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Review

Contribution of Inhibitor of Differentiation (ID) and Estrogenic Endocrine Disruptors to Neurocognitive Disorders

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Abstract: The devastating growth in the worldwide frequency of neurocognitive disorders and its allied difficulties such as decline in memory, spatial competency, and ability to focus poses a significant psychological public health problem. Inhibitor of Differentiation (ID) proteins are members of a family of helix-loop-helix (HLH) transcription factors. ID proteins have been demonstrated to be involved in neurodevelopmental & depressive diseases and thus may influence neurocognitive deficiencies due to environmental exposure. Previously, it has been demonstrated that environmental factors such as estrogenic endocrine disruptors (EEDs) have played an essential role in the influence of various neurocognitive disorders such as Alzheimer's, Dementia, and Parkinson's disease. Based on this increasing number of reports, we consider the impact of these environmental pollutants on ID proteins. Better understanding of how these ID proteins by which EED exposure can affect neurocognitive disorders in populations will prospectively deliver valuable information in the impediment and regulation of these diseases linked with environmental factor exposure.

Keywords: endocrine disruptor; environmental health sciences; gene-environment; inhibitor of differentiation; neurocognitive disorders

1. Introduction

Neurocognitive disorders, which was earlier identified as dementia, denotes a range of disorders that affect the brain and cause worsening in one or more cognitive areas. Deterioration in cognition need not only be damage to cognitive abilities, but also visible by others and tested by cognitive assessment. This type of disorder frequently affects older people, however is not part of the standard aging development and has the capability to affect young people as well. Neurocognitive disorders can affect language, memory, attention, social cognition, learning, and perception [1-2]. Today, there are main and trivial neurocognitive disorders that are reliant on how severely the symptoms influence an individual's capability to function self-sufficiently in daily activities such as Alzheimer's, Parkinson's, Creutzfeldt-Jakob disease, Huntington's disease, and Vascular Dementia. Factors inducing various forms of neurocognitive ailments can include endocrine & metabolic ailments, substance abuse, infections, trauma, and nutritional deficiencies [2]. Presently, there is a necessity to recognize how factors such as estrogenic endocrine disruptors contribute to neurocognitive disorder susceptibility.

Estrogen, which belongs to a class of hormones, has been shown to have various functions including the regulation of metabolism and endocrine growth & development [2]. Furthermore, estrogen has been previously demonstrated to affect neurocognitive outcomes [3-8]. Due to this, neurocognitive disorders may be susceptible to estrogenic endocrine disruptors or EEDs. Endocrine

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disruptors modify hormone function or production including anthropogenic chemicals, heavy metals, and phytoestrogens. More particularly, EEDs consist of arsenic, DES, phthalates, bisphenol A (BPA), and polychlorinated biphenyls (PCBs) [9-13]. Studies have reported links between EED exposure and neurocognitive disorders [14-16]. Based on findings that demonstrate that a family of proteins, Inhibitor of Differentiation (ID) has been associated with neurocognitive disorders [16], we will also highlight how EED exposure from the environment may potentiate neurocognitive outcomes via ID proteins. This review is concentrated on connecting EEDs to ID interactions leading to altered outcomes in neurocognitive disorders. More study in these capacities may uncover innovative or additional applicable beneficial modalities and deliver approaches for neurocognitive outcomes with EED exposure.

2. Inhibitor of Differentiation (ID)

2.1 Structure & Function

Inhibitor of Differentiation is a family of proteins that consist of four genes (ID1, ID2, ID3, & ID4). The members of the ID family share an extensive amino acid sequence homology within their HLH (helix-loop-helix) domain (69-78%) [17-18]. It has been reported that ID protein acts as a transcription regulator, which regulate transcription in a dominant-negative manner by dimerizing with basic HLH transcription factors like HEB, E47, and E12 [19-21]. ID proteins are pleiotropic proteins involved in the modulation of biological processes such as cell proliferation & differentiation, cell cycle control, senescence, apoptosis or angiogenesis, and metastasis [22-23]. In case of the central nervous system, ID1 and ID3 are greatly expressed in the premature stages of nervous tissue development, but their levels decline in later stages [24-25]. Although ID1 and ID3 expression cease as tissue matures, ID2 and ID4 expression remain constant throughout the nervous tissue development [26-28]. Therefore, ID proteins play a very important role in nervous tissue biology. Intriguingly, reactivation of ID proteins in adult tissues is held responsible for the involvement of various cancers [29-30]. Researchers have shown the reactive oxygen species (ROS) induced ID protein-mediated cell proliferation and dysregulation of tissue biology in vitro and in vivo conditions [31-33]. Similarly, in another study Das et al have shown the exposure of 17-β estradiol (E2) and estrogenic endocrine disruptors (EED) like polychlorinated biphenyl 153 (PCB153) to vascular endothelial cells (ECs) increase ROS. While ID3 is a redox-sensitive gene, it acts as an important determinant of the ROS-induced proliferation of E2 and ECs exposed to PCB153 [34-36]. Neurodegenerative disorders like Alzheimer's and Parkinson's are the main causes of dementia, and their symptoms worsen slowly over the time. The causes of neurodegenerative diseases apart from genetic mutations are mainly environmental factors, head injuries, depression, and hypertension. Researchers have shown that these causes are strongly interconnected with elevated levels of ROS [31, 37-38]. The increased levels of ROS affect human tissues at a molecular level over time. As age increases, longer exposure to ROS may result in increasing tissue injury and severe disease symptoms. Since ID proteins are shown to be redox sensitive, we predict EEDs exposure boosts ROS-induced ID proteins levels, which may be responsible for the onset of neurocognitive deficiencies.

2.2 ID Proteins and Neurocognitive Disorders

There has been accumulative evidence demonstrating the role of ID proteins in various neurological deficiencies & disorders. One essential pathological hallmark of Alzheimer's disease (AD) is the buildup of senile plaques largely comprised of amyloid beta-peptide (Aβ) in the patients' brains. Hung et al investigated if Aβ may stimulate Sonic hedgehog (SHH) expression and its essential mechanisms. Aβ25-35 induced ID1, which has been exhibited to stabilize HIF-1α. Further, Aβ25-35-mediated induction of HIF-1α and SHH was both suppressed by ID1 siRNA. Taken together, the pathway inhibitor cyclopamine SHH and its antibody reduced Aβ cytotoxicity. Based

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on these lines of evidence, results showed a signaling pathway of Aβ → ID1 → HIF-1 → SHH [39]. Kitajima et al investigated ID2 mRNA-expressing cells in the adult mouse brain. Results showed that ID2 mRNA is identified in more diverse brain areas, including the amygdaloidal complex, globus pallidus, substantia nigra pars reticulata, suprachiasmatic nucleus caudate putamen, and the frontal part of the sub-ventricular zone. These suggest that ID2 may have a function in cognitive and neural activity. Additionally, expression of ID3 (moderate or low) was demonstrated alongside high expression in some specific areas such as the molecular layer of the dentate gyrus. ID4 mRNA was detected in the regions such as the lateral amygdaloidal nucleus. Based on these lines of evidence, the ID2 pattern expression is distinctive from those of partnering ID proteins [40]. Donepezil, is a common medication for Alzheimer's disease. Acetylcholinesterase (AChE) has been demonstrated to play a role in osteoblast function, however the mechanism of AChE on osteoclastogenesis nevertheless remains uncertain. Donepezil reduced receptor activator of nuclear factor-kappa B ligand (RANKL) expression in bone marrow macrophages (BMMs), resulting in the up-regulation of ID2 and inhibition of osteoclast differentiation with down-regulation of c-Fos. These particular results show that inhibition of osteoclast function due to Donepezil prevents bone loss, which may suggest the chance that donepezil reduces fracture risk in patients with Alzheimer's disease [41].

Uncertainties in rhythm circadian-related developments are recurrently established in anxiety and depressed-driven patients. Several genes have been recognized as factors for the progression of mood disorders. It was demonstrated that mild stress-stimulated chronic anhedonic behavior is connected amongst distressed diurnal alternation of the expression of CLOCK, CRY2, PER3 PER1, REV-ERBα, ID2, ROR-β and ROR-γ in the mouse basolateral amygdala [42]. Furthermore, premature life abandonment increases risk for the psychopathological development through both childhood and adulthood, including anxiety disorders and depression. It was recently reported that epigenetic changes in DNA resulted in three genes predicting depression in maltreated children: GRIN1, ID3, & TPPP. Behavioral tests demonstrated that GRIN1, ID3, and TPPP gene expression were established to significantly predict behavioral alterations. These lines of evidence support the role of these genes in the etiology of anxiety and depressive phenotypes succeeding premature life stress [43]. Transcriptome wide association studies have furthermore been used to predict various epigenetic markers of depression. Methylation in 3 genes developed as predictors of depression: ID3, NMDA, GRIN1, and TPPP [44].

Similarly, Becker et al targeted a strategy to uncover foundations of variability in subcortical brain areas. Results demonstrated important improvement of genomic loci that affect the area of the hippocampus, a result that strongly passed the adjusted threshold for testing of multiple brain phenotypes. Investigation of individual single nucleotide polymorphisms (SNPs) also revealed a connection upstream of the ID2 gene with rs7588305. Results show that targeting recognized regulatory regions indicates ways to comprehend the biology that links genotypes to phenotypes. [45]. Previously, Kepa et al identified a network of HLH transcriptional regulators controlled by myelin transcription factor 1-like (MYT1L), as specified in the human brain and neural stem cells. It was demonstrated that MYT1L is essential for neuronal differentiation and identified ID1 as a target. Furthermore, MYT1L prohibited ID1 expression and induced expression of a large quantity of terminal differentiation genes. Consistent expression of MYT1L corresponded with neuronal maturation and linked ID1 and ID3 during the lifecycle. Additionally, genetic polymorphisms that abridged expression of MYT1L in the hippocampus caused enlarged ID1 and ID3 expression, reduced TCF4 & NEUROD6 levels and reduced gene expression involved in cancer, neurodegeneration, long-term potentiation, and synaptic transmission. As a result, these outcomes indicate that MYT1L controls memory-related developments by regulating a neuronal proliferation & differentiation mechanism of ID family proteins [46]. Additionally, six genes displaying at least differential expression among hemispheres (BAIAP2, DAPPER1, LMO4, NEUROD6, ATP2B3, and ID2) in a case-control association study in an initial Spanish sample of ADHD patients and control subjects. Outcomes support the contribution of genomic factors in the stability of ADHD in some of the populations examined and may supply influencing deviant cerebral lateralization in this condition [47].

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Fetal Alcohol Spectrum Disorders, or FASD, signify a variety of antagonistic developmental ailments triggered by prenatal ethanol exposure (PrEE) from parental intake of alcohol. A mouse model of FASD demonstrated stable phenotypes transmitting by the male germline to the unexposed third generation. Global DNA methylation levels, modifications in ectopic intraneocortical connectivity, and up-regulation of neocortical Rzrβ & ID2 was seen. These phenotypes may contribute to sensorimotor, cerebral, and communicative insufficiencies seen in individuals with FASD. Therefore, understanding the conceivable epigenetic mechanisms may uncover innovative targets for beneficial mediation of FASD [48].

2.3 ID Proteins & Estrogenic Endocrine Disruptors

Previously, we demonstrated how ID3 influence obesity and metabolic health in reaction to environmental influences. We also highlighted the understanding of how ID3 may contribute to multifaceted diseases through metabolic perturbations [16, 20]. PCBs are a class of organochlorine compounds that are persistent and have the potential to disrupt the homeostasis of thyroid hormones (THs). In this study, thyroid histology, plasma TH levels, and iodothyronine deiodinase (ID proteins including ID1, ID2, and ID3) gene expression patterns were examined in juvenile Japanese flounder (Paralichthys olivaceus) following exposure to environmentally relevant concentrations of a commercial PCB mixture, Aroclor 1254. Exposure to Aroclor 1254 for 50 days increased follicular cell height, colloid depletion, and hyperplasia. Profiles of the changes in mRNA expression levels of IDs were detected in the liver and kidney, which may be associated with a reduction in plasma THs levels. ID2 mRNA expression in the liver exhibited an increase based on dose-dependence, signifying that this isotype may function as a constant marker for thyroid-disrupting chemical (TDC) exposure. Overall, results suggest that applicable levels of Aroclor 1254 produce noteworthy thyroid disruption [49].

Micro-vascular lesions from endothelial cell dysfunction are formed in various areas of patients with complex chronic diseases such as the lung, brain, retina, and kidney. The mechanisms dependable for starting micro-vascular injury remain weakly distinct, while factors have been suggested, including oxidative stress induced by environmental chemicals. Heightened neovascularization has been associated in the progression or development of proliferative vascular lesions. Previously, support for how ROS via PCBs may contribute to neo-vascular phenotype development with the aim of revealing the function of environmental chemicals in endothelial dysfunction with a concentration on ID3 has been shown. Results demonstrated that PCB-induced ROS intermediated neo-vascular phenotype are additionally depended on ID3 and Pyk2. Additionally, treatment of PCB153 enlarged the dimension of endothelial spheroids with circumstances that function on behalf of stem cell spheroid clonal selection. Elevated ID3 protein expression compared with a larger amount of oxidative DNA damage marker 8-OHdG in blood vessels. The results provide the potential role of ID3 in regulating development of micro-vascular lesions and vascular endothelial cell survival prompted by environmental chemicals such as PCB153 [34-35]. Furthermore, another study determined if in utero exposure to Bisphenol A (BPA) stimulated reproductive tract irregularities in the adult male testis. Adult males including hospathology, anogenital distance, and sex-organ weights were exposure in utero through oral gavage to sesame oil, 50 μg/kg BPA, 1000 μg/kg BPA, or 2 μg/kg diethylstilbestrol (DES) from gestational days 10 to 16 was examined in C57/BI6 mice. Adult mRNA levels of genes connected with differentiation and sexual maturation, GATA4 and ID2, were lower only in testes exposed to DES. At the molecular level, DES exposure via in utero, not BPA, leads to reduced mRNA expression of genes linked with Sertoli cell differentiation [50].

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3. Influence of EED Exposure on Neurocognitive Disorders

Exposure to estrogenic endocrine disruptors has been previously shown in various population and animal studies. Previously Bell et al tested the effects of PCBs on prenatal or juvenile individuals. The effects had differential results on age-dependent and sex behaviors. Females demonstrated different social and anxiety behavior in adolescence, while males exhibited small but significant changes in socio-sexual preferences in adulthood [51]. Exposure to low levels of PCBs is known to lead to anxious behavior in offspring mice, both young and adult. At further advanced life stages, an effect on the mouse brain of neuronal stress induced by the AB peptide was evaluated. Significant impairment in long-duration memory was identified in the mice treated lacatational with non dioxin-like PCBs (NDL-PCBs). Early exposure to low levels of NDL-PCBs stimulates late neuronal susceptibility to amyloid tension [52]. Exposure to PCBs may result in changed procreative behaviors in adulthood. Rat dams (pregnant) were injected on gestational days with PCB mixture Aroclor 1221 at one of two doses. Females were unaffected but males treated with A1221 presented decreased indicators of anxiety [53]. Researchers have also studied sub-chronic embryonic exposure to PCBs concerning anxiety-associated components. Exposure induced behavioral deficiencies at 7 days post-fertilization was detected. Outcomes demonstrated that exposed larvae had enhanced edge preference relative to the control. Furthermore, larvae that were exposed reacted contrarily to a graphical risk comparative to control larvae [54]. Comprehensive gene expression profiles in cerebellar exhibiting the highest suggestive stimulation of anxiety-like behavior has been warranted via male mice. Outcomes demonstrated alterations in the expression of genes in the neurons of the PCB-exposed mice [55]. Furthermore, studies have analyzed the relationship between work-related PCB exposures. Analysis including individuals with their plasma PCBs collected via bio monitoring and the psychological syndromes assessed with a consistent screening method. Results showed greater PCB burdened individuals had greater depression but not anxiety syndrome [56].

Chronic exposure to PCBs has also been demonstrated to cause neurocognitive abnormalities. Repressor element 1-silencing transcription factor (REST) plays an important role in neuronal phenotype expansion in both neural progenitor cells and non-neuronal cells. Chronic exposure to the PCB mixture Aroclor-1254 caused cell death thru the initiation of calpain but not caspase-3. The mixture of PCBs reduced acetylation of the histone proteins H3 and H4. Together, these outcomes indicate that A-1254 employs its toxic influence via REST by down-regulating synapsin-1 and diminishing H3 and H4 acetylation [57]. Alterations in calcium signaling, thyroid hormones, and neurotransmitters have been hypothesized as candidate mechanisms for developmental neurotoxicity in animal models via PCBs. Expression of gene levels in the cerebellum and hippocampus from postnatal days (PNDs) 7 and 14 animals were determined. In the cerebellum, transcripts demonstrated modification at PND7 compared to transcripts at PND14 by Aroclor-1254 exposure, with only one transcript disturbed at both ages. Examination indicates that pathways associated to calcium homeostasis (GNG3, RYR2, TRDN, CACNA1A), intracellular signaling (CAMK2D, STK17B, PACSIN2, RYR2, TRIO, FERT2, PTK2B), axonal guidance (LUM, MXD3, AKAP11, GUCY1B3), aryl hydrocarbon receptor signaling (NFIA, 2COL1A2), involvement in cell proliferation (GSPT2, CDKN1C, PTK2B), and differentiation (LFITM31, HPCA, ZFP260, LGSF4A, HES5) leading to nervous system development were suggestively changed by Aroclor-1254 exposure. Aroclor-1254-induced genomic changes were greater in the hippocampus than the cerebellum. The outcomes indicate that stimulated neurotoxic effects via PCB were due to disturbance of standard ontogenetic design of nervous system growth and development by adjusting signaling pathways [58].

Individuals were exposed to PCBs and polychlorinated dibenzofurans (PCDFs) due to absorption of polluted cooking oil in Taiwan. Neurocognitive performance in individuals exposed to PCDFs and PCBs with that of unexposed was compared. Evaluation of neurocognitive examinations was directed. In exposed men, outcomes were comparable to the reference group; conversely, exposed women had diminished functioning in attention and digit span visual memory span, and verbal memory recalls. The study demonstrated neurocognitive deficits in certain dose-dependent

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aspects of attention, learning ability, and visual memory in women previously exposed to PCBs and PCDFs however, not in exposed men [59]. Samples taken from women and blood samples during birth, pregnancy, from the umbilical cord, and breast milk were tested for PCB congeners and organochlorine pesticides. PCB153 levels in these media were comparatively low in relation to other studies. Measurements of PCBs in samples taken during the second trimester of pregnancy, at birth, and in the umbilical cord were strongly associated. Particular measurements of PCB153 and PCB180 among those subjects with concluded sampling of blood samples from mothers and cord samples were significantly correlated. Maternal blood measurement can reliably estimate the fetal exposure to PCBs during the second trimester. This assessment is consistent for PCB 153 and PCB 180 [60].

Additionally, BPA was examined in urine samples from women in the 1st and 3rd trimester of pregnancy. Psychomotor alongside cognitive growth was measured using psychologist-based scales. BPA exposure concentrations in the highest tectile were associated with a reduction of psychomotor scores at 1 year of age, however no associations with psychomotor outcomes at 4 years were shown. Exposure to BPA was linked with a higher risk of ADHD symptoms at 4 years old. Overall, the results indicate that BPA exposure prenatally does not disturb cognitive growth up to 4 years old. Links are demonstrated with ADHD-correlated signs and psychomotor development at initial ages but do not appear to remain until later ages [61]. Furthermore, hormone-induced alterations in brain composition and role indicate that EED exposure may be connected with sex-specific modifications in behavior. BPA has shown to alter androgen, estrogen, and thyroid hormone signaling pathways. Mothers with measurable prenatal urinary BPA were correlated with relatively higher affecting and expressing depressed behavior, somatic problems, and ODD behaviors in boys. The results indicate higher behavior problems in school aged boys but not girls [62]. Additionally, it has been shown that communicative effects of developmental exposure to a low dose of BPA with detail to the maternal environment, time of exposure, and sex & age. During both testing ages, females whom were exposed presented suggestion of higher anxiety and were less disposed to search a new environment. The results specify that sexually dimorphic behaviors are delicate to endocrine disruption during important developmental periods, specifically during important early neonatal stages [63]. BPA exposure during gestation has been additionally suggested as a risk element of neurobehavioral disorders. Exposure to a regular low-dose of BPA during pregnancy tested offspring of mice. Mice who were exposed had offspring that had increased anxiety-like behavior [64].

4. Interaction of ID proteins & EEDs in neurocognitive disorders

In order to investigate how ID proteins and environmental exposures affect neurocognitive deficiencies at a genetic level, we used various publicly accessible databases to help support our understanding. First we used Comparative Toxicogenomic Database (CTD), a research tool that determines chemical-gene and chemical-disease association, to help decipher gene-environment or gene-EED interactions involved in the production of various neurocognitive deficiencies [65]. To demonstrate an overlapping interaction between neurocognitive disorders, we established a list of neurocognitive-interacting genes (36,367), mood disorder interacting-genes (31,182), and neurodegenerative-interacting genes (30,127). As shown in Figure 1, 26,081 genes are commonly interacting. We also selected interacting genes with estrogenic endocrine disruptors PCB & BPA. We established a gene list for both: PCBs having 7,825 interacting genes and BPA having 20,504 interacting genes. Because ID proteins are our candidate gene group, we also generated a list of overlapping genes between each of the ID proteins (ID1, ID2, ID3, & ID4) and established interacting genes between the two chosen EEDs and neurocognitive disorder categories. We established that 63 genes interact with EEDs, our ID proteins, and neurocognitive disorders as shown in Figure 2 and Table 1 [65]. To demonstrate an interaction between these 63 genes; we furthermore inputted them in

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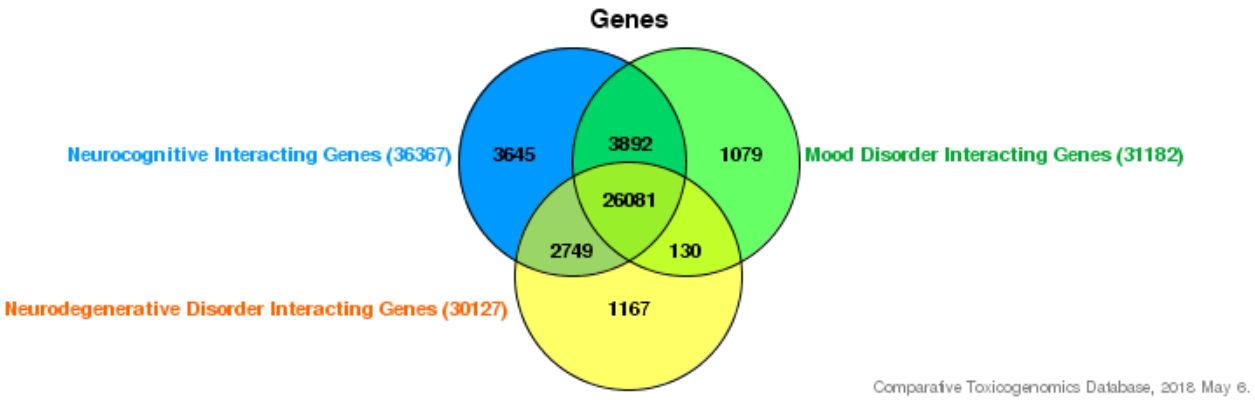

Figure 1. Interacting genes of neurocognitive categories. Shown are 26,081 genes that interact within the three categories.

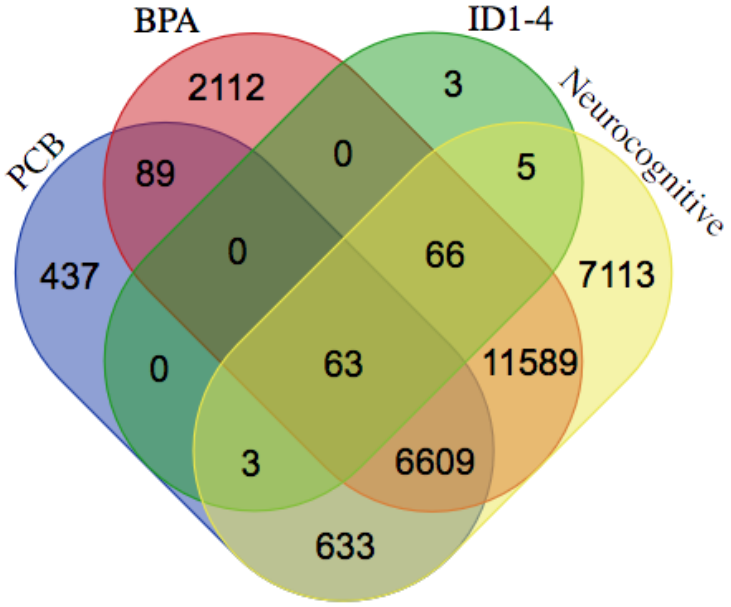

Figure 2. Venn diagram displaying interacting genes between EEDs (PCBs & BPA), ID1-4, and neurocognitive disorders. Results show 63 overlapping genes.

Table 1. Gene symbols & gene names of 63 overlapping EED-ID protein-neurocognitive genes.

Gene Symbol	Gene Name
ATF3	Activating transcription factor 3 (ATF3)
BCAR1	BCAR1, Cas family scaffolding protein (BCAR1)
BUD31	BUD31 homolog (BUD31)
CAV1	caveolin 1 (CAV1)
CDC20	cell division cycle 20 (CDC20)
CDK2	cyclin-dependent kinase 2 (CDK2)
CFDP1	craniofacial development protein 1 (CFDP1)
CLASP2	cytoplasmic linker associated protein 2 (CLASP2)
COL12A1	collagen type XII alpha 1 chain (COL12A1)
COPS7A	COP9 signalosome subunit 7A (COPS7A)

DIDO1	death inducer-obliterator 1 (DIDO1)
DNMT3L	DNA methyltransferase 3 like (DNMT3L)
DYRK1B	dual specificity tyrosine phosphorylation regulated kinase 1B (DYRK1B)
E2F4	E2F transcription factor 4 (E2F4)
ELOC	elongin c (ELOC)
ERP44	endoplasmic reticulum protein 44 (ERP44)
FHL2	four and a half LIM domains 2 (FHL2)
GATA4	GATA binding protein 4 (GATA4)
HSPA1A	heat shock protein family A member 1A (HSPA1A)
HSPA5	heat shock protein family A member 5 (HSPA5)
HSPA8	heat shock protein family A member 8 (HSPA8)
HSPA9	heat shock protein family A member 9 (HSPA9)
ID1	inhibitor of DNA binding 1, HLH protein (ID1)
ID2	inhibitor of DNA binding 2, HLH protein (ID2)
ID3	inhibitor of DNA binding 3, HLH protein (ID3)
ID4	inhibitor of DNA binding 4, HLH protein (ID4)
IKBKG	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma (IKBKG)
KIF20B	kinesin family member 20B (KIF20B)
MACF1	microtubule-actin crosslinking factor 1 (MACF1)
MAPK1	mitogen-activated protein kinase 1 (MAPK1)
MAPK3	mitogen-activated protein kinase 3 (MAPK3)
MAPK8	mitogen-activated protein kinase 8 (MAPK8)
MSC	Musculin (MSC)
MYOG	Myogenin (MYOG)
NEDD9	neural precursor cell expressed, developmentally down-regulated 9 (NEDD9)
NEUROG3	neurogenin 3 (NEUROG3)
NR0B2	nuclear receptor subfamily 0 group B member 2 (NR0B2)
PHF3	PHD finger protein 3 (PHF3)
PIAS1	protein inhibitor of activated STAT 1 (PIAS1)
POT1	protection of telomeres 1 (POT1)
PPP1CA	protein phosphatase 1 catalytic subunit alpha (PPP1CA)
PRMT5	protein arginine methyltransferase 5 (PRMT5)
RBL1	RB transcriptional corepressor like 1 (RBL1)
RBL2	RB transcriptional corepressor like 2 (RBL2)
RBM26	RNA binding motif protein 26 (RBM26)
RCBTB2	RCC1 and BTB domain containing protein 2 (RCBTB2)
RND1	RNA binding motif protein 26(RBM26) Rho family GTPase 1 (RND1)
RUNX1T1	RUNX1 translocation partner 1 (RUNX1T1)
SMURF2	SMAD specific E3 ubiquitin protein ligase 2 (SMURF2)
SREBF1	sterol regulatory element binding transcription factor 1 (SREBF1)
STK38	serine/threonine kinase 38 (STK38)
SYMPK	Symplekin (SYMPK)
TCF12	transcription factor 12 (TCF12)
TCF4	transcription factor 4 (TCF4)
THOC2	THO complex 2(THOC2)
TSTA3	tissue specific transplantation antigen P35B (TSTA3)

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TUBA1B	tubulin alpha 1b (TUBA1B)
TXNL4A	thioredoxin like 4A (TXNL4A)
UNC119	unc-119 Lipid Bind Chaperone (UNC119)
USP1	ubiquitin specific peptidase 1 (USP1)
USP15	ubiquitin specific peptidase 15 (USP15)
WBP11	WW domain binding protein 11 (WBP11)
ZC3H13	zinc finger CCCH-type containing 13 (ZC3H13)

STRING, a recognized database that can provide protein-to-protein interactions. Overall, the interactions contain either indirect (functional) or direct (physical) connections, which stem from interactions gathered from various databases, computational prediction, and from transfer of knowledge between organisms. As seen in Figure 3, STRING provides a network of these common 63 genes and additionally provides connections between all the genes [66-67]. Furthermore, to demonstrate importance of these genes we also used KEGG pathway, a collection of pathways representing knowledge for molecular reaction, interaction, and relation networks. We established that these genes were involved in 71 biological/molecular pathways [68]. The top 5 are represented in Table 2 and it is revealed that these pathways play functionality in neurocognitive disorders [69-74].

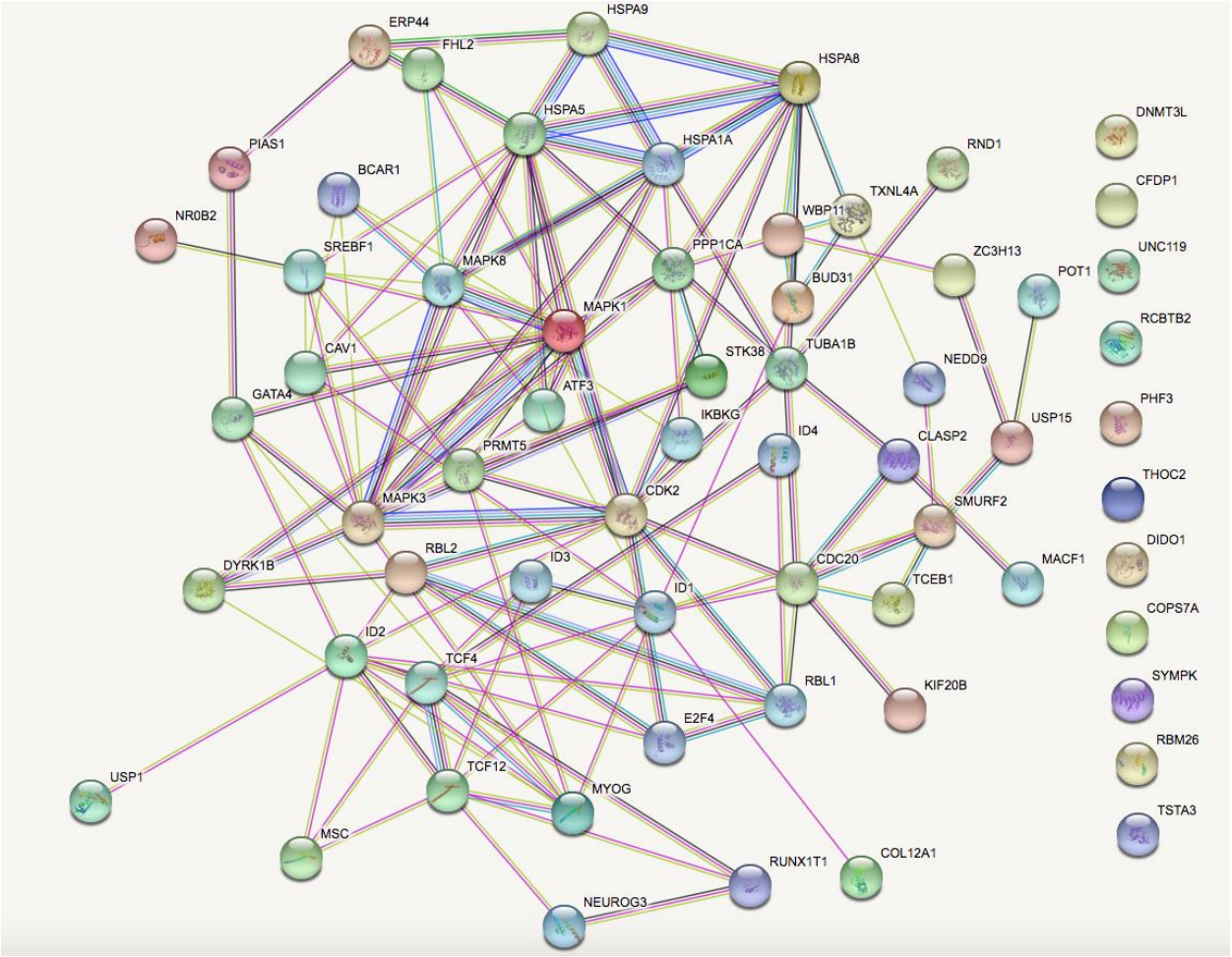

Figure 3. Gene network of 63 common interacting genes between EEDs, ID proteins, & neurocognitive disorders.

Table 2. Top 5 pathways with common 63 interacting genes with EEDs, ID, & neurocognitive disorders.

Pathway Name	Gene Count	Matching Genes in Network (Nodes)
TGF-beta signaling pathway	9	E2F4, ID1, ID2, ID3, ID4, MAPK1, MAPK3, RBL1, SMURF2
Toxoplasmosis	6	HSPA1A, HSPA8, IKBKG, MAPK1, MAPK3, MAPK8
Focal adhesion	6	HSPA1A, HSPA5, MAPK1, MAPK3
Viral carcinogenesis	6	FHL2, IKBKG, MAPK1, MAPK3, MAPK8
MAPK signaling pathway	6	BCAR1, CAV1, MAPK1, MAPK3, MAPK8, PPP1CA

5. Conclusion

ID proteins have been demonstrated to be involved with neurocognitive disorders. Studies have reported links between neurocognitive disorders and exposure to EEDs such as PCBs & BPA. Based on the evidence discussed in this review, we have demonstrated that exposure to EEDs may activate ID proteins to alter molecular mechanisms, additionally changing neurocognitive disorder outcomes. It is important to understand how the influence of EEDs and ID proteins affects neurocognitive perturbations. This essential information will allow research scientists, toxicologists, and public health professionals to discover novel avenues for the prevention and treatment of these types of disorders.

Conflict of Interest: The authors declare no conflict of interest.

References:

[1] Grohol, J. (2017). Symptoms of Major Neurocognitive Disorder. Psych Central. Retrieved on May 9, 2018, from https://psychcentral.com/disorders/symptoms-of-major-neurocognitive-disorder/

[2] Nall, R. (2017, September 22). "What is dementia (neurocognitive disorder)." Medical News Today. Retrieved from https://www.medicalnewstoday.com/articles/314850.php.

[3] Zhang MR, Qu C, Sun J, Wang C, Li HY, Zhang YJ, Zhang BQ, Zou W. Different subtypes of estrogen receptor α and related signal molecules in the hippocampus are associated with spatial cognitive impairment of diabetic mice. Sheng Li Xue Bao. 2017 Jun 25; 69(3): 252-260.

[4] Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. Neurotoxicology. 2017 Jul; 61:143-187. doi: 10.1016/j.neuro.2017.03.006. Epub 2017 Mar 29.

[5] Shafi O. Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review. BMC Neurol. 2016 Nov 22; 16(1): 236.

[6] Nemeth VL, Must A1, Horvath S, Király A, Kincses ZT, Vécsei L. Gender-Specific Degeneration of Dementia-Related Subcortical Structures Throughout the Lifespan. J Alzheimers Dis. 2017; 55(3):865-880.

[7] Chaves AC, Fraga VG, Guimarães HC, Teixeira AL, Barbosa MT, Carvalho MD, Mota AP, Silva IF, Caramelli P, Gomes KB, Alpoim PN. Estrogen receptor-alpha gene XbaI A > G polymorphism influences

short-term cognitive decline in healthy oldest-old individuals. Arq Neuropsiquiatr. 2017 Mar; 75(3):172-175. doi: 10.1590/0004-282X20170018.

[8] Lai YJ, Liu L, Hu XT, He L, Chen GJ. Estrogen Modulates ubc9 Expression and Synaptic Redistribution in the Brain of APP/PS1 Mice and Cortical Neurons. J Mol Neurosci. 2017 Mar;61(3):436-448. doi: 10.1007/s12031-017-0884-2. Epub 2017 Feb 1.

[9] A. Nadal, A. B. Ropero, O. Laribi, M. Maillet, E. Fuentes, and B. Soria, "Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor α and estrogen receptor β," Proceedings of the National Acadamy of Sciences of the United States of America, vol. 97, no. 21, pp. 11603–11608, 2000.

[10] C. S. Watson, N. N. Bulayeva, A. L. Wozniak, and C. C. Finnerty, "Signaling from the membrane via membrane estro- gen receptor-α: Estrogens, xenoestrogens, and phytoestrogens," Steroids, vol. 70, no. 5-7, pp. 364–371, 2005.

[11] P. omas and J. Dong, "Binding and activation of the seven- transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disrup- tion," e Journal of Steroid Biochemistry and Molecular Biology, vol. 102, no. 1–5, pp. 175–179, 2006.

[12] K. S. Korach, P. Sarver, K. Chae, J. A. McLachlan, and J. D. McKinney, "Estrogen receptor-binding activity of polychlo- rinated hydroxybiphenyls: Conformationally restricted struc- tural probes," Molecular Pharmacology, vol. 33, no. 1, pp. 120– 126, 1988.

[13] E. C. Bonefeld-Jorgensen, H. R. Andersen, T. H. Rasmussen, and A. M. Vinggaard, "E ect of highly bioaccumulated poly- chlorinated biphenyl congeners on estrogen and androgen receptor activity," Toxicology, vol. 158, no. 3, pp. 141–153, 2001.

[14] Jiang W, Cao L, Wang F, Ge H, Wu PC, Li XW, Chen GH. Accelerated reduction of serum thyroxine and hippocampal histone acetylation links to exacerbation of spatial memory impairment in aged CD-1 mice pubertally exposed to bisphenol-a. Age (Dordr). 2016 Dec; 38(5-6): 405-418. doi: 10.1007/s11357-016-9947-5. Epub 2016 Sep 9.

[15] Masuo Y, Ishido M. Neurotoxicity of endocrine disruptors: possible involvement in brain development and neurodegeneration. J Toxicol Environ Health B Crit Rev. 2011; 14(5-7):346-69. doi: 10.1080/10937404.2011.578557.

[16] Avecilla V, Doke M, Felty Q. Contribution of Inhibitor of DNA Binding/Differentiation-3 and Endocrine Disrupting Chemicals to Pathophysiological Aspects of Chronic Disease. Biomed Res Int. 2017; 2017:6307109. doi: 10.1155/2017/6307109. Epub 2017 Jul 13.

[17] D. Lyden, A. Z. Young, D. Zagzag et al., "Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts," Nature, vol. 401, no. 6754, pp. 670–677, 1999.

[18] J. Yang, X. Li, and N. W. Morrell, "Id proteins in the vasculature: From molecular biology to cardiopulmonary medicine," Cardiovascular Research, vol. 104, no. 3, pp. 388–398, 2014.

Peer-reviewed version available at *Med. Sci.* **2018**, *6*, 61; doi:10.3390/medsci6030061

[19] Benezra, R., Davis, R. L., Lockshon, D., Turner, D. L., & Weintraub, H. (1990). The protein Id: a negative regulator of helix-loop-helix DNA binding proteins. *Cell*, *61*(1), 49–59. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2156629

[20] Doke, M., Avecilla, V., & Felty, Q. (2018). Inhibitor of Differentiation-3 and Estrogenic Endocrine Disruptors: Implications for Susceptibility to Obesity and Metabolic Disorders. BioMed Research International, 2018, 1–16. https://doi.org/10.1155/2018/6821601

[21] Norton, J. D. (2000). ID helix-loop-helix proteins in cell growth, differentiation and tumorigenesis. J Cell Sci, 113 (Pt 2, 3897–3905. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11058077

[22] Lyden, D., Young, A. Z., Zagzag, D., Yan, W., Gerald, W., O'Reilly, R., … Benezra, R. (1999). Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts. Nature, 401(6754), 670–677. https://doi.org/10.1038/44334

[23] Ruzinova, M. B., & Benezra, R. (2003). Id proteins in development, cell cycle and cancer. Trends in Cell Biology, 13(8), 410–418. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12888293

[24] Ellmeier, W., & Weith, A. (1995). Expression of the helix-loop-helix gene Id3 during murine embryonic development. Developmental Dynamics, 203(2), 163–173. https://doi.org/10.1002/aja.1002030205

[25] Jen, Y., Manova, K., & Benezra, R. (1997). Each member of the Id gene family exhibits a unique expression pattern in mouse gastrulation and neurogenesis. Developmental Dynamics, 208(1), 92–106. https://doi.org/10.1002/(SICI)1097-0177(199701)208:1<92::AID-AJA9>3.0.CO;2-X

[26] Neuman, T., Keen, A., Zuber, M. X., Kristjansson, G. I., Gruss, P., & Nornes, H. O. (1993). Neuronal Expression of Regulatory Helix-Loop-Helix Factor Id2 Gene in Mouse. Developmental Biology, 160(1), 186–195. https://doi.org/10.1006/dbio.1993.1297

[27] Roschger, C., & Cabrele, C. (2017). The Id-protein family in developmental and cancer-associated pathways. Cell Communication and Signaling : CCS, 15(1), 7. https://doi.org/10.1186/s12964-016-0161-y

[28] Tzeng, S. F., & de Vellis, J. (1998). Id1, Id2, and Id3 gene expression in neural cells during development. Glia, 24(4), 372–381. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9814817

[29] Gupta, G. P., Perk, J., Acharyya, S., de Candia, P., Mittal, V., Todorova-Manova, K., … Massague, J. (2007). ID genes mediate tumor reinitiation during breast cancer lung metastasis. Proceedings of the National Academy of Sciences, 104(49), 19506–19511. https://doi.org/10.1073/pnas.0709185104

[30] Sharma, P., Patel, D., & Chaudhary, J. (2012). Id1 and Id3 expression is associated with increasing grade of prostate cancer: Id3 preferentially regulates CDKN1B. Cancer Medicine, 1(2), 187–197. https://doi.org/10.1002/cam4.19

[31] Akeel, S., El-awady, A., Hussein, K., El-Refaey, M., Elsalanty, M., Sharawy, M., & Al-Shabrawey, M. (2012). Recombinant bone morphogenetic protein-2 induces up-regulation of vascular endothelial growth factor and interleukin 6 in human pre-osteoblasts: Role of reactive oxygen species. Archives of Oral Biology, 57(5), 445–452. https://doi.org/10.1016/J.ARCHORALBIO.2011.10.002

[32] Mueller, C., Baudler, S., Welzel, H., Böhm, M., & Nickenig, G. (2002a). Identification of a novel redox-sensitive gene, Id3, which mediates angiotensin II-induced cell growth. Circulation, 105(20), 2423–2428. https://doi.org/10.1161/01.CIR.0000016047.19488.91

[33] NICKENIG, G., BAUDLER, S., MÜLLER, C., WERNER, C., WERNER, N., WELZEL, H., … BÖHM, M. (2002). Redox-sensitive vascular smooth muscle cell proliferation is mediated by GKLF and Id3 in vitro and in vivo. The FASEB Journal, 16(9), 1077–1086. https://doi.org/10.1096/fj.01-0570com

[34] Das, J. K., & Felty, Q. (2014a). Microvascular Lesions by Estrogen-Induced ID3: Its Implications in Cerebral and Cardiorenal Vascular Disease. Journal of Molecular Neuroscience, 618–631. https://doi.org/10.1007/s12031-014-0401-9

[35] Das, J. K., & Felty, Q. (2014b). PCB153-induced overexpression of ID3 contributes to the development of microvascular lesions. PloS One, 9(8), e104159. https://doi.org/10.1371/journal.pone.0104159

[36] Mueller, C., Baudler, S., Welzel, H., Böhm, M., & Nickenig, G. (2002b). Identification of a novel redox-sensitive gene, Id3, which mediates angiotensin II-induced cell growth. Circulation, 105(20), 2423–2428. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12021231

[37] Datla, S. R., & Griendling, K. K. (2010). Reactive oxygen species, NADPH oxidases, and hypertension. Hypertension (Dallas, Tex. : 1979), 56(3), 325–330. https://doi.org/10.1161/HYPERTENSIONAHA.109.142422

[38] Shohami, E., Beit-Yannai, E., Horowitz, M., & Kohen, R. (1997). Oxidative Stress in Closed-Head Injury: Brain Antioxidant Capacity as an Indicator of Functional Outcome. Journal of Cerebral Blood Flow & Metabolism, 17(10), 1007–1019. https://doi.org/10.1097/00004647-199710000-00002.

[39] Hung YH, Chang SH, Huang CT, Yin JH, Hwang CS, Yang LY, Yang DI. Inhibitor of Differentiation-1 and Hypoxia-Inducible Factor-1 Mediate Sonic Hedgehog Induction by Amyloid Beta-Peptide in Rat Cortical Neurons. Mol Neurobiol. 2016 Mar; 53(2): 793-809. doi: 10.1007/s12035-014-9046-5.

[40] Kitajima K, Takahashi R, Yokota Y. Localization of Id2 mRNA in the adult mouse brain. Brain Res. 2006 Feb 16;1073-1074:93-102. Epub 2006 Jan 27.

[41] Sato T, Enoki Y, Sakamoto Y, Yokota K, Okubo M, Matsumoto M, Hayashi N, Usui M, Kokabu S, Mimura T, Nakazato Y, Araki N, Fukuda T, Okazaki Y, Suda T, Takeda S, Yoda T. Donepezil prevents RANK-induced bone loss via inhibition of osteoclast differentiation by downregulating acetylcholinesterase. Heliyon. 2015 Sep 21; 1(1):e00013. doi: 10.1016/j.heliyon.2015.e00013. eCollection 2015 Sep.

[42] Savalli, Diao W, Schulz S, Todtova K, Pollak DD. Diurnal oscillation of amygdala clock gene expression and loss of synchrony in a mouse model of depression. Int J Neuropsychopharmacol. 2014 Dec 11; 18(5). pii: pyu095. doi: 10.1093/ijnp/pyu095.

[43] Montalvo-Ortiz JL, Bordner KA, Carlyle BC, Gelernter J, Simen AA, Kaufman J. The role of genes involved in stress, neural plasticity, and brain circuitry in depressive phenotypes: Convergent findings in a mouse model of neglect. Behav Brain Res. 2016 Dec 15; 315:71-4. doi: 10.1016/j.bbr.2016.08.010. Epub 2016 Aug 6.

[44] Weder N, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, Lipschitz D, Douglas-Palumberi H, Ge M, Perepletchikova F, O'Loughlin K, Hudziak JJ, Gelernter J, Kaufman J. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. J Am Acad Child Adolesc Psychiatry. 2014 Apr; 53(4):417-24.e5. doi: 10.1016/j.jaac.2013.12.025. Epub 2014 Jan 27.

[45] Becker M, Guadalupe T, Franke B, Hibar DP, Renteria ME6, Stein JL5,7, Thompson PM5, Francks C1,2, Vernes SC1,2, Fisher SE1,2. Early developmental gene enhancers affect subcortical volumes in the adult human brain. Hum Brain Mapp. 2016 May;37(5):1788-800. doi: 10.1002/hbm.23136. Epub 2016 Feb 18.

[46] Kepa A, Martinez Medina L, Erk S, Srivastava DP, Fernandes A, Toro R, Lévi S, Ruggeri B, Fernandes C, Degenhardt F10, Witt SH11, Meyer-Lindenberg A, Poncer JC, Martinot JL, Paillère Martinot ML, Müller CP, Heinz A, Walter H, Schumann G, Desrivières S. Associations of the Intellectual Disability Gene MYT1L with Helix-Loop-Helix Gene Expression, Hippocampus Volume and Hippocampus Activation During Memory Retrieval. Neuropsychopharmacology. 2017 Dec;42(13):2516-2526. doi: 10.1038/npp.2017.91. Epub 2017 May 4.

[47] Ribasés M, Bosch R, Hervás A, Ramos-Quiroga JA, Sánchez-Mora C, Bielsa A, Gastaminza X, Guijarro-Domingo S, Nogueira M, Gómez-Barros N, Kreiker S, Gross-Lesch S, Jacob CP, Lesch KP, Reif A, Johansson S, Plessen KJ, Knappskog PM, Haavik J, Estivill X, Casas M, Bayés M, Cormand B. Case-control study of six genes asymmetrically expressed in the two cerebral hemispheres: association of BAIAP2 with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2009 Nov 15;66(10):926-34. doi: 10.1016/j.biopsych.2009.06.024. Epub 2009 Sep 5.

[48] Abbott CW, Rohac DJ, Bottom RT, Patadia S, Huffman KJ. Prenatal Ethanol Exposure and Neocortical Development: A Transgenerational Model of FASD. Cereb Cortex. 2017 Jul 6:1-14. doi: 10.1093/cercor/bhx168. [Epub ahead of print]

[49] Dong Y, Tian H, Wang W, Zhang X, Liu J , Ru S. Disruption of the thyroid system by the thyroid-disrupting compound Aroclor 1254 in juvenile Japanese flounder (Paralichthys olivaceus). PLoS One. 2014 Aug 4; 9(8):e104196. doi: 10.1371/journal.pone.0104196. eCollection 2014.

[50] LaRocca J, Boyajian A, Brown C, Smith SD, Hixon M. Effects of in utero exposure to Bisphenol A or diethylstilbestrol on the adult male reproductive system. Birth Defects Res B Dev Reprod Toxicol. 2011 Dec; 92(6):526-33. doi: 10.1002/bdrb.20336. Epub 2011 Sep 15.

[51] Bell, M.R., Thompson, L.M., Rodriguez, K., & Gore, A.C. (2016). Two-hit exposure to polychlorinated biphenyls at gestational and juvenile life stages: 1. Sexually dimorphic effects on social and anxiety-like behaviors. Hormones and Behaviors, 78, 168-177.

[52] Elnar, A.A., Allouche, A.A., Desor, F., Yen, F.T., Soulimani, R., & Oster, T. (2016). Lactational exposure of mice to low levels of non-dioxin-like polychlorinated biphenyls increases susceptibility to neuronal stress at a mature age. NeuroToxicology, 53, 314-320.

[53] Gillette, R., Reilly, M.P., Topper, V.Y., Thompson, L.M., Crews, D., & Gore, A.C. (2017). Anxiety-like behaviors in adulthood are altered in male but not female rats exposed to low dosages of polychlorinated biphenyls in utero. Hormones and Behaviors, 87, 8-15.

[54] Gonzalez, S.T., Remick, D., Creton, R., & Colwill, R.M. (2016). Effects of embryonic exposure to polychlorinated biphenyls (PCBs) on anxiety-related behavior in larval zebrafish. NeuroToxicology, 53, 93-101.

[55] Elnar, A.A., Desor, F., Marin, F., Soulimani, R., & Nemos, C. (2015). Lactational exposure to low levels of the six indicator non-dioxin-like polychlorinated biphenyls induces DNA damage and repression of neuronal activity in juvenile male mice. Toxicology, 328, 57-65.

[56] Guam, P.M., Esser, A., Schettgen, T., Gube, M., Kraus, T., & Lang, J. (2014). Prevalence and iincidence rates of mental syndromes after occupational exposure to polychlorinated biphenyls. International Journal of Hygiene and Environmental Health, 217, 765-774.

[57] Formisano L, Guida N, Cocco S, Secondo A, Sirabella R, Ulianich L, Paturzo F, Di Renzo G, Canzoniero LM. The repressor element 1-silencing transcription factor is a novel molecular target for the neurotoxic effect of the polychlorinated biphenyl mixture aroclor 1254 in neuroblastoma SH-SY5Y cells. J Pharmacol Exp Ther. 2011 Sep; 338(3): 997-1003. doi: 10.1124/jpet.111.181289. Epub 2011 Jun 21.

[58] Royland JE, Wu J, Zawia NH, Kodavanti PR. Gene expression profiles in the cerebellum and hippocampus following exposure to a neurotoxicant, Aroclor 1254: developmental effects. Toxicol Appl Pharmacol. 2008 Sep 1;231(2):165-78. doi: 10.1016/j.taap.2008.04.022. Epub 2008 May 6.

[59] Lin KC, Guo NW, Tsai PC, Yang CY, Guo YL. Neurocognitive changes among elderly exposed to PCBs/PCDFs in Taiwan. Environ Health Perspect. 2008 Feb; 116(2): 184-9. doi: 10.1289/ehp.10134.

[60] Jarrell J, Chan S, Hauser R, Hu H. Longitudinal assessment of PCBs and chlorinated pesticides in pregnant women from Western Canada. Environ Health. 2005 Jun 1; 4:10.

[61] Rubio, S., Julvez, J., Sunyer, J., & Vrijheid, M. (2015). Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. Environmental Research, 142, 671-679.

[62] Evans, S.F., Kobrosly, R.W., Barrett, E.S., Thurston, S.W., Calafat, A.M., Weiss, B., Stahlhut, R., Yolton, K., Swan, S.H. (2014). Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. NeuroToxicology, 45, 91-99.

[63] Gioiosa, L., Parmigiani, S., vom Saal, F.S., & Palanza, P. (2013). The effects of bisphenol A on emotional behavior depend upon the timing of exposure, age and gender in mice. Hormones and Behavior, 63, 598-605.

[64] Harris, E.P., Allardice, H.A., Schenk, A.K., & Rissman, E.F. (2017). Effects of maternal or paternal bisphenol A exposure on offspring behavior. Horm Behav. 2017 Oct 4. pii: S0018-506X(17)30246-5. doi: 10.1016/j.yhbeh.2017.09.017.

[65] Davis AP, Grondin CJ, Johnson RJ, Sciaky D, King BL, McMorran R, Wiegers J, Wiegers TC, Mattingly CJ. The Comparative Toxicogenomics Database: update 2017. Nucleic Acids Res. 2016 Sep 19; [Epub ahead of print]

[66] Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M, Santos A, Doncheva NT, Roth A, Bork P, Jensen LJ, von Mering C. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res. 2017 Jan; 45:D362-68

[67] Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, Kuhn M, Bork P, Jensen LJ, von Mering C. STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res. 2015 Jan; 43:D447-52

[68] Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 2000 Jan 1; 28(1): 27-30.

[69] Ene L, Marcotte TD, Umlauf A, Grancea C, Temereanca A, Bharti A, Achim CL, Letendre S, Ruta SM. Latent toxoplasmosis is associated with neurocognitive impairment in young adults with and without chronic HIV infection. J Neuroimmunol. 2016 Oct 15;299:1-7. doi: 10.1016/j.jneuroim.2016.08.003. Epub 2016 Aug 4.

[70] Yan H, Chen Y, Li L, Jiang J, Wu G, Zuo Y, Zhang JH, Feng H, Yan X, Liu F. Decorin alleviated chronic hydrocephalus via inhibiting TGF-β1/Smad/CTGF pathway after subarachnoid hemorrhage in rats. Brain Res. 2016 Jan 1;1630:241-53. doi: 10.1016/j.brainres.2015.11.004. Epub 2015 Nov 10.

[71] Gonzalez, S.T., Remick, D., Creton, R., & Colwill, R.M. (2016). Effects of embryonic exposure to polychlorinated biphenyls (PCBs) on anxiety-related behavior in larval zebrafish. NeuroToxicology, 53, 93-101.

[72] Sampey GC, Saifuddin M, Schwab A, Barclay R, Punya S, Chung MC, Hakami RM1, Zadeh MA, Lepene B, Klase ZA, El-Hage N, Young M, Iordanskiy S, Kashanchi F. Exosomes from HIV-1-infected Cells Stimulate Production of Pro-inflammatory Cytokines through Trans-activating Response (TAR) RNA. J Biol Chem. 2016 Jan 15;291(3):1251-66. doi: 10.1074/jbc.M115.662171. Epub 2015 Nov 9.

[73] Ma C, Cheng F, Wang X, Zhai C, Yue W, Lian Y, Wang Q. Erythropoietin Pathway: A Potential Target for the Treatment of Depression. nt J Mol Sci. 2016 May 6;17(5). pii: E677. doi: 10.3390/ijms17050677.

[74] Vithayathil J, Pucilowska J, Goodnough LH, Atit RP, Landreth GE. Dentate Gyrus Development Requires ERK Activity to Maintain Progenitor Population and MAPK Pathway Feedback Regulation. J Neurosci. 2015 Apr 29;35(17):6836-48. doi: 10.1523/JNEUROSCI.4196-14.2015