continued*)

Gene Symbol	Full Gene Name	Combined		Female		Male	
		log2 FC	*p*-value	log2 FC	*p*-value	log2 FC	*p*-value
tada2b	transcriptional adaptor 2B	−5.87	0.0058	-	-	−4.75	0.0074
tbc1d23	TBC1 domain family, member 23	−1.13	0.0365	-	-	-	-
tbr1b	T-box brain transcription factor 1b	-	-	-	-	1.72	0.0141
tgif1	TGFB-induced factor homeobox 1	−1.92	0.0042	−1.12	0.0173	-	-
tmem35	transmembrane protein 35	−6.06	0.0005	-	-	−4.40	0.0010
trh	thyrotropin-releasing hormone	-	-	-	-	−1.04	0.0007
trib3	tribbles pseudokinase 3	1.85	0.0079	1.52	0.0018	-	-
tshba	thyroid stimulating hormone subunit beta a	7.53	0.0063	5.33	0.0075	-	-
uba1	ubiquitin-like modifier activating enzyme 1	−1.19	0.0028	-	-	-	-
ucp2	uncoupling protein 2	4.53	<0.0001	2.46	0.0002	2.08	0.0013
vsnl1b	visinin-like 1b	-	-	-	-	−2.25	0.0401

5C; −6.05, $p < .05$), *metrn* (meteorin, glial cell differentiation regulator; −1.19, $p < .05$), *klf7b* (Kruppel-like factor 7b; −2.42, $p < .01$), *fezf2* (FEZ family zinc finger 2; −3.29, $p < .01$), *neurod6a* (neuronal differentiation 6a; −1.23, $p < .05$), *fgf13a* (fibroblast growth factor 13a; −2.54, $p < .05$), and *egln3* (egl-9 family hypoxia-inducible factor 3; −2.36, $p < .01$).

A subset of dysregulated genes, such as *hypk* (huntingtin interacting protein K; −1.65, $p < .05$), *sncaip* (synuclein, alpha interacting protein; −5.56, $p < .05$), *trib3* (tribbles pseudokinase 3; 1.84, $p < .01$), *uba1* (ubiquitin-like modifier activating enzyme 1; −1.19, $p < .01$), and *ucp2* (uncoupling protein 2; 4.53, $p <. 0001$), were specifically implicated in neurodegeneration and disease. Neurobehavioral genes with a role in psychiatric disease and circadian rhythm pathways were mostly upregulated, such as *fkbp5* (FKBP prolyl isomerase 5; 7.58, $p < .0001$), *dusp1* (dual specificity phosphatase 1; 2.26, $p < .05$), *aanat2* (arylalkylamine N-acetyltransferase 2; 5.29, $p < .01$), *per2* (period circadian clock 2; 1.68, $p < .01$), and *nr1d2a* (nuclear receptor subfamily 1, group D, member 2a; 2.24, p < .01). Interestingly, a small subset of vision-related genes was also highly differentially expressed, the majority of which were upregulated, including *crx* (cone-rod homeobox; 5.62, $p < .01$), *arr3a* [arrestin 3a, retinal (X-arrestin); 3.98, $p < .05$], *opn1lw1* [opsin 1 (cone pigments), long-wave-sensitive, 1; 6.99, $p < .01$], and *gdf6a* (growth differentiation factor 6a; −5.96, $p < .05$).

We identified a subset of differentially expressed genes implicated in several types of epigenetic modification, some of which were sex-dependent (Table 4). Across all fish, lead exposure downregulated the expression of several types of histone modifying enzymes, including: histone deacetylases *hdac4* (histone deacetylase 4; −3.59, $p < .01$) and *hdac8* (histone deacetylase 8; −1.55, $p < .05$); histone acetyltransferase *tada2b* (transcriptional adaptor 2B; −5.87, $p < .01$) and histone demethylase *phf8* (PHD finger protein 8; −2.84, $p < .05$). Alterations in histone and DNA methyltransferase-related activity tended to be sex-specific; for example, we saw female-specific changes in *smyd2b* (SET and MYND domain containing 2b; 3.37, $p < .05$) and *prdm12b* (PR domain containing 12b; −1.44, $p < .05$) and male-specific changes in *dpy30* (dpy-30 histone methyltransferase complex regulatory subunit; −1.09, $p < .05$) and *dnmt3bb.1* [DNA (cytosine-5-)-methyltransferase 3 beta, duplicate b.1; −1.96, $p < .05$]. Genes involved in other epigenetic processes were also commonly downregulated, including *mecp2* (methyl CpG binding protein 2; −4.14, $p < .05$), *bmi1a* (bmi1 polycomb ring finger oncogene 1a; −1.21, $p < .05$), *dmap1* (DNA methyltransferase 1 associated protein 1; −4.72, $p < .05$), and *smarcd1* (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1; −1.11, $p < .05$).

Considering the integral role of the endocrine system in regulating neurological function (Yu, 2014), it is not unexpected that IPA analysis revealed endocrine homeostasis to be one of the most altered pathways due to ancestral lead exposure, with 323 altered genes (50% of total) associated with endocrine system disorders and 80 (12% of total) genes affected in lipid metabolism pathways in combined fish (Table 2A). Lead exposure altered endocrine system pathways across all fish and in females alone, but not in males alone (Table 2). Table 5 indicates the differentially expressed genes implicated in various endocrine processes across all samples, females alone, and males alone. Specifically, genes related to glycoprotein hormone activity were all highly upregulated, including *cga* (glycoprotein hormones, alpha polypeptide; 6.40, $p < .05$), *lhb* (luteinizing hormone subunit beta; 5.50, $p < .05$), *fshb* (follicle stimulating hormone subunit beta; 7.16, $p < .01$), *tshba* (thyroid stimulating hormone subunit beta a; 7.53, $p < .01$), and *anos1b* (anosmin 1b; 1.79, $p < .05$). Other affected genes are implicated in adipocytokine function, including *adipor1b* (adiponectin receptor 1b; −1.22, $p < .05$) and *lepr* (leptin receptor; −4.35, $p < .05$).

3.2. qRT-PCR

Differentially expressed genes from Quant-Seq analysis with high fold changes and/or low p-values were selected for qRT-PCR validation (Supplemental Table S4). The direction of fold change for all genes was consistent between Quant-Seq analysis and qRT-PCR validation.

4. Discussion

This study uncovered dysregulation of neurodevelopmental and endocrine transcriptional networks in the adult brains of F_2 10 μM Pb^{2+}-lineage zebrafish, highlighting the transgenerational neurotoxicity of developmental lead exposure. Previous work using the same dose and developmental exposure period revealed that both F_0 and F_2 10 μM Pb^{2+}-lineage zebrafish (referred to as F_3 in the original manuscript) demonstrated impaired learning of an avoidance conditioning response (Xu et al., 2016). This persistent neurobehavioral phenotype suggests transgenerational inheritance of epimutations, which is consistent with our findings of dysregulation in nervous system-related and epigenetic transcriptional networks in F_2 lead-lineage zebrafish.

Corresponding with the inherited phenotype of avoidance learning deficits in F_2 lead-lineage fish, we found downregulation of intracellular signaling genes linked to learning, memory, and conditioning, such as transcription factor *creb1b*, classically involved in long term memory formation, neuronal plasticity, and spatial memory (Silva et al., 1998; Kandel, 2012), as well as several genes in various pathways upstream of CREB. For instance, the kinase *mapk1*, a well-studied component of signal transduction critical for long-term potentiation (LTP; Di Cristo et al., 2001; Peng et al., 2010; Ribeiro et al., 2005), and *camkk1a,* part of the Ca^{2+} signaling cascade and regulator of the calmodulin kinase involved

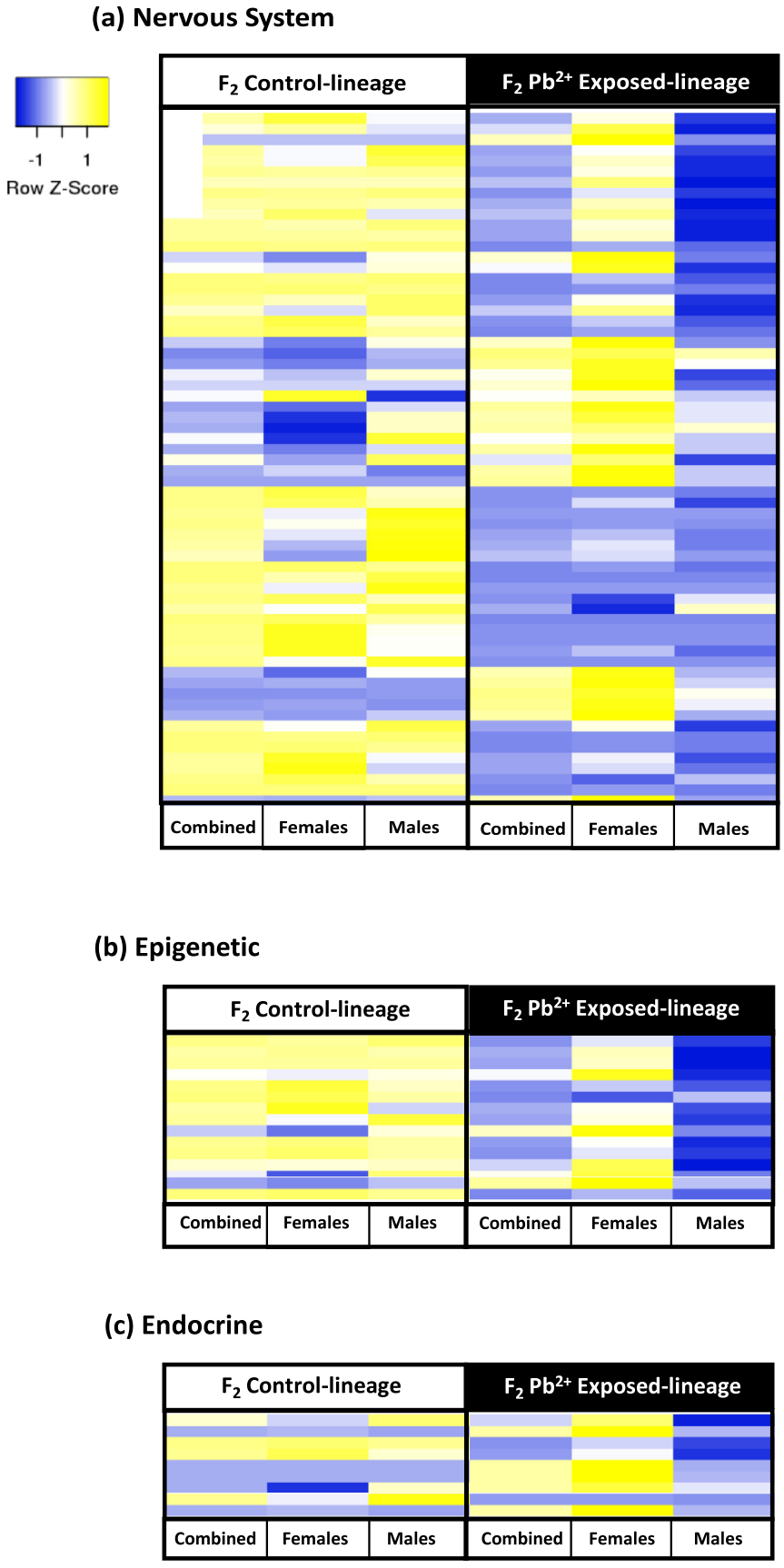

Fig. 2. Differentially expressed genes involved in a) nervous system, b) epigenetic modification, and c) endocrine system function in combined, female-only, and male-only lead-lineage F_2 fish. Differentially expressed transcripts were hierarchically clustered by similar expression level (row clustering) using Euclidean distance. Columns are grouped by treatment (lead-lineage vs control-lineage) and sex (combined, females, and males), with each column indicating average values for that respective group. The scale indicates normalized (z-score) transcript levels. Heatmapper (http://www.heatmapper.ca/expression/; Babicki et al., 2016).

Table 2
Top diseases and biological functions output from Ingenuity Pathway Analysis (IPA) of genes with significant changes in expression between F_2 control and lead lineage fish in a) combined males and females, b) females alone, and c) males alone.

All Samples Top Diseases and Biological Functions		
Category	P-value	#of genes
Diseases and Disorders		
Cancer	2.21E-03-4.19E-15	409
Organismal Injury and Abnormalities	2.21E-03-4.19E-15	414
Neurological Disease	2.20E-03-6.78E-09	138
Endocrine System Disorders	1.80E-03-1.08E-08	323
Infectious Diseases	1.79E-03-1.54E-07	82
Molecular and Cellular Functions		
Cellular Function and Maintenance	2.00E-03-2.57E-09	156
Cellular Movement	1.88E-03-3.43E-08	121
Cell Death and Survival	2.06E-03-4.55E-08	163
Lipid Metabolism	1.13E-03-1.11E-06	80
Molecular Transport	2.17E-03-1.11E-06	116
Physiological System Development and Function		
Organismal Survival	3.92E-10-3.92E-10	125
Embryonic Development	1.69E-03-7.04E-08	114
Organismal Development	1.95E-03-7.04E-08	172
Nervous System Development and Function	2.03E-03-9.16E-08	117
Connective Tissue Development and Function	2.04E-03-3.32E-07	89
Female Top Diseases and Biological Functions		
Category	P-value	# of genes
Diseases and Disorders		
Cancer	5.97E-03-7.08E-10	187
Organismal Injury and Abnormalities	6.28E-03-7.08E-10	190
Endocrine System Disorders	5.70E-03-2.74E-06	151
Reproductive System Disease	5.60E-03-2.74E-06	83
Cardiovascular Disease	6.26E-03-6.61E-06	31
Molecular and Cellular Functions		
Lipid Metabolism	6.04E-03-8.73E-08	49
Molecular Transport	4.85E-03-8.73E-08	65
Small Molecule Biochemistry	6.04E-03-8.73E-08	67
Carbohydrate Metabolism	6.04E-03-2.33E-07	47
Protein Synthesis	6.08E-03-5.51E-06	32
Physiological System Development and Function		
Nervous System Development and Function	5.96E-03-1.96E-07	58
Behavior	5.02E-03-9.35E-07	26
Embryonic Development	5.30E-03-1.48E-06	63
Organism al Development	6.26E-03-1.48E-06	87
Organism al Survival	4.49E-03-7.97E-06	59
Male Top Diseases and Biological Functions		
Category	P-value	# of genes
Diseases and Disorders		
Cancer	1.14E-02-1.26E-06	246
Organismal Injury and Abnormalities	1.14E-02-1.26E-06	254
Developmental Disorder	1.13E-02-2.54E-06	54
Neurological Disease	1.13E-02-5.48E-05	77
Gastrointestinal Disease	9.61E-03-9.84E-05	210
Molecular and Cellular Functions		
Cell Death and Survival	1.13E-02-2.25E-07	110
Cellular Assembly and Organization	1.13E-02-9.18E-07	56
Cellular Movement	8.07E-03-2.78E-06	56
Cell-To-Cell Signaling and Interaction	1.13E-02-5.84E-06	49
Cellular Growth and Proliferation	1.13E-02-1.00E-05	108
Physiological System Development and Function		
Organismal Survival	3.16E-04-1.44E-07	78
Embryonic Development	1.13E-02-2.54E-06	88
Organismal Development	1.13E-02-2.54E-06	100
Tissue Morphology	9.62E-03-2.54E-06	68
Nervous System Development and Function	1.13E-02-8.54E-06	60

in synaptic plasticity and memory consolidation (Blaeser et al., 2006; Wayman et al., 2008; Markovac and Goldstein, 1988), were both dysregulated. MAPK1 is known to regulate genes across a variety of learning and memory related pathways affected by ancestral lead exposure; for example, *gsk3b*, involved in synaptic plasticity (Goold and Gordon-Weeks, 2005), neuronal polarization gene *fgf13a* (Lin et al., 2019), and *dusp1*, involved in psychiatric disease and neuronal survival (Pérez-Sen et al., 2019). Lead mediates many neurotoxic effects through an ability to substitute for the second messenger Ca^{2+}, thus disrupting regular signaling cascades resulting in mitochondrial dysfunction-induced apoptosis and glutamatergic excitotoxicity (Lidsky and Schneider, 2003). Downstream of CREB, several transcription factors were also differentially expressed. *Egr1*, which modulates expression of synaptic plasticity-

Table 3
Genes implicated in nervous system development and function pathways that are differentially expressed between F_2 control and lead (10 μM Pb^{2+}) exposed lineage adult zebrafish brains. * **indicates combined samples, ^ indicates females alone, # indicates males alone.**

Genes Involved in Nervous System Development and Function	
Pathways	Genes
Axonogenesis	*ephb2b*#, anos1b*, metrn*, tbc1d23*, isl1l^, rab33ba^, spon1a#*
Brain Development	*hdac4*^#, tgif1*^, phf8*#, kif5c*, tbc1d23*, rab33ba^, syngap1b#, vsnl1b#,*
Neurogenesis	*hdac4*^#, mapk1*^#, fezf2*^, neurod6a*^, fgf13a*#, klf7b*#, mecp2*#, negr1*#, abhd14a*, bmi1a*, cenpo*, egln3*, smarcd1*, avil^, dmrt3a^, ngdn^, prdm12b^, kbtbd8#, tbr1b#*
Synaptic Function and Plasticity	*stxbp1a*#, synj1*#, adra2b*, erbb4a*, nlgn3a*, dlg4b^, grin1a^, slc6a17#, sypa#*
Neurodegeneration and Disease	*ucp2*^#, sncaip*^, trib3*^, pla2g6*#, synj1*#, hypk*, uba1**
Memory, Learning, and Behavior	*fkbp5*^#, gdi1*^#, hdac4*^#, mapk1*^#, atp1a1a.4*^, creb1b*^, mtor*^, tmem35*#, camkk1a*, cebpd*, egr1*, gsk3b*, lepr*, mmp9*, smarcd1**
Circadian Rhythm	*aanat2*^, crx*^, nr1d2a*^, per2*^*
Psychiatric Disease	*atp1a1a.4*^, fkbp5*^#, nr1d2a*^, dusp1**
Vision	*crx*^, opn1lw1*#, arr3a*, gdf6a**

Table 4
Genes implicated in epigenetic pathways that are differentially expressed between F_2 control and lead (10 μM Pb^{2+}) exposed lineage adult zebrafish brains. * **indicates combined samples, ^ indicates females alone, # indicates males alone.**

Genes Involved in Epigenetic Modification	
Pathways	Genes
Histone demethylases/methyltransferases	*phf8*#, prdm12b^, smyd2b^, dpy30#*
Histone deacetylases/acetyltransferases	*hdac4*^#, tada2b*#, hdac8**
Other methylation-linked genes	*mettl7a*^, mat1a^, mettl3^, dnmt3bb.1#*
Other epigenetic modifiers	*mecp2*#, bmi1a*, dmap1*, smarcd1**

Table 5
Genes implicated in endocrine pathways that are differentially expressed between F_2 control and lead (10 μM Pb^{2+}) exposed lineage adult zebrafish brains. * **indicates combined samples, ^ indicates females alone, # indicates males alone**.

Genes Involved in Endocrine System Function	
Pathways	Genes
Glycoprotein Hormone	*fshb*^, tshba*^, anos1b*, cga*, kiss1*, lhb*, trh#*
Adipocytokine	*adipor1b*, lepr**

linked genes, was downregulated (Duclot and Kabbaj, 2017), as previously observed (Reddy and Zawia, 2000), while *cebpd* was upregulated, promoting microglial activation and inflammation response (Pan et al., 2010; Ko et al., 2014). This latter finding is consistent with inflammation as another mechanism of lead-induced neurotoxicity (Lidsky and Schneider, 2003) and corresponds with reports that lead exposure increases microglial-neuronal cross-talk, resulting in impaired hippocampal LTP, and consequently, impaired learning and memory (Liu et al., 2012).

Early-life lead exposure is known to alter hippocampal dendritic spine plasticity and density in rodents and dysregulate synapse related genes in zebrafish (Zhao et al., 2018; Peterson et al., 2011). Accordingly, we found genes specifically involved in synaptic function to be downregulated in lead-lineage fish, including transmembrane receptors *erbb4a*, implicated in modulating synaptic NMDA function and neuronal migration (Bennett et al., 2012; Rio et al., 1997), and *ephb2b*, involved in trans-synaptic modification of dendritic spine complexity (Talebian and Henkemeyer, 2019). Altered NMDA activity is a classic endpoint of lead exposure closely linked to impaired learning and memory outcomes (Neal et al., 2010). Ancestral lead exposure also resulted in downregulation of *gsk3b* and reciprocal upregulation of *mtor*. This relationship is not surprising, as GSK3B is a known inhibitor of MTOR (Ma et al., 2010), and the interaction between these kinases tightly regulates the balance between LTP and long-term depression (LTD) to maintain synaptic plasticity in the brain (Peineau et al., 2007). Several downregulated genes are implicated in synapse structure and vesicle processing, such as: *synj1*, a phosphatase involved in synaptic vesicle endocytosis and recycling (Mani et al., 2007; McPherson et al., 1994); *nlgn3a*, a neuronal cell surface protein involved in synapse formation (Graf et al., 2004); and *stxbp1a*, a synapse maintenance protein necessary for vesicle fusion and neurotransmitter release (Verhage et al., 2000). Accordant with our findings, others have reported the ability of lead to downregulate expression of synaptic vesicle proteins, decreasing rate of vesicular release (Neal et al., 2010), and alter the density of multiple types of neurotransmitter receptors in the brain (Rossouw et al., 1987).

Disruption of central nervous system development, axonogenesis, neurogenesis, and brain development transcriptomic pathways, as well as decreased axonal density, are well-characterized outcomes of early-life lead exposure in the zebrafish model (Lee et al., 2018; Peterson et al., 2011; Zhang et al., 2011). Lead exposure is also known to alter axonal myelination and decrease prefrontal cortex gray matter volume in adults, induce pathological early-life apoptotic neurodegeneration in rodents, and decrease neuronal differentiation in human cell models (Brubaker et al., 2009; Cecil et al., 2008; Dribben et al., 2011; Engstrom et al., 2015). Corresponding with these outcomes, we observed downregulation of genes involved in cortical development, including the transcriptional repressor *tgif1*, which regulates transforming growth factor-β/Nodal signaling to maintain proper forebrain patterning (Taniguchi et al., 2012), and the vesicle trafficking protein *tbc1d23*, implicated in cortical neuron positioning and pontocerebellar hypoplasia (Ivanova et al., 2017). Genes with a

role in axonogenesis also showed decreased expression, including the kinesin motor protein *kif5c*, important in axonal polarization and mitochondrial localization (Calderon de Anda and Tsai, 2011; Cho et al., 2007), and *metrn*, which promotes glial cell differentiation and axonal network formation (Nishino et al., 2004). Lastly, we detected downregulation in neurogenesis genes. For example: the neuronal differentiation transcription factors *klf7b*, *fezf2*, and *neurod6a* (Laub et al., 2001; Chen et al., 2008; Zhang et al., 2014; Liao et al., 1999); *fgf13a*, a growth factor implicated in tubule stabilization and neuronal polarization (Wu et al., 2012); and *egln3*, which promotes normal neuronal apoptosis in development (Lee et al., 2005). Our findings correspond with others that found dysregulated transcriptional networks involved in axonogenesis, neurogenesis, and synaptic function due to early-life lead exposure (Sánchez-Martín et al., 2013). The downregulation of these genes in the lead-lineage F_2 generation strongly suggests that early-life lead exposure not only impairs nervous system function in the exposed generation, but induces heritable, pervasive epigenetic changes across neurodevelopmental networks.

We observed differential expression of genes involved in neurodegeneration and disease due to ancestral lead exposure. Evidence strongly links early lead exposure to development of neurodegenerative disorders later in life. For example, higher developmental blood lead levels were associated with decreased levels of plasma $A\beta_{42}$ in adults, indicating localization to the brain and increased risk for Alzheimer's disease (Mazumdar et al., 2012). Additionally, early-life lead exposure induced neuroinflammation and tau hyperphosphorylation in rodents as well as β-amyloid deposition in primate brains, and altered expression of genes associated with an increased risk for Alzheimer's disease in zebrafish (vonderEmbse et al., 2017; Bihaqi et al., 2014; Wu et al., 2008; Lee and Freeman, 2016). However, both the lifespan and transgenerational neurodegenerative effects of early-life lead exposure remain to be fully characterized. Several mechanisms for lead-induced neurodegeneration have been suggested, including developmental changes in brain structure and function that deplete later-life cognitive reserves, which correspond with our findings of dysregulated nervous system development pathways. Another mechanism posits that lead exposure during development causes epigenetic modification of genes that are differentially expressed later in life, directly influencing neurodegenerative disease pathology (Reuben, 2018). In this vein, the downregulation of two neurodegenerative genes in the F_2 generation, *hypk* and *sncaip*, which have protective roles against neuronal toxicity in Huntington's disease and Parkinson's disease (Das and Bhattacharyya, 2016; Shishido et al., 2019), potentially indicates an increased risk of later-life neurodegenerative disease. We detected changes in several other genes involved in more general neurodegenerative processes, including: increased *trib3*, a pseudokinase that is implicated in neuronal cell death and upregulated in various forms of dementia (Lorenzi et al., 2018); decreased *uba1*, a ubiquitin-activating enzyme critical in protein turnover that can lead to downstream protein accumulation and associated neurodegenerative phenotypes when downregulated (Groen and Gillingwater, 2015); and upregulated *ucp2*, a mitochondrial gene with dual roles in regulating reactive oxygen species (ROS) and mitophagy, the disruption of which can result in neuronal damage (Bechmann et al., 2002; Hass and Barnstable, 2016, 2019). To our knowledge, this is the first report of lead-induced transgenerational changes in neurodegenerative disease-linked genes in a vertebrate model.

Transcriptomic data also confirms upregulation of a subset of genes implicated in psychiatric disorders in the brains of F_2 lead-lineage fish, including the MAPK phosphatase *dusp1*, implicated in depressive-like behaviors and neuronal survival (Duric et al., 2010; Barthas et al., 2017; Pérez-Sen et al., 2019), and *fkbp5*, a chaperone of the glucocorticoid receptor that mediates the stress response, resulting in dysregulated learning and memory and increased risk of Posttraumatic Stress Disorder (PTSD) (Zannas et al., 2016; Blair et al., 2019; Wilker et al., 2014). The circadian clock genes *crx*, *aanat2*, *per2*, and *nr1d2a* were also upregulated (Rohde et al., 2014; Xu et al., 2007; Yin et al., 2007). These findings correspond to longitudinal studies correlating early-life blood lead levels with increased general psychopathology in adulthood (Reuben et al., 2019) and preadolescent sleep disturbance (Liu et al., 2015), as well as disruption of circadian clock genes due to chronic lead exposure in rodents (Sabbar et al., 2017). Little is known, however, about the transgenerational inheritance of lead-induced psychiatric disorders or circadian rhythm dysfunction. Although the existence or directionality of a causal relationship between circadian dysfunction and psychiatric disease is unclear (Karatsoreos, 2014), disruption of circadian rhythm pathways is correlated with the severity of depressive symptoms in humans (Emens et al., 2009) and linked to persistent impairment of hippocampal neurogenesis and subsequent learning and memory deficits in rodents (Gibson et al., 2010). As the circadian rhythm and visual development and processing systems are closely intertwined (Laranjeiro and Whitmore, 2014), it is not surprising that we also observed changes in genes involved in vision, including: *crx* and *arr3a*, both involved in photoreceptor maturation and visual perception; *opn1lw1*, a red opsin regulated by circadian clock genes; and *gdf6a*, a growth factor that regulates lens differentiation (Huang et al., 2012; Renninger et al., 2011; Tovin et al., 2012; French et al., 2009). Lead exposure is classically known to induce retinal degeneration and/or structural changes in humans and rodent models (Fox et al., 1998; He et al., 2003; Giddabasappa et al., 2011), as well as impair visual response in adult zebrafish exposed as embryos (Rice et al., 2011). The degree to which visual impairment, as opposed to cognitive deficits induced by lead exposure, contributes to adverse learning, memory, and attention outcomes has been minimally studied in exposed children or their descendants (Rice, 2006). Future efforts to tease out the interaction between sensory and cognitive deficits will inform the design and implementation of early-life intervention approaches.

We and others have uncovered a wide array of cognitive and behavioral deficits due to early-life lead exposure, including impaired visual discrimination and spatial memory, attention deficits, and decreased IQ in children (Needleman et al., 1979; Evans et al., 1994; Canfield et al., 2004), along with impaired spatial learning, memory, fear/avoidance conditioning, and altered social behaviors across primates, rodents, and zebrafish (Rice, 1990; Bazrgar et al., 2015; Anderson et al., 2016; Xu et al., 2016; Chen et al., 2012; Weber and Ghorai, 2013). As found in our pathway analysis results, nervous system development and function is one of the primary targets of early-life lead exposure. Although F_0 lead exposure is generally well studied, recent discoveries that behavioral effects of lead exposure may span generations (Trombini et al., 2001; Chen et al., 2017; Yu et al., 2013) vastly expand the pool of individuals at risk, opening the door to a critical dimension of lead-related research: the mechanisms underlying transgenerational inheritance of neurobehavioral disease.

The persistence of adverse neurobehavioral effects in both the developmentally-exposed F_0 fish and their descendants, coupled with the widespread transcriptomic dysregulation we observe in the F_2 lead-lineage fish, indicates that early-life lead exposure may disrupt epigenetic modification pathways to cause heritable epimutations. Many studies report the ability of lead exposure to modify epigenetic pathways across the lifespan, affecting global and promoter-specific DNA methylation (Devóz et al., 2017; Li et al.,

2011a, 2014; Pilsner et al., 2009), levels of modified histones (Bihaqi et al., 2011), and expression of epigenome-modifying genes, including MeCP2, DNMT1, and MAT2a (Stansfield et al., 2012; Eid et al., 2016). However, only a few novel studies report the inheritance of lead-induced epigenetic effects across generations; for instance, alterations in the methylome were found to persist in the grandchildren of lead-exposed pregnant women (Sen et al., 2015). In the F_2 lead-lineage fish, we observed downregulation of epigenetic modification genes across multiple categories, including a subset of histone-modifying enzymes. Altered histone methyltransferase (HMT) genes include *prdm12b*, which methylates the repressive mark H3K9 to modulate neural crest development (Matsukawa et al., 2015; Zannino et al., 2014), *smyd2b*, a gene critical in early development that methylates the permissive mark H3K36 and interacts with the repressive complex HDAC1 (Brown et al., 2006; Sesé et al., 2013), and *dpy30*, an integral core subunit of SET1 methyltransferase activity, which facilitates methylation of the generally permissive mark H3K4 (Yang et al., 2014; Ernst and Vakoc, 2012). Decreased expression of H4K20/H3K9 demethylase *phf8*, critical for hippocampal LTP, learning and memory, and neuronal differentiation (Qi et al., 2010; Chen et al., 2018), was also noted. Histone deacetylases *hdac4* and *hdac8*, both downregulated in this study, are globally implicated in maintaining a repressive chromatin configuration (Wang et al., 2014). HDAC4 specifically complexes with MEF2 to promote neuronal survival (Bolger et al., 2007), and is implicated in cerebellar degeneration, as well as learning and memory impairment when decreased (Majdzadeh et al., 2008; Kim et al., 2012). *Tada2b*, a transcriptional adaptor protein that coordinates permissive histone acetyltransferase activity, is also downregulated (Barlev et al., 2003). Interestingly, chronic metabolic disease was found in one study to downregulate the vast majority of histone-modifying enzymes, suggesting the possibility that similar upstream mechanistic factors are implicated in chronic metabolic disease and lead-induced neuropathology (Shao et al., 2016).

Other epigenetic genes with general silencing function were also downregulated due to ancestral lead exposure. One such gene is the DNA methyltransferase (DNMT) *dnmt3bb.1,* implicated in maintaining hematopoietic stem cells and silencing the expression of retinal development genes, some of which we also found to be dysregulated (see discussion of vision-related genes below; Gore et al., 2016, 2018). Others have also found *de novo* DNMTs, specifically DNMT3b orthologs *dnmt3* and *dnmt4*, to be dysregulated by lead exposure in the zebrafish model (Sanchez et al., 2017). Another downregulated gene is *bmi1a*, a component of the polycomb repressive complex 1 that also silences genes through mono-ubiquitinylating H2A, along with a role in maintaining neural precursor cells and preventing neuronal apoptosis (Abdouh et al., 2016; Molofsky et al., 2003; Chatoo et al., 2009). Also dysregulated is the methsyl-CpG-binding protein *mecp2*, a classic modifier of transcriptional activity that binds to methylated DNA, exerting its typically repressive regulatory function by recruiting HDAC repressor complexes (Nan et al., 1998). MECP2 function is critical in neuronal survival and differentiation, mature nerve cell function, synaptogenesis, and spatial memory (Gao et al., 2015; Luikenhuis et al., 2004; Li et al., 2011b), and is usually downregulated due to lead exposure, as we observed (Schneider et al., 2012; Eid et al., 2016; Sobolewski et al., 2018). Another modifying gene, *dmap1*, also acts as a transcriptional co-repressor that interacts with the *de novo* DNA methyltransferase DNMT1 and HDAC2 to mediate gene silencing (Rountree et al., 2000), as well as promote H4K16 acetylation and subsequent chromatin relaxation as a member of a histone acetyltransferase complex (Penicud and Behrens, 2014). Finally, *smarcd1* is part of the SWI/SNF chromatin remodeling complex, involved in regulating neurodevelopmental gene expression in flies and interacting with the glucocorticoid receptor (Nixon et al., 2018; Hsiao et al., 2003). Lead-induced downregulation of genes with silencing function may cause aberrant transcriptional activity that could be linked to the upregulation we observed in pathways including endocrine homeostasis and psychiatric disease. Many of these enzymes have the capability to both enhance and repress transcriptional activity, depending on which DNA or histone residues are targeted, and/or which transcriptional complexes are recruited (Handy et al., 2011; Sawan and Herceg, 2010; Kim and Kaang, 2017). Thus, prediction of the specific transcriptomic consequences of downregulated epigenetic enzyme activity poses a challenge until the affected residues are discovered. Analysis of the specific type and genomic location of epimutations is the logical next step in uncovering potential mechanisms through which these epigenetic pathways interact to mediate transgenerational effects.

As evidenced in our pathway analysis, endocrine homeostasis is a well-established target of lead exposure, with reported effects of hormonal dysregulation at all levels of the hypothalamic-pituitary-gonadal (HPG) axis (Saxena et al., 1989; Gustafson et al., 1989; Sierra and Tiffany-Castiglioni, 1992; Chang et al., 2006; Naicker et al., 2010). We observed several highly upregulated glycoprotein hormone genes indicating disruption of the HPG axis: *cga*, *fshb,* and *lhb,* all gonadotropin subunits; *anos1b*, which promotes the migration of gonadotropin-releasing hormone (GnRH) neurons (Cariboni et al., 2004); and *tshba*, a TSH subunit. Although the reported effects of lead exposure on gonadotropin expression vary considerably depending on factors including sex, developmental window of exposure, and level of exposure (Chen et al., 2016; Daku et al., 2016; Doumouchtsis et al., 2009; Sokol et al., 2002; Ronis et al., 1996), lead-induced changes in NMDA receptor activity may be a potential mechanism for the overall increase in gonadotropin-related genes we observed, as excitatory amino acids regulate gonadotropin release and activity (Bonavera et al., 1998). The relationship between lead-induced changes in gonadotropin levels and cognitive function remains to be well-characterized, but several studies indicate that increases in LH, FSH and LH receptor expression are associated with neurodegenerative disease and poor memory performance (Blair et al., 2015; Koebele and Bimonte-Nelson, 2017). Interestingly, GnRH is also thought to interact with various epigenome-modifying enzymes through calmodulin kinase pathways, which were also altered due to ancestral lead exposure and could contribute to inheritance of a dysregulated transcriptome (Melamed et al., 2018). Findings of *tshba* upregulation are consistent with increased TSH in lead-exposed workers (Lidsky and Schneider, 2003; Pekcici et al., 2010) and the known ability of lead to disrupt normal thyroid function.

Genes implicated in adipocytokine function were generally found to be downregulated, including the adiponectin receptor *adipor1* and leptin receptor *lepr*, both of which promote decreased CNS inflammation, increased insulin sensitivity, and synaptic plasticity (Rastegar et al., 2019; Balthasar et al., 2004; Bloemer et al., 2018; Holland et al., 2011; Signore et al., 2008; Paz-Filho et al., 2012; Patraca et al., 2017; Irving and Harvey, 2014). Although little evidence exists linking lead exposure to changes in overall adipocytokine function, lead is known to promote an insulin-resistant and inflammatory phenotype (Whittle et al., 1983; Faulk et al., 2014). Adipocytokine activity directly modulates synapse function and indirectly promotes neuronal health by mediating energy homeostasis and inflammatory factors, thus lead-induced downregulation of these receptors could reasonably contribute to neurobehavioral deficits. Taken together, ancestral lead exposure extensively alters a variety of endocrine pathways crucial in maintaining nervous system health and function, suggesting their

involvement in mediating neurobehavioral toxicity.

Our transcriptomic analysis revealed some sex-specific outcomes; we found more genes altered in males than females, with more downregulated genes in males alone and more upregulated genes in females alone. Other studies have also reported that lead induces sex-dependent transcriptomic effects (Schneider et al., 2011; Kasten-Jolly and Lawrence, 2017), differences in synaptic transmission (Tena et al., 2019), and loss of frontal lobe volume in adulthood, the latter found to be more severe in males (Brubaker et al., 2010; Cecil et al., 2008). Although our study did not evaluate the role of sex in lead-induced effects on cognition or neurobehavior (Xu et al., 2016), no clear pattern has been reported for these outcomes previously. Some studies have indicated worse outcomes in cognitive and neurobehavioral function, more aggression, and increased anxiety in human and rodent males (Polanska et al., 2018; Dietrich et al., 1987; Bellinger et al., 1990; Kasten-Jolly et al., 2012; Soeiro et al., 2007), while others have found worse neuropsychological outcomes, decreased IQ, reduced exploratory behaviors, impaired reference memory, and increased depressive-like behavior in human and rodent females (McMichael et al., 1992; Rabinowitz et al., 1991; Kasten-Jolly et al., 2012; Jett et al., 1997; de Souza Lisboa et al., 2005). While the general understanding is that males tend to be more susceptible to certain outcomes of lead exposure, evidence indicates that sex-specific neurological effects are dependent upon factors including exposure window, length of exposure, dose amount and route/regimen, endpoints assessed, and time to assessment (Anderson et al., 2016).

Our pathway analysis of lead-lineage fish uncovered that endocrine system dysfunction was enriched across all fish and females alone, but not in males alone. This finding contrasts with another study that reported greater dysregulation of endocrine pathways in exposed males as compared to females; however, differences in exposure concentration and generation assessed may contribute to these diverging outcomes (Lee et al., 2018). Additionally, we observed that differential expression of histone and DNA methyltransferases was generally sex-specific; for instance, *smyd2b* and *prdm12b* were altered in females alone, while *dpy30* and *dnmt3bb.1* were altered in males alone. As males and females exhibit distinct patterns of hormonal regulation characteristic to reproductive development and maturity, sex-specific endocrine pathways that are already modified by environmental insult are likely to interact uniquely with dysregulated transcriptomic networks across the lifespan. Because hormonal regulation is known to interact reciprocally with epigenetic mechanisms like histone modification and DNA methylation, this relationship may mediate any sex-specific transgenerational epimutations that we see in the F_2 generation (Singh et al., 2018), and is a promising direction for future study.

We selected a dose of 10 μM Pb^{2+} both for consistency with previous studies (Carvan et al., 2004; Rice et al., 2011), and to determine whether neurobehavioral and transcriptomic effects of lead exposure could be inherited transgenerationally in a zebrafish model. Although this dose is above environmental levels, as indicated by the current action levels for drinking water (15 μg/L) and blood lead (5 μg/dL) (EPA, 2008; Filippelli et al., 2005), our experimental paradigm may provide insight into potential health effects in the descendants of those who were developmentally exposed to high environmental lead levels characteristic of the 1960s–80s, during which about 2% of individuals surveyed by NHANES reported blood lead levels exceeding 30 μg/dL (Mahaffey et al., 1982) and 80 μg/dL, or ~3.9 μM, was recommended as the upper limit for a "safe" blood lead level (Lane et al., 1968). Future studies will utilize additional, environmentally-relevant doses to further characterize this transgenerational response.

This study, as one of the first to link inherited lead-induced neurobehavioral and transcriptomic outcomes in a zebrafish model, contributes novel findings to the small body of work on the transgenerational effects of lead exposure (Sen et al., 2015; Chen et al., 2017). Although many of the affected neurobehavioral pathways that we observed are classically altered due to early-life lead exposure, including LTM-associated intracellular signaling, synaptic function and plasticity, neurogenesis, endocrine homeostasis, epigenetic modification, neurodegeneration, and circadian rhythm, few studies have characterized their transgenerational sequelae. Our findings indicate that F_2 patterns of transcriptomic dysregulation are remarkably consistent with expected effects of direct lead exposure. This suggests that specific lead-induced epimutations are likely not moderated across generations, but persist at minimum to the F_2 generation in zebrafish. Future studies that expand the generational scope of this project will clarify the extent of this inheritance. Several epigenetic modification pathways were differentially regulated in the F_2 lead-lineage fish; these are promising targets for mediating these stable effects on the epigenome and also deserve to be fully characterized in future studies. The Centers for Disease Control posits that no safe blood lead level has been identified (CDC, 2013). Thus, our transcriptomic and previous behavioral findings that the profound neurological effects of lead are not limited to the exposed generation are of great concern to public health, compelling investigation into the specific genetic and epigenetic mechanisms of this environmentally-induced disease, as well as potential targets for intervention in each affected generation.

Author contributions

Conceptualization: DW, TRB; Data curation: DNM, EJC, KG; Formal analysis: DNM, EJC, CA, KG, TRB; Funding acquisition: TRB, DW; Investigation: EJC, CA, RF; Methodology: EJC, RF; Project administration: DW, TRB; Resources: DW, TRB; Software: KG; Supervision: BBB, DW, TRB; Validation: CA; Visualization: DNM, EJC, KG; Writing- original draft: DNM, EJC, BBB, TRB; Writing- review and editing: all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2019.125527.

References

Abdouh, M., Hanna, R., El Hajjar, J., Flamier, A., Bernier, G., 2016. The polycomb repressive complex 1 protein BMI1 is required for constitutive heterochromatin formation and silencing in mammalian somatic cells. J. Biol. Chem. 291 (1), 182–197. https://doi.org/10.1074/jbc.M115.662403.

Agency for Toxic Substances and Disease Registry (ATSDR), 2019. Toxicological Profile for Lead. (Draft for Public Comment. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Anderson, D.W., Mettil, W., Schneider, J.S., 2016. Effects of low level lead exposure on associative learning and memory in the rat: influences of sex and developmental timing of exposure. Toxicol. Lett. 246, 57–64. https://doi.org/10.1016/j.toxlet.2016.01.011.

Babicki, S., Arndt, D., Marcu, A., Liang, Y., Grant, J.R., Maciejewski, A., Wishart, D.S., 2016. Heatmapper: web-enabled heat mapping for all. Nucleic Acids Res. 44 (W1), W147–W153. https://doi.org/10.1093/nar/gkw419.

Baker, T.R., Peterson, R.E., Heideman, W., 2014. Using zebrafish as a model system for studying the transgenerational effects of dioxin. Toxicol. Sci.: Off. J. Soc. Toxicol. 138 (2), 403–411. https://doi.org/10.1093/toxsci/kfu006.

Balthasar, N., Coppari, R., McMinn, J., Liu, S.M., Lee, C.E., Tang, V., et al., 2004. Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. Neuron 42 (6), 983–991. https://doi.org/10.1016/j.neuron.2004.06.004.

Barlev, N.A., Emelyanov, A.V., Castagnino, P., Zegerman, P., Bannister, A.J., Sepulveda, M.A., et al., 2003. A novel human Ada2 homologue functions with Gcn5 or Brg1 to coactivate transcription. Mol. Cell. Biol. 23 (19), 6944–6957. https://doi.org/10.1128/mcb.23.19.6944-6957.2003.

Barthas, F., Humo, M., Gilsbach, R., Waltisperger, E., Karatas, M., Leman, S., et al., 2017. Cingulate overexpression of mitogen-activated protein kinase phosphatase-1 as a key factor for depression. Biol. Psychiatry 82 (5), 370–379. https://doi.org/10.1016/j.biopsych.2017.01.019.

Bazrgar, M., Goudarzi, I., Lashkarbolouki, T., Elahdadi Salmani, M., 2015. Melatonin ameliorates oxidative damage induced by maternal lead exposure in rat pups. Physiol. Behav. 151, 178–188. https://doi.org/10.1016/j.physbeh.2015.06.040.

Bechmann, I., Diano, S., Warden, C.H., Bartfai, T., Nitsch, R., Horvath, T.L., 2002. Brain mitochondrial uncoupling protein 2 (UCP2): a protective stress signal in neuronal injury. Biochem. Pharmacol. 64 (3), 363–367. https://doi.org/10.1016/s0006-2952(02)01166-8.

Bellinger, D., Leviton, A., Sloman, J., 1990. Antecedents and correlates of improved cognitive performance in children exposed in utero to low levels of lead. Environ. Health Perspect. 89, 5–11. https://doi.org/10.1289/ehp.90895.

Bennett, M.R., Farnell, L., Gibson, W.G., 2012. A model of neuregulin control of NMDA receptors on synaptic spines. Bull. Math. Biol. 74 (3), 717–735. https://doi.org/10.1007/s11538-011-9706-9.

Bernal, A.J., Jirtle, R.L., 2010. Epigenomic disruption: the effects of early developmental exposures. Birth Defects Research. Part A Clin. Mol. Teratol. https://doi.org/10.1002/bdra.20685.

Bihaqi, S.W., Bahmani, A., Adem, A., Zawia, N.H., 2014. Infantile postnatal exposure to lead (Pb) enhances tau expression in the cerebral cortex of aged mice: relevance to AD. Neurotoxicology (Little Rock) 44, 114–120. https://doi.org/10.1016/j.neuro.2014.06.008.

Bihaqi, S.W., Huang, H., Wu, J., Zawia, N.H., 2011. Infant exposure to lead (Pb) and epigenetic modifications in the aging primate brain: implications for Alzheimer's disease. J. Alzheimer's Dis.: JAD 27 (4), 819–833. https://doi.org/10.3233/JAD-2011-111013.

Blaeser, F., Sanders, M.J., Truong, N., Ko, S., Wu, L.J., Wozniak, D.F., et al., 2006. Long-term memory deficits in Pavlovian fear conditioning in Ca2+/calmodulin kinase kinase alpha-deficient mice. Mol. Cell. Biol. 26 (23), 9105–9115. https://doi.org/10.1128/MCB.01452-06.

Blair, J.A., McGee, H., Bhatta, S., Palm, R., Casadesus, G., 2015. Hypothalamic-pituitary-gonadal axis involvement in learning and memory and Alzheimer's disease: more than "just" estrogen. Front. Endocrinol. 6 (45) https://doi.org/10.3389/fendo.2015.00045.

Blair, L.J., Criado-Marrero, M., Zheng, D., Wang, X., Kamath, S., Nordhues, B.A., et al., 2019. The disease-associated chaperone FKBP51 impairs cognitive function by accelerating AMPA receptor recycling. ENeuro 6 (1). https://doi.org/10.1523/ENEURO.0242-18.2019.

Bloemer, J., Pinky, P.D., Govindarajulu, M., Hong, H., Judd, R., Amin, R.H., et al., 2018. Role of adiponectin in central nervous system disorders. Neural Plast. 2018 (4593530) https://doi.org/10.1155/2018/4593530.

Bolger, T.A., Zhao, X., Cohen, T.J., Tsai, C.-C., Yao, T.-P., 2007. The neurodegenerative disease protein ataxin-1 antagonizes the neuronal survival function of myocyte enhancer factor-2. J. Biol. Chem. 282 (40), 29186–29192. https://doi.org/10.1074/jbc.M704182200.

Bonavera, J.J., Swerdloff, R.S., Hakim, Sinha, AP, Lue, Y.H., Wang, C., 1998. Aging results in attenuated gonadotropin releasing hormone-luteinizing hormone axis responsiveness to glutamate receptor agonist N-methyl-D-aspartate. J. Neuroendocrinol. 10 (2), 93–99. https://doi.org/10.1046/j.1365-2826.1998.00177.x.

Brown, L.L., Schneider, J.S., Lidsky, T.I., 1997. Sensory and cognitive functions of the basal ganglia. Curr. Opin. Neurobiol. 7 (2), 157–163. https://doi.org/10.1016/S0959-4388(97)80003-7.

Brown, M.A., Sims, R.J., Gottlieb, P.D., Tucker, P.W., 2006. Identification and characterization of Smyd2: a split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase that interacts with the Sin3 histone deacetylase complex. Mol. Cancer 5 (26). https://doi.org/10.1186/1476-4598-5-26.

Brubaker, C.J., Dietrich, K.N., Lanphear, B.P., Cecil, K.M., 2010. The influence of age of lead exposure on adult gray matter volume. Neurotoxicology (Little Rock) 31 (3), 259–266. https://doi.org/10.1016/j.neuro.2010.03.004.

Brubaker, C.J., Schmithorst, V.J., Haynes, E.N., Dietrich, K.N., Egelhoff, J.C., Lindquist, D.M., et al., 2009. Altered myelination and axonal integrity in adults with childhood lead exposure: a diffusion tensor imaging study. Neurotoxicology (Little Rock) 30 (6), 867–875. https://doi.org/10.1016/j.neuro.2009.07.007.

Calderon de Anda, F., Tsai, L.-H., 2011. Axon selection. Commun. Integr. Biol. 4 (3), 304–307. https://doi.org/10.4161/cib.4.3.14781.

Campbell, C., Greenberg, R., Mankikar, D., Ross, R.D., 2016. A case study of environmental injustice: the failure in Flint. Int. J. Environ. Res. Public Health 13 (10). https://doi.org/10.3390/ijerph13100951.

Canfield, R.L., Gendle, M.H., Cory-Slechta, D.A., 2004. Impaired neuropsychological functioning in lead-exposed children. Dev. Neuropsychol. 26 (1), 513–540. https://doi.org/10.1207/s15326942dn2601_8.

Cariboni, A., Pimpinelli, F., Colamarino, S., Zaninetti, R., Piccolella, M., Rumio, C., et al., 2004. The product of X-linked Kallmann's syndrome gene (KAL1) affects the migratory activity of gonadotropin-releasing hormone (GnRH)-producing neurons. Hum. Mol. Genet. 13 (22), 2781–2791. https://doi.org/10.1093/hmg/ddh309.

Carrel, M., Zahrieh, D., Young, S.G., Oleson, J., Ryckman, K.K., Wels, B., et al., 2017. High prevalence of elevated blood lead levels in both rural and urban Iowa newborns: spatial patterns and area-level covariates. PLoS One 12 (5). https://doi.org/10.1371/journal.pone.0177930.

Carvan, M.J., Loucks, E., Weber, D.N., Williams, F.E., 2004. Ethanol effects on the developing zebrafish: neurobehavior and skeletal morphogenesis. Neurotoxicol. Teratol. 26 (6), 757–768. https://doi.org/10.1016/j.ntt.2004.06.016.

Cecil, K.M., Brubaker, C.J., Adler, C.M., Dietrich, K.N., Altaye, M., Egelhoff, J.C., et al., 2008. Decreased brain volume in adults with childhood lead exposure. PLoS Med. 5 (5), e112. https://doi.org/10.1371/journal.pmed.0050112.

Centers for Disease Control and Prevention, 2013. Lead. National biomonitoring program factsheet. Retrieved from, October 28, 2019. https://www.cdc.gov/biomonitoring/Lead_factsheet.html.

Chang, S.-H., Cheng, B.-H., Lee, S.-L., Chuang, H.-Y., Yang, C.-Y., Sung, F.-C., Wu, T.-N., 2006. Low blood lead concentration in association with infertility in women. Environ. Res. 101 (3), 380–386. https://doi.org/10.1016/j.envres.2005.10.004.

Chatoo, W., Abdouh, M., David, J., Champagne, M.-P., Ferreira, J., Rodier, F., Bernier, G., 2009. The polycomb group gene Bmi1 regulates antioxidant defenses in neurons by repressing p53 pro-oxidant activity. J. Neurosci.: Off. J. Soc. Neurosci. 29 (2), 529–542. https://doi.org/10.1523/JNEUROSCI.5303-08.2009.

Chen, B., Wang, S.S., Hattox, A.M., Rayburn, H., Nelson, S.B., McConnell, S.K., 2008. The Fezf2-Ctip2 genetic pathway regulates the fate choice of subcortical projection neurons in the developing cerebral cortex. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 105, pp. 11382–11387. https://doi.org/10.1073/pnas.0804918105, 32.

Chen, J., Chen, Y., Liu, W., Bai, C., Liu, X., Liu, K., et al., 2012. Developmental lead acetate exposure induces embryonic toxicity and memory deficit in adult zebrafish. Neurotoxicol. Teratol. 34, 581–586.

Chen, C., Wang, N., Zhai, H., Nie, X., Sun, H., Han, B., et al., 2016. Associations of blood lead levels with reproductive hormone levels in men and postmenopausal women: results from the SPECT-China Study. Sci. Rep. 6 https://doi.org/10.1038/srep37809.

Chen, L., Wang, X., Zhang, X., Lam, P.K.S., Guo, Y., Lam, J.C.W., Zhou, B., 2017. Transgenerational endocrine disruption and neurotoxicity in zebrafish larvae after parental exposure to binary mixtures of decabromodiphenyl ether (BDE-209) and lead. Environ. Pollut. 230, 96–106. https://doi.org/10.1016/j.envpol.2017.06.053.

Chen, X., Wang, S., Zhou, Y., Han, Y., Li, S., Xu, Q., et al., 2018. Phf8 histone demethylase deficiency causes cognitive impairments through the mTOR pathway. Nat. Commun. 9 (1) https://doi.org/10.1038/s41467-017-02531-y.

Cho, K.I., Cai, Y., Yi, H., Yeh, A., Aslanukov, A., Ferreira, P.A., 2007. Association of the kinesin-binding domain of RanBP2 to KIF5B and KIF5C determines mitochondria localization and function. Traffic 8 (12), 1722–1735. https://doi.org/10.1111/j.1600-0854.2007.00647.x.

Cory-Slechta, D.A., 1997. Relationships between Pb-induced changes in neurotransmitter system function and behavioral toxicity. Neurotoxicology (Little Rock) 18 (3), 673–688. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/9339816.

Costa, L.G., Aschner, M., Vitalone, A., Syversen, T., Soldin, O.P., 2004. Developmental neuropathology of environmental agents. Annu. Rev. Pharmacol. Toxicol. 44, 87–110. https://doi.org/10.1146/annurev.pharmtox.44.101802.121424.

Daku, A.B., Salisu, A.I., El-ta'alu, A.B., 2016. Age-related effects of lead poisoning on sex hormones in adult male Wistar rats. J. Physiol. Pathophysiol. 7 (4), 23–27. https://doi.org/10.5897/jpap2015.0104.

d'Amora, M., Giordani, S., 2018. The utility of zebrafish as a model for screening developmental neurotoxicity. Front. Neurosci. 12 https://doi.org/10.3389/fnins.2018.00976.

Das, S., Bhattacharyya, N.P., 2016. Huntingtin interacting protein HYPK is a negative regulator of heat shock response and is downregulated in models of Huntington's Disease. Exp. Cell Res. 343 (2), 107–117. https://doi.org/10.1016/j.yexcr.2016.03.021.

de Souza Lisboa, S.F., Gonçalves, G., Komatsu, F., Queiroz, Salci, CA, Aparecido

Almeida, A., Gastaldello Moreira, E., 2005. Developmental lead exposure induces depressive-like behavior in female rats. Drug Chem. Toxicol. 28 (1), 67–77. https://doi.org/10.1081/DCT-39696.
Devóz, P.P., Gomes, W.R., De Araújo, M.L., Ribeiro, D.L., Pedron, T., Greggi Antunes, L.M., et al., 2017. Lead (Pb) exposure induces disturbances in epigenetic status in workers exposed to this metal. J. Toxicol. Environ. Health Part A 80 (19–21), 1098–1105. https://doi.org/10.1080/15287394.2017.1357364.
Di Cristo, G., Berardi, N., Cancedda, L., Pizzorusso, T., Putignano, E., Ratto, G.M., Maffei, L., 2001. Requirement of ERK activation for visual cortical plasticity. Science (New York, N.Y.) 292 (5525), 2337–2340. https://doi.org/10.1126/science.1059075.
Dietrich, K.N., Krafft, K.M., Bornschein, R.L., Hammond, P.B., Berger, O., Succop, P.A., Bier, M., 1987. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 80 (5), 721–730.
Dietrich, K.N., Succop, P.A., Berger, O.G., Hammond, P.B., Bornschein, R.L., 1991. Lead exposure and the cognitive development of urban preschool children: the Cincinnati Lead Study cohort at age 4 years. Neurotoxicol. Teratol. 13 (2), 203–211. https://doi.org/10.1016/0892-0362(91)90012-l.
Dietrich, K.N., Douglas, R.M., Succop, P.A., Berger, O.G., Bornschein, R.L., 2001. Early exposure to lead and juvenile delinquency. Neurotoxicol. Teratol. 23 (6), 511–518. https://doi.org/10.1016/S0892-0362(01)00184-2.
Dobin, A., Davis, C.A., Schlesinger, F., Drenkow, J., Zaleski, C., Jha, S., et al., 2013. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29 (1), 15–21. https://doi.org/10.1093/bioinformatics/bts635.
Doumouchtsis, K.K., Doumouchtsis, S.K., Doumouchtsis, E.K., Perrea, D.N., 2009. The effect of lead intoxication on endocrine functions. J. Endocrinol. Investig. 32 (2), 175–183. https://doi.org/10.1007/BF03345710.
Dribben, W.H., Creeley, C.E., Farber, N., 2011. Low-level lead exposure triggers neuronal apoptosis in the developing mouse brain. Neurotoxicol. Teratol. 33 (4), 473–480. https://doi.org/10.1016/j.ntt.2011.05.006.
Duclot, F., Kabbaj, M., 2017. The role of early growth response 1 (EGR1) in brain plasticity and neuropsychiatric disorders. Front. Behav. Neurosci. 11 (35) https://doi.org/10.3389/fnbeh.2017.00035.
Duric, V., Banasr, M., Licznerski, P., Schmidt, H.D., Stockmeier, C.A., Simen, A.A., et al., 2010. A negative regulator of MAP kinase causes depressive behavior. Nat. Med. 16 (11), 1328–1332. https://doi.org/10.1038/nm.2219.
Eid, A., Bihaqi, S.W., Renehan, W.E., Zawia, N.H., 2016. Developmental lead exposure and lifespan alterations in epigenetic regulators and their correspondence to biomarkers of Alzheimer's disease. Alzheimer's Dementia 2, 123–131. https://doi.org/10.1016/j.dadm.2016.02.002.
Emens, J., Lewy, A., Kinzie, J.M., Arntz, D., Rough, J., 2009. Circadian misalignment in major depressive disorder. Psychiatry Res. 168 (3), 259–261. https://doi.org/10.1016/j.psychres.2009.04.009.
Engstrom, A., Wang, H., Xia, Z., 2015. Lead decreases cell survival, proliferation, and neuronal differentiation of primary cultured adult neural precursor cells through activation of the JNK and p38 MAP kinases. Toxicol. In Vitro: Int. J. Publ. Assoc. BIBRA 29 (5), 1146–1155. https://doi.org/10.1016/j.tiv.2015.05.001.
Environmental Protection Agency (EPA), 2008. Lead and copper rule: a quick reference Guide. Report. U.S. Environmental Protection Agency, Washington, D.C.
Ernst, P., Vakoc, C.R., 2012. WRAD: enabler of the SET1-family of H3K4 methyltransferases. Briefings Funct. Genomics Proteomics 11 (3), 217–226. https://doi.org/10.1093/bfgp/els017.
Evans, H.L., Daniel, S.A., Marmor, M., 1994. Reversal learning tasks may provide rapid determination of cognitive deficits in lead-exposed children. Neurotoxicol. Teratol. 16 (5), 471–477. https://doi.org/10.1016/0892-0362(94)90125-2.
Faulk, C., Barks, A., Sánchez, B.N., Zhang, Z., Anderson, O.S., Peterson, K.E., Dolinoy, D.C., 2014. Perinatal lead (Pb) exposure results in sex-specific effects on food intake, fat, weight, and insulin response across the murine life-course. PLoS One 9 (8), e104273. https://doi.org/10.1371/journal.pone.0104273.
Filippelli, G.M., Laidlaw, M.A.S., Latimer, J.C., Raftis, R., 2005. Urban lead poisoning and medical geology: an unfinished story. GSA Today (Geol. Soc. Am.) 15 (1), 4–11. https://doi.org/10.1130/1052-5173.
Fox, D.A., He, L., Poblenz, A.T., Medrano, C.J., Blocker, Y.S., Srivastava, D., 1998. Lead-induced alterations in retinal cGMP phosphodiesterase trigger calcium overload, mitochondrial dysfunction and rod photoreceptor apoptosis. In: Toxicology Letters, vols. 102–103, pp. 359–361. https://doi.org/10.1016/S0378-4274.
French, C.R., Erickson, T., French, D.V., Pilgrim, D.B., Waskiewicz, A.J., 2009. Gdf6a is required for the initiation of dorsal-ventral retinal patterning and lens development. Dev. Biol. 333 (1), 37–47. https://doi.org/10.1016/j.ydbio.2009.06.018.
Gao, H., Bu, Y., Wu, Q., Wang, X., Chang, N., Lei, L., et al., 2015. Mecp2 regulates neural cell differentiation by suppressing the Id1 to Her2 axis in zebrafish. J. Cell Sci. 128 (12), 2340–2350. https://doi.org/10.1242/jcs.167874.
Gibson, E.M., Wang, C., Tjho, S., Khattar, N., Kriegsfeld, L.J., 2010. Experimental "jet lag" inhibits adult neurogenesis and produces long-term cognitive deficits in female hamsters. PLoS One 5 (12). https://doi.org/10.1371/journal.pone.0015267.
Giddabasappa, A., Ryan Hamilton, W., Chaney, S., Xiao, W., Johnson, J.E., Mukherjee, S., Fox, D.A., 2011. Low-level gestational lead exposure increases retinal progenitor cell proliferation and rod photoreceptor and bipolar cell neurogenesis in mice. Environ. Health Perspect. 119 (1), 71–77. https://doi.org/10.1289/ehp.1002524.
Goldstein, G.W., 1990. Lead poisoning and brain cell function. Environ. Health Perspect. 89, 91–94. https://doi.org/10.1289/ehp.908991.
Goldstein, G.W., 1992. Neurologic concepts of lead poisoning in children. Pediatr. Ann. https://doi.org/10.3928/0090-4481-19920601-11.
Goold, R.G., Gordon-Weeks, P.R., 2005. The MAP kinase pathway is upstream of the activation of GSK3beta that enables it to phosphorylate MAP1B and contributes to the stimulation of axon growth. Mol. Cell. Neurosci. 28 (3), 524–534. https://doi.org/10.1016/j.mcn.2004.11.005.
Gore, A.V., Athans, B., Iben, J.R., Johnson, K., Russanova, V., Castranova, D., et al., 2016. Epigenetic regulation of hematopoiesis by DNA methylation. ELife 5, e11813. https://doi.org/10.7554/eLife.11813.
Gore, A.V., Tomins, K.A., Iben, J., Ma, L., Castranova, D., Davis, A.E., et al., 2018. An epigenetic mechanism for cavefish eye degeneration. Nat. Ecol.; Evol. 2 (7), 1155–1160. https://doi.org/10.1038/s41559-018-0569-4.
Graf, E.R., Zhang, X., Jin, S.-X., Linhoff, M.W., Craig, A.M., 2004. Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. Cell 119 (7), 1013–1026. https://doi.org/10.1016/j.cell.2004.11.035.
Groen, E.J.N., Gillingwater, T.H., 2015. UBA1: at the crossroads of ubiquitin homeostasis and neurodegeneration. Trends Mol. Med. 21 (10), 622–632. https://doi.org/10.1016/j.molmed.2015.08.003.
Gustafson, A., Hedner, P., Schütz, A., Skerfving, S., 1989. Occupational lead exposure and pituitary function. Int. Arch. Occup. Environ. Health 61 (4), 277–281. https://doi.org/10.1007/bf00381426.
Handy, D.E., Castro, R., Loscalzo, J., 2011. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation 123 (19), 2145–2156. https://doi.org/10.1161/CIRCULATIONAHA.110.956839.
Hass, D.T., Barnstable, C.J., 2019. Mitochondrial uncoupling protein 2 knock-out promotes mitophagy to decrease retinal ganglion cell death in a mouse model of glaucoma. J. Neurosci.: Off. J. Soc. Neurosci. 39 (18), 3582–3596. https://doi.org/10.1523/JNEUROSCI.2702-18.2019.
Hass, D.T., Barnstable, C.J., 2016, August 1. Uncoupling protein 2 in the glial response to stress: implications for neuroprotection. Neural Regeneration Research. Editor. Board Neural Regen. Res. https://doi.org/10.4103/1673-5374.189159.
He, L., Perkins, G.A., Poblenz, A.T., Harris, J.B., Hung, M., Ellisman, M.H., Fox, D.A., 2003. Bcl-xL overexpression blocks bax-mediated mitochondrial contact site formation and apoptosis in rod photoreceptors of lead-exposed mice. Proc. Natl. Acad. Sci. U.S.A. 100 (3), 1022–1027. https://doi.org/10.1073/pnas.0333594100.
Holland, W.L., Miller, R.A., Wang, Z.V., Sun, K., Barth, B.M., Bui, H.H., et al., 2011. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat. Med. 17 (1), 55–63. https://doi.org/10.1038/nm.2277.
Horzmann, K.A., Freeman, J.L., 2018. Making Waves: New Developments in Toxicology with the Zebrafish. Toxicological Sciences. Oxford University Press. https://doi.org/10.1093/toxsci/kfy044.
Hsiao, P.-W., Fryer, C.J., Trotter, K.W., Wang, W., Archer, T.K., 2003. BAF60a mediates critical interactions between nuclear receptors and the BRG1 chromatin-remodeling complex for transactivation. Mol. Cell. Biol. 23 (17), 6210–6220. https://doi.org/10.1128/mcb.23.17.6210-6220.2003.
Huang, L., Xiao, X., Li, S., Jia, X., Wang, P., Guo, X., Zhang, Q., 2012. CRX variants in cone-rod dystrophy and mutation overview. Biochem. Biophys. Res. Commun. 426 (4), 498–503. https://doi.org/10.1016/j.bbrc.2012.08.110.
Irving, A.J., Harvey, J., 2014. Leptin regulation of hippocampal synaptic function in health and disease. Philosophical Transactions of the Royal Society of London. Ser. B Biol. Sci. 369 (1633), 20130155 https://doi.org/10.1098/rstb.2013.0155.
Ivanova, E.L., Mau-Them, F.T., Riazuddin, S., Kahrizi, K., Laugel, V., Schaefer, E., et al., 2017. Homozygous truncating variants in TBC1D23 cause pontocerebellar hypoplasia and alter cortical development. Am. J. Hum. Genet. 101 (3), 428–440. https://doi.org/10.1016/j.ajhg.2017.07.010.
Jaako-Movits, K., Zharkovsky, T., Romantchik, O., Jurgenson, M., Merisalu, E., Heidmets, L.-T., Zharkovsky, A., 2005. Developmental lead exposure impairs contextual fear conditioning and reduces adult hippocampal neurogenesis in the rat brain. Int. J. Dev. Neurosci.: Off. J. Int. Soc. Dev. Neurosci. 23 (7), 627–635. https://doi.org/10.1016/j.ijdevneu.2005.07.005.
Jain, R.B., 2016. Trends and variability in blood lead concentrations among US children and adolescents. Environ. Sci. Pollut. Res. Int. 23 (8), 7880–7889. https://doi.org/10.1007/s11356-016-6039-0.
Jedrychowski, W., Perera, F.P., Jankowski, J., Mrozek-Budzyn, D., Mroz, E., Flak, E., et al., 2009. Very low prenatal exposure to lead and mental development of children in infancy and early childhood. Neuroepidemiology 32 (4), 270–278. https://doi.org/10.1159/000203075.
Jett, D.A., Kuhlmann, A.C., Farmer, S.J., Guilarte, T.R., 1997. Age-dependent effects of developmental lead exposure on performance in the Morris water maze. Pharmacol., Biochem. Behav. 57 (1–2), 271–279. https://doi.org/10.1016/s0091-3057(96)00350-4.
Jones, L., Parker, J.D., Mendola, P., 2010. Blood lead and mercury levels in pregnant women in the United States- 2003–2008. NCHS Data Brief 52, 1–8.
Kandel, E.R., 2012. The molecular biology of memory: CAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. Mol. Brain. https://doi.org/10.1186/1756-6606-5-14.
Karatsoreos, I.N., 2014. Links between circadian rhythms and psychiatric disease. Front. Behav. Neurosci. https://doi.org/10.3389/fnbeh.2014.00162. Frontiers Research Foundation.
Kasten-Jolly, J., Lawrence, D.A., 2017. Sex-specific effects of developmental lead exposure on the immune-neuroendocrine network. Toxicol. Appl. Pharmacol. 334, 142–157. https://doi.org/10.1016/j.taap.2017.09.009.
Kasten-Jolly, J., Pabello, N., Bolivar, V.J., Lawrence, D.A., 2012. Developmental lead effects on behavior and brain gene expression in male and female BALB/cAnNTac mice. NeuroToxicology 33 (5), 1005–1020. https://doi.org/10.1016/j.neuro.2012.04.017.

Kim, M.-S., Akhtar, M.W., Adachi, M., Mahgoub, M., Bassel-Duby, R., Kavalali, E.T., et al., 2012. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J. Neurosci.: Off. J. Soc. Neurosci. 32 (32), 10879–10886. https://doi.org/10.1523/JNEUROSCI.2089-12.2012.

Kim, S., Kaang, B.K., 2017. Epigenetic regulation and chromatin remodeling in learning and memory. Exp. Mol. Med. https://doi.org/10.1038/emm.2016.140. Nature Publishing Group.

Ko, C.-Y., Wang, W.-L., Wang, S.-M., Chu, Y.-Y., Chang, W.-C., Wang, J.-M., 2014. Glycogen synthase kinase-3β-mediated CCAAT/enhancer-binding protein delta phosphorylation in astrocytes promotes migration and activation of microglia/macrophages. Neurobiol. Aging 35 (1), 24–34. https://doi.org/10.1016/j.neurobiolaging.2013.07.021.

Koebele, S.V., Bimonte-Nelson, H.A., 2017. The endocrine-brain-aging triad where many paths meet: female reproductive hormone changes at midlife and their influence on circuits important for learning and memory. Exp. Gerontol. 94, 14–23. https://doi.org/10.1016/j.exger.2016.12.011.

Lane, R.E., Hunter, D., Malcolm, D., Williams, M.K., Hudson, T.G.F., Browne, R.C., et al., 1968. Diagnosis of inorganic lead poisoning: a statement. Br. Med. J. 4, 501–504.

Laranjeiro, R., Whitmore, D., 2014. Transcription factors involved in retinogenesis are co-opted by the circadian clock following photoreceptor differentiation. Development (Cambridge, England) 141 (13), 2644–2656. https://doi.org/10.1242/dev.104380.

Laub, F., Aldabe, R., Friedrich, V., Ohnishi, S., Yoshida, T., Ramirez, F., 2001. Developmental expression of mouse Krüppel-like transcription factor KLF7 suggests a potential role in neurogenesis. Dev. Biol. 233 (2), 305–318. https://doi.org/10.1006/dbio.2001.0243.

Lee, J., Freeman, J.L., 2014a. Zebrafish as a model for developmental neurotoxicity assessment: the Application of the zebrafish in defining the effects of arsenic, methylmercury, or lead on early neurodevelopment. Toxics. MDPI AG. https://doi.org/10.3390/toxics2030464.

Lee, J., Freeman, J.L., 2014b. Zebrafish as a model for investigating developmental lead (Pb) neurotoxicity as a risk factor in adult neurodegenerative disease: a mini-review. NeuroToxicology 43, 57–64. https://doi.org/10.1016/j.neuro.2014.03.008.

Lee, J., Freeman, J.L., 2016. Embryonic exposure to 10 ug/L lead results in female-specific expression changes in genes associated with nervous system development and function and Alzheimer's disease in aged adult zebrafish brain. Metallomics 8, 589–596.

Lee, J., Horzmann, K.A., Freeman, J.L., 2018. An embryonic 100 ug/L lead exposure results in sex-specific changes in genes associated with the neurological system in female or cancer in male adult zebrafish brains. Neurotoxicol. Teratol. 65, 60–69.

Lee, S., Nakamura, E., Yang, H., Wei, W., Linggi, M.S., Sajan, M.P., et al., 2005. Neuronal apoptosis linked to EglN3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. Cancer Cell 8 (2), 155–167. https://doi.org/10.1016/j.ccr.2005.06.015.

Li, C., Xu, M., Wang, S., Yang, X., Zhou, S., Zhang, J., et al., 2011a. Lead exposure suppressed ALAD transcription by increasing methylation level of the promoter CpG islands. Toxicol. Lett. 203 (1), 48–53. https://doi.org/10.1016/j.toxlet.2011.03.002.

Li, C., Yang, X., Xu, M., Zhang, J., Sun, N., 2014. Association between GSTP1 CpG methylation and the early phase of lead exposure. Toxicol. Mech. Methods 24 (2), 111–115. https://doi.org/10.3109/15376516.2013.859195.

Li, H., Zhong, X., Chau, K.F., Williams, E.C., Chang, Q., 2011b. Loss of activity-induced phosphorylation of MeCP2 enhances synaptogenesis, LTP and spatial memory. Nat. Neurosci. 14 (8), 1001–1008. https://doi.org/10.1038/nn.2866.

Liao, J., He, J., Yan, T., Korzh, V., Gong, Z., 1999. A class of neuroD-related basic helix-loop-helix transcription factors expressed in developing central nervous system in zebrafish. DNA Cell Biol. 18 (4), 333–344. https://doi.org/10.1089/104454999315394.

Lidsky, T.I., Schneider, J.S., 2003. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain. https://doi.org/10.1093/brain/awg014.

Liu, J., Liu, X., Pak, V., Wang, Y., Yan, C., Pinto-Martin, J., Dinges, D., 2015. Early blood lead levels and sleep disturbance in preadolescence. Sleep 38 (12), 1869–1874. https://doi.org/10.5665/sleep.5230.

Lin, H., Lu, P., Zhou, M., Wu, F., Weng, L., Meng, K., et al., 2019. Purification of recombinant human fibroblast growth factor 13 in E. coli and its molecular mechanism of mitogenesis. Appl. Microbiol. Biotechnol. 103 (17), 7017–7027. https://doi.org/10.1007/s00253-019-09973-y.

Liu, M.C., Liu, X.Q., Wang, W., Shen, X.F., Che, H.L., Guo, Y.Y., et al., 2012. Involvement of microglia activation in the lead induced long-term potentiation impairment. PLoS One 7 (8). https://doi.org/10.1371/journal.pone.0043924.

Lorenzi, M., Altmann, A., Gutman, B., Wray, S., Arber, C., Hibar, D.P., , et al.Alzheimer's Disease Neuroimaging Initiative, 2018. Susceptibility of brain atrophy to TRIB3 in Alzheimer's disease, evidence from functional prioritization in imaging genetics. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 115, pp. 3162–3167. https://doi.org/10.1073/pnas.1706100115, 12.

Luikenhuis, S., Giacometti, E., Beard, C.F., Jaenisch, R., 2004. Expression of MeCP2 in postmitotic neurons rescues Rett syndrome in mice. Proc. Natl. Acad. Sci. U.S.A. 101 (16), 6033–6038. https://doi.org/10.1073/pnas.0401626101.

Ma, T., Hoeffer, C.A., Capetillo-Zarate, E., Yu, F., Wong, H., Lin, M.T., et al., 2010. Dysregulation of the mTOR pathway mediates impairment of synaptic plasticity in a mouse model of Alzheimer's disease. PLoS One 5 (9), 1–10. https://doi.org/10.1371/journal.pone.0012845.

Mahaffey, K.R., Annest, J.L., Roberts, J., Murphy, R.S., 1982. National estimates of blood lead levels: United States, 1976-1980: association with selected demographic and socioeconomic factors. N. Engl. J. Med. 307 (10), 573–579. https://doi.org/10.1056/NEJM198209023071001.

Majdzadeh, N., Wang, L., Morrison, B.E., Bassel-Duby, R., Olson, E.N., D'Mello, S.R., 2008. HDAC4 inhibits cell-cycle progression and protects neurons from cell death. Dev. Neurobiol. 68 (8), 1076–1092. https://doi.org/10.1002/dneu.20637.

Mani, M., Lee, S.Y., Lucast, L., Cremona, O., Di Paolo, G., De Camilli, P., Ryan, T.A., 2007. The dual phosphatase activity of synaptojanin1 is required for both efficient synaptic vesicle endocytosis and reavailability at nerve terminals. Neuron 56 (6), 1004–1018. https://doi.org/10.1016/j.neuron.2007.10.032.

Markovac, J., Goldstein, G.W., 1988. Picomolar concentrations of lead stimulate brain protein kinase C. Nature 334 (6177), 71–73. https://doi.org/10.1038/334071a0.

Matsukawa, S., Miwata, K., Asashima, M., Michiue, T., 2015. The requirement of histone modification by PRDM12 and Kdm4a for the development of preplacodal ectoderm and neural crest in Xenopus. Dev. Biol. 399 (1), 164–176. https://doi.org/10.1016/j.ydbio.2014.12.028.

Mazumdar, M., Xia, W., Hofmann, O., Gregas, M., Sui, S.H., Hide, W., et al., 2012. Prenatal lead levels, plasma amyloid β levels, and gene expression in young adulthood. Environ. Health Perspect. 120 (5), 702–707. https://doi.org/10.1289/ehp.1104474.

McMichael, A.J., Baghurst, P.A., Vimpani, G.V., Robertson, E.F., Wigg, N.R., Tong, S.L., 1992. Sociodemographic factors modifying the effect of environmental lead on neuropsychological development in early childhood. Neurotoxicol. Teratol. 14 (5), 321–327. https://doi.org/10.1016/0892-0362(92)90038-C.

McPherson, P.S., Takei, K., Schmid, S.L., De Camilli, P., 1994. p145, a major Grb2-binding protein in brain, is co-localized with dynamin in nerve terminals where it undergoes activity-dependent dephosphorylation. J. Biol. Chem. 269 (48), 30132–30139. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/7982917.

Melamed, P., Haj, M., Yosefzon, Y., Rudnizky, S., Wijeweera, A., Pnueli, L., Kaplan, A., 2018. Multifaceted targeting of the chromatin mediates gonadotropin-releasing hormone effects on gene expression in the gonadotrope. Front. Endocrinol. 9 (58) https://doi.org/10.3389/fendo.2018.00058.

Molofsky, A.V., Pardal, R., Iwashita, T., Park, I.-K., Clarke, M.F., Morrison, S.J., 2003. Bmi-1 dependence distinguishes neural stem cell self-renewal from progenitor proliferation. Nature 425 (6961), 962–967. https://doi.org/10.1038/nature02060.

Naicker, N., Norris, S.A., Mathee, A., Becker, P., Richter, L., 2010. Lead exposure is associated with a delay in the onset of puberty in South African adolescent females: findings from the Birth to Twenty cohort. Sci. Total Environ. 408 (21), 4949–4954. https://doi.org/10.1016/j.scitotenv.2010.07.037.

Nan, X., Ng, H.H., Johnson, C.A., Laherty, C.D., Turner, B.M., Eisenman, R.N., Bird, A., 1998. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 393 (6683), 386–389. https://doi.org/10.1038/30764.

Neal, A.P., Stansfield, K.H., Worley, P.F., Thompson, R.E., Guilarte, T.R., 2010. Lead exposure during synaptogenesis alters vesicular proteins and impairs vesicular release: potential role of NMDA receptor-dependent BDNF signaling. Toxicol. Sci.: Off. J. Soc. Toxicol. 116 (1), 249–263. https://doi.org/10.1093/toxsci/kfq111.

Needleman, H.L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., Barrett, P., 1979. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300 (13), 689–695. https://doi.org/10.1056/NEJM197903293001301.

Needleman, H.L., Landrigan, P.J., 2004. What level of lead in blood is toxic for a child? [3]. Am. J. Public Health. Am. Public Health Assoc. Inc. https://doi.org/10.2105/AJPH.94.1.8.

Nishino, J., Yamashita, K., Hashiguchi, H., Fujii, H., Shimazaki, T., Hamada, H., 2004. Meteorin: a secreted protein that regulates glial cell differentiation and promotes axonal extension. EMBO J. 23 (9), 1998–2008. https://doi.org/10.1038/sj.emboj.7600202.

DDD study Nixon, K.C.J., Rousseau, J., Stone, M.H., Sarikahya, M., Ehresmann, S., Mizuno, S., et al., 2018. Identification of SMARCD1 as a syndromic intellectual disability gene that is required for memory and context-dependent regulation of neuronal genes in Drosophila. BioRxiv 422188. https://doi.org/10.1101/422188.

Pan, Y.C., Li, C.F., Ko, C.Y., Pan, M.H., Chen, P.J., Tseng, J.T., et al., 2010. CEBPD reverses RB/E2F1-mediated gene repression and participates in HMDB-induced apoptosis of cancer cells. Clin. Cancer Res. 16 (23), 5770–5780. https://doi.org/10.1158/1078-0432.CCR-10-1025.

Patraca, I., Martínez, N., Busquets, O., Martí, A., Pedrós, I., Beas-Zarate, C., et al., 2017. Anti-inflammatory role of Leptin in glial cells through p38 MAPK pathway inhibition. Pharmacol. Rep.: PR 69 (3), 409–418. https://doi.org/10.1016/j.pharep.2016.12.005.

Paz-Filho, G., Mastronardi, C., Wong, M.-L., Licinio, J., 2012. Leptin therapy, insulin sensitivity, and glucose homeostasis. Indian J. Endocrinol. Metabol. 16 (Suppl. 3), S549–S555. https://doi.org/10.4103/2230-8210.105571.

Peineau, S., Taghibiglou, C., Bradley, C., Wong, T.P., Liu, L., Lu, J., et al., 2007. LTP inhibits LTD in the hippocampus via regulation of GSK3beta. Neuron 53 (5), 703–717. https://doi.org/10.1016/j.neuron.2007.01.029.

Pekcici, R., Kavlakoğlu, B., Yilmaz, S., Şahin, M., Delibaşi, T., 2010. Effects of lead on thyroid functions in lead-exposed workers. Cent. Eur. J. Med. 5 (2), 215–218. https://doi.org/10.2478/s11536-009-0092-8.

Peng, S., Zhang, Y., Zhang, J., Wang, H., Ren, B., 2010. ERK in learning and memory: a

review of recent research. Int. J. Mol. Sci. https://doi.org/10.3390/ijms11010222.
Penicud, K., Behrens, A., 2014. DMAP1 is an essential regulator of ATM activity and function. Oncogene 33 (4), 525–531. https://doi.org/10.1038/onc.2012.597.
Pérez-Sen, R., Queipo, M.J., Gil-Redondo, J.C., Ortega, F., Gomez-Villafuertes, R., Miras-Portugal, M.T., Delicado, E.G., 2019. Dual-specificity phosphatase regulation in neurons and glial cells. Int. J. Mol. Sci. 20 (8) https://doi.org/10.3390/ijms20081999, 1999.
Peterson, S.M., Zhang, J., Weber, G., Freeman, J.L., 2011. Global gene expression analysis reveals dynamic and developmental stage-dependent enrichment of lead-induced neurological gene alterations. Environ. Health Perspect. 119, 615–621.
Pilsner, J.R., Hu, H., Ettinger, A., Sánchez, B.N., Wright, R.O., Cantonwine, D., et al., 2009. Influence of prenatal lead exposure on genomic methylation of cord blood DNA. Environ. Health Perspect. 117 (9), 1466–1471. https://doi.org/10.1289/ehp.0800497.
Polanska, K., Hanke, W., Pawlas, N., Wesolowska, E., Jankowska, A., Jagodic, M., et al., 2018. Sex-dependent impact of low-level lead exposure during prenatal period on child psychomotor functions. Int. J. Environ. Res. Public Health 15 (10). https://doi.org/10.3390/ijerph15102263.
Qi, H.H., Sarkissian, M., Hu, G.-Q., Wang, Z., Bhattacharjee, A., Gordon, D.B., et al., 2010. Histone H4K20/H3K9 demethylase PHF8 regulates zebrafish brain and craniofacial development. Nature 466 (7305), 503–507. https://doi.org/10.1038/nature09261.
Rabinowitz, M.B., Wang, J.D., Soong, W.T., 1991. Dentine lead and child intelligence in Taiwan. Arch. Environ. Health 46 (6), 351–360. https://doi.org/10.1080/00039896.1991.9934402.
Rastegar, S., Parimisetty, A., Cassam Sulliman, N., Narra, S.S., Weber, S., Rastegar, M., et al., 2019. Expression of adiponectin receptors in the brain of adult zebrafish and mouse: links with neurogenic niches and brain repair. J. Comp. Neurol. 527 (14), 2317–2333. https://doi.org/10.1002/cne.24669.
Reddy, G.R., Zawia, N.H., 2000. Lead exposure alters Egr-1 DNA-binding in the neonatal rat brain. Int. J. Dev. Neurosci.: Off. J. Int. Soc. Dev. Neurosci. 18 (8), 791–795. https://doi.org/10.1016/s0736-5748(00)00048-4.
Renninger, S.L., Gesemann, M., Neuhauss, S.C.F., 2011. Cone arrestin confers cone vision of high temporal resolution in zebrafish larvae. Eur. J. Neurosci. 33 (4), 658–667. https://doi.org/10.1111/j.1460-9568.2010.07574.x.
Reuben, A., 2018. Childhood lead exposure and adult neurodegenerative disease. Journal of Alzheimer's Disease. JAD 64 (1), 17–42. https://doi.org/10.3233/JAD-180267.
Reuben, A., Schaefer, J.D., Moffitt, T.E., Broadbent, J., Harrington, H., Houts, R.M., et al., 2019. Association of childhood lead exposure with adult personality traits and lifelong mental health. JAMA Psychiatry 76 (4), 418–425. https://doi.org/10.1001/jamapsychiatry.2018.4192.
Ribeiro, M.J., Schofield, M.G., Kemenes, I., O'Shea, M., Kemenes, G., Benjamin, P.R., 2005. Activation of MAPK is necessary for long-term memory consolidation following food-reward conditioning. Learn. Mem. 12 (5), 538–545. https://doi.org/10.1101/lm.8305.
Rice, C., Ghorai, J.K., Zalewski, K., Weber, D.N., 2011. Developmental lead exposure causes startle response deficits in zebrafish. Aquat. Toxicol. 105 (3–4), 600–608. https://doi.org/10.1016/j.aquatox.2011.08.014.
Rice, D.C., 1990. Lead-induced behavioral impairment on a spatial discrimination reversal task in monkeys exposed during different periods of development. Toxicol. Appl. Pharmacol. 106 (2), 327–333. https://doi.org/10.1016/0041-008X(90)90251-O.
Rice, D.C., 2006. Animal models of cognitive impairment produced by developmental lead exposure. In: Levin, E.D., Buccafusco, J.J. (Eds.), Animal Models of Cognitive Impairment. CRC Press/Taylor & Francis, Boca Raton (FL). Chapter 6. https://www.ncbi.nlm.nih.gov/books/NBK2524/.
Rio, C., Rieff, H.I., Qi, P., Corfas, G., 1997. Neuregulin and erbB receptors play a critical role in neuronal migration. Neuron 19 (1), 39–50. https://doi.org/10.1016/S0896-6273(00)80346-3.
Robinson, M.D., McCarthy, D.J., Smyth, G.K., 2009. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. Bioinformatics 26 (1), 139–140. https://doi.org/10.1093/bioinformatics/btp616.
Rohde, K., Rovsing, L., Ho, A.K., Møller, M., Rath, M.F., 2014. Circadian dynamics of the cone-rod homeobox (CRX) transcription factor in the rat pineal gland and its role in regulation of arylalkylamine N-acetyltransferase (AANAT). Endocrinology 155 (8), 2966–2975. https://doi.org/10.1210/en.2014-1232.
Ronis, M.J., Badger, T.M., Shema, S.J., Roberson, P.K., Shaikh, F., 1996. Reproductive toxicity and growth effects in rats exposed to lead at different periods during development. Toxicol. Appl. Pharmacol. 136 (2), 361–371. https://doi.org/10.1006/taap.1996.0044.
Rossouw, J., Offermeier, J., van Rooyen, JM, 1987. Apparent central neurotransmitter receptor changes induced by low-level lead exposure during different developmental phases in the rat. Toxicol. Appl. Pharmacol. 91 (1), 132–139. https://doi.org/10.1016/0041-008x(87)90200-6.
Rountree, M.R., Bachman, K.E., Baylin, S.B., 2000. DNMT1 binds HDAC2 and a new co-repressor, DMAP1, to form a complex at replication foci. Nat. Genet. 25 (3), 269–277. https://doi.org/10.1038/77023.
Sabbar, M., Dkhissi-Benyahya, O., Benazzouz, A., Lakhdar-Ghazal, N., 2017. Circadian clock protein content and daily rhythm of locomotor activity are altered after chronic exposure to lead in rat. Front. Behav. Neurosci. 11 (178) https://doi.org/10.3389/fnbeh.2017.00178.
Sakai, C., Ijaz, S., Hoffman, E.J., 2018. Zebrafish models of neurodevelopmental disorders: past, present, and future. Frontiers in molecular neuroscience. Frontiers media S.A. https://doi.org/10.3389/fnmol.2018.00294.
Sánchez-Martín, F.J., Fan, Y., Lindquist, D.M., Xia, Y., Puga, A., 2013. Lead induces similar gene expression changes in brains of gestationally exposed adult mice and in neurons differentiated from mouse embryonic stem cells. PLoS One 8 (11). https://doi.org/10.1371/journal.pone.0080558.
Sanchez, O.F., Lee, J., Yu King Hing, N., Kim, S.E., Freeman, J.L., Yuan, C., 2017. Lead (Pb) exposure reduces global DNA methylation level by non-competitive inhibition and alteration of dnmt expression. Metallomics 9 (2), 149–160. https://doi.org/10.1039/c6mt00198j.
Sawan, C., Herceg, Z., 2010. Histone modifications and cancer. Adv. Genet. 70, 57–85. https://doi.org/10.1016/B978-0-12-380866-0.60003-4.
Saxena, D.K., Murthy, R.C., Singh, C., Chandra, S.V., 1989. Zinc protects testicular injury induced by concurrent exposure to cadmium and lead in rats. Res. Commun. Chem. Pathol. Pharmacol. 64 (2), 317–329. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/2740621.
Schneider, J.S., Anderson, D.W., Sonnenahalli, H., Vadigepalli, R., 2011. Sex-based differences in gene expression in hippocampus following postnatal lead exposure. Toxicol. Appl. Pharmacol. 256 (2), 179–190. https://doi.org/10.1016/j.taap.2011.08.008.
Schneider, J.S., Mettil, W., Anderson, D.W., 2012. Differential effect of postnatal lead exposure on gene expression in the hippocampus and frontal cortex. J. Mol. Neurosci.: MN 47 (1), 76–88. https://doi.org/10.1007/s12031-011-9686-0.
Sen, A., Heredia, N., Senut, M.-C., Land, S., Hollocher, K., Lu, X., et al., 2015. Multigenerational epigenetic inheritance in humans: DNA methylation changes associated with maternal exposure to lead can be transmitted to the grandchildren. Sci. Rep. 5 (14466) https://doi.org/10.1038/srep14466.
Sesé, B., Barrero, M.J., Fabregat, M.-C., Sander, V., Izpisua Belmonte, J.C., 2013. SMYD2 is induced during cell differentiation and participates in early development. Int. J. Dev. Biol. 57 (5), 357–364. https://doi.org/10.1387/ijdb.130051ji.
Shao, Y., Chernaya, V., Johnson, C., Yang, W.Y., Cueto, R., Sha, X., et al., 2016. Metabolic diseases downregulate the majority of histone modification enzymes, making a few upregulated enzymes novel therapeutic Targets–"Sand out and gold stays. J. Cardiovasc. Transl. Res. 9 (1), 49–66. https://doi.org/10.1007/s12265-015-9664-y.
Shishido, T., Nagano, Y., Araki, M., Kurashige, T., Obayashi, H., Nakamura, T., et al., 2019. Synphilin-1 has neuroprotective effects on MPP+-induced Parkinson's disease model cells by inhibiting ROS production and apoptosis. Neurosci. Lett. 690, 145–150. https://doi.org/10.1016/j.neulet.2018.10.020.
Sierra, E.M., Tiffany-Castiglioni, E., 1992. Effects of low-level lead exposure on hypothalamic hormones and serum progesterone levels in pregnant Guinea pigs. Toxicology 72 (1), 89–97. https://doi.org/10.1016/0300-483x(92)90088-v.
Signore, A.P., Zhang, F., Weng, Z., Gao, Y., Chen, J., 2008. Leptin neuroprotection in the CNS: mechanisms and therapeutic potentials. J. Neurochem. 106 (5), 1977–1990. https://doi.org/10.1111/j.1471-4159.2008.05457.x.
Silva, A.J., Kogan, J.H., Frankland, P.W., Kida, S., 1998. Creb and memory. Annu. Rev. Neurosci. 21 (1), 127–148. https://doi.org/10.1146/annurev.neuro.21.1.127.
Singh, G., Singh, V., Sobolewski, M., Cory-Slechta, D.A., Schneider, J.S., 2018. Sex-dependent effects of developmental lead exposure on the brain. Front. Genet. 9 (89) https://doi.org/10.3389/fgene.2018.00089.
Sobolewski, M., Varma, G., Adams, B., Anderson, D.W., Schneider, J.S., Cory-Slechta, D.A., 2018. Developmental lead exposure and prenatal stress result in sex-specific reprograming of adult stress physiology and epigenetic profiles in brain. Toxicol. Sci.: Off. J. Soc. Toxicol. 163 (2), 478–489. https://doi.org/10.1093/toxsci/kfy046.
Soeiro, A.C., Gouvêa, T.S., Moreira, E.G., 2007. Behavioral effects induced by subchronic exposure to Pb and their reversion are concentration and gender dependent. Hum. Exp. Toxicol. 26 (9), 733–739. https://doi.org/10.1177/0960327107083016.
Sokol, R.Z., Wang, S., Wan, Y.-J.Y., Stanczyk, F.Z., Gentzschein, E., Chapin, R.E., 2002. Long-term, low-dose lead exposure alters the gonadotropin-releasing hormone system in the male rat. Environ. Health Perspect. 110 (9), 871–874. https://doi.org/10.1289/ehp.02110871.
Stansfield, K.H., Pilsner, J.R., Lu, Q., Wright, R.O., Guilarte, T.R., 2012. Dysregulation of BDNF-TrkB signaling in developing hippocampal neurons by Pb(2+): implications for an environmental basis of neurodevelopmental disorders. Toxicol. Sci.: Off. J. Soc. Toxicol. 127 (1), 277–295. https://doi.org/10.1093/toxsci/kfs090.
Talebian, A., Henkemeyer, M., 2019. EphB2 receptor cell-autonomous forward signaling mediates auditory memory recall and learning-driven spinogenesis. Commun. Biol. 2 (1) https://doi.org/10.1038/s42003-019-0625-x, 372.
Taniguchi, K., Anderson, A.E., Sutherland, A.E., Wotton, D., 2012. Loss of tgif function causes holoprosencephaly by disrupting the Shh signaling pathway. PLoS Genet. 8 (2) https://doi.org/10.1371/journal.pgen.1002524.
Teame, T., Zhang, Z., Ran, C., Zhang, H., Yang, Y., Ding, Q., et al., 2019. The use of zebrafish (Danio rerio) as biomedical models. Animal Frontiers 9 (3), 68–77. https://doi.org/10.1093/af/vfz020.
Tena, A., Peru, E., Martinetti, L.E., Cano, J.C., Baltazar, Loyola, CD, Wagler, A.E., et al., 2019. Long-term consequences of early postnatal lead exposure on hippocampal synaptic activity in adult mice. Brain and Behavior 9 (8). https://doi.org/10.1002/brb3.1307 e01307.
Tovin, A., Alon, S., Ben-Moshe, Z., Mracek, P., Vatine, G., Foulkes, N.S., et al., 2012. Systematic identification of rhythmic genes reveals camk1gb as a new element in the circadian clockwork. PLoS Genet. 8 (12) https://doi.org/10.1371/journal.pgen.1003116.
Trombini, T.V., Pedroso, C.G., Ponce, D., Almeida, A.A., Godinho, A.F., 2001. Developmental lead exposure in rats: is a behavioral sequel extended at F2

generation? Pharmacol., Biochem. Behav. 68 (4), 743–751. https://doi.org/10.1016/s0091-3057(01)00473-7.
Turnbull, A.K., Selli, C., Martinez-Perez, C., Fernando, A., Renshaw, L., Keys, J., et al., 2018. Unlocking the transcriptomic potential of formalin-fixed paraffin embedded breast cancer tissues for high-throughput genomic analysis [Abstract], 2018 Dec 4-8. In: Proceedings of the 2018 San Antonio Breast Cancer Symposium. TX. Philadelphia (PA); AACR; Cancer Research, San Antonio, 2019; 79 (4 Suppl). Abstract nr P3-06-17.
Verhage, M., Maia, A.S., Plomp, J.J., Brussaard, A.B., Heeroma, J.H., Vermeer, H., et al., 2000. Synaptic assembly of the brain in the absence of neurotransmitter secretion. Science 287 (5454), 864–869. https://doi.org/10.1126/science.287.5454.864.
vonderEmbse, A.N., Hu, Q., DeWitt, J.C., 2017. Developmental toxicant exposure in a mouse model of Alzheimer's disease induces differential sex-associated microglial activation and increased susceptibility to amyloid accumulation. J. Dev. Orig. Health Dis. 8 (4), 493–501. https://doi.org/10.1017/S2040174417000277.
Wang, Z., Qin, G., Zhao, T.C., 2014. Histone deacetylase 4 (HDAC4): mechanism of regulations and biological functions. Epigenomics 6 (1), 139–150. https://doi.org/10.2217/epi.13.73.Histone.
Wayman, G.A., Lee, Y.-S., Tokumitsu, H., Silva, A.J., Silva, A., Soderling, T.R., 2008. Calmodulin-kinases: modulators of neuronal development and plasticity. Neuron 59 (6), 914–931. https://doi.org/10.1016/j.neuron.2008.08.021.
Weber, D.N., Ghorai, J.K., 2013. Experimental design affects social behavior outcomes in adult zebrafish developmentally exposed to lead. Zebrafish 10, 294–302.
Westerfield, M., 2000. The Zebrafish Book. A Guide for the Laboratory Use of Zebrafish (Danio Rerio), fourth ed. University of Oregon Press, Eugene.
White, L.D., Cory-Slechta, D.A., Gilbert, M.E., Tiffany-Castiglioni, E., Zawia, N.H., Virgolini, M., et al., 2007. New and evolving concepts in the neurotoxicology of lead. Toxicol. Appl. Pharmacol. 225 (1), 1–27. https://doi.org/10.1016/j.taap.2007.08.001.
Whittle, E., Singhal, R.L., Collins, M., Hrdina, P.D., 1983. Effects of subacute low level lead exposure on glucose homeostasis. Res. Commun. Chem. Pathol. Pharmacol. 40 (1), 141–154. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/6306742.
Wilker, S., Pfeiffer, A., Kolassa, S., Elbert, T., Lingenfelder, B., Ovuga, E., et al., 2014. The role of FKBP5 genotype in moderating long-term effectiveness of exposure-based psychotherapy for posttraumatic stress disorder. Transl. Psychiatry 4. https://doi.org/10.1038/tp.2014.49.
Wu, J., Basha, M.R., Brock, B., Cox, D.P., Cardozo-Pelaez, F., McPherson, C.A., et al., 2008. Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. J. Neurosci.: Off. J. Soc. Neurosci. 28 (1), 3–9. https://doi.org/10.1523/JNEUROSCI.4405-07.2008.
Wu, Q.-F., Yang, L., Li, S., Wang, Q., Yuan, X.-B., Gao, X., et al., 2012. Fibroblast growth factor 13 is a microtubule-stabilizing protein regulating neuronal polarization and migration. Cell 149 (7), 1549–1564. https://doi.org/10.1016/j.cell.2012.04.046.
Xu, X., Weber, D., Burge, R., VanAmberg, K., 2016. Neurobehavioral impairments produced by developmental lead exposure persisted for generations in zebrafish (Danio rerio). Neurotoxicology (Little Rock) 52, 176–185. https://doi.org/10.1016/j.neuro.2015.12.009.
Xu, Y., Toh, K.L., Jones, C.R., Shin, J.Y., Fu, Y.H., Ptáček, L.J., 2007. Modeling of a human circadian mutation yields insights into clock regulation by PER2. Cell 128 (1), 59–70. https://doi.org/10.1016/j.cell.2006.11.043.
Yang, Z., Augustin, J., Chang, C., Hu, J., Shah, K., Chang, C.-W., et al., 2014. The DPY30 subunit in SET1/MLL complexes regulates the proliferation and differentiation of hematopoietic progenitor cells. Blood 124 (13), 2025–2033. https://doi.org/10.1182/blood-2014-01-549220.
Yin, L., Wu, N., Curtin, J.C., Qatanani, M., Szwergold, N.R., Reid, R.A., et al., 2007. Rev-erbalpha, a heme sensor that coordinates metabolic and circadian pathways. Science (New York, N.Y.) 318 (5857), 1786–1789. https://doi.org/10.1126/science.1150179.
Yu, J., 2014. Endocrine disorders and the neurologic manifestations. Ann. Pediatric Endocrinol.; Metabol. 19 (4) https://doi.org/10.6065/apem.2014.19.4.184, 184.
Yu, Z., Chen, X., Zhang, J., Wang, R., Yin, D., 2013. Transgenerational effects of heavy metals on L3 larva of Caenorhabditis elegans with greater behavior and growth inhibitions in the progeny. Ecotoxicol. Environ. Saf. 88, 178–184. https://doi.org/10.1016/j.ecoenv.2012.11.012.
Zannas, A.S., Wiechmann, T., Gassen, N.C., Binder, E.B., 2016. Gene-stress-epigenetic regulation of FKBP5: clinical and translational implications. Neuropsychopharmacology. https://doi.org/10.1038/npp.2015.235. Nature Publishing Group.
Zannino, D.A., Downes, G.B., Sagerström, C.G., 2014. prdm12b specifies the p1 progenitor domain and reveals a role for V1 interneurons in swim movements. Dev. Biol. 390 (2), 247–260. https://doi.org/10.1016/j.ydbio.2014.02.025.
Zhang, J., Peterson, S.M., Weber, G.J., Zhu, X., Zheng, W., Freeman, J.L., 2011. Decreased axonal density and altered expression profiles of axonal guidance genes underlying lead (Pb) neurodevelopmental toxicity at early embryonic stages in the zebrafish. Neurotoxicol. Teratol. 33, 715–720.
Zhang, S., Li, J., Lea, R., Vleminckx, K., Amaya, E., 2014. Fezf2 promotes neuronal differentiation through localised activation of Wnt/β-catenin signalling during forebrain development. Development (Cambridge, England) 141 (24), 4794–4805. https://doi.org/10.1242/dev.115691.
Zhao, Z.-H., Zheng, G., Wang, T., Du, K.-J., Han, X., Luo, W.-J., et al., 2018. Low-level gestational lead exposure alters dendritic spine plasticity in the Hippocampus and reduces learning and memory in rats. Scientific Reports, 8(1) 3533. https://doi.org/10.1038/s41598-018-21521-8.
Zheng, W., Lu, Y.M., Lu, G.Y., Zhao, Q., Cheung, O., Blaner, W.S., 2001. Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. Toxicol. Sci. 61 (1), 107–114. https://doi.org/10.1093/toxsci/61.1.107.