Electronic Supplementary Material (ESI) for Metallomics.

Supplementary Material

Table S1: Detailed overview of alterations in biometals across neurological disorders (*conflicting data). PIXE: Particle Induced X-ray Emission; XFM: X-ray Fluorescence microprobe imaging; XRF: X-Ray Fluorescence Spectroscopy; WB: Western Blot; ICP: Inductively Coupled Plasma Mass Spectrometry; INAA: Instrumental Neutron Activation Analysis; ELISA: Enzyme Linked Immunosorbent Assay; AAS: Atomic Absorption Spectroscopy; eCp: Enzymatic Oxidase Assay; GFAAS: Graphite Furnace Atomic Absorption Spectroscopy; MRM: Magnetic resonance microscopy; EPR: Electron paramagnetic resonance spectroscopy (= electron spin resonance (ESR)); ESI-MS: Electrospray Ionisation Mass Spectrometry; MRE: Magnetic resonance elastography; EDX: Energy Dispersive X-ray spectroscopy.

Disease	Biometals	Tissue tested	Method	Background	Publication
Alzheimer's Disease	Cu, Zn, Fe, Mn ↑	Senile plaques, neuropil	Micro-PIXE, XRF microprobe, XFM, WB, colorimetric, magnetometry	Association of Cu, Fe and Zn with senile plaques	1–7
	Zn ↑	CSF	ICP, INAA, ELISA		8,9
	Hg ↑	Brain		High affinity of Hg to selenoproteins leads to displacement of Se	10–13
	Cu, Zn ↓ Al ↑	Serum, plasma	ICP, AAS, eCp	Plaque sequestration of Cu and Zn may result in Cu and Zn deficiency.	14–18
Autism Spectrum Disorders	Ca, Fe, Mg, Mn, Se, Zn ↓ Al, As, Cd, Cu, Hg, Pb ↑	Hair, nails	ICP, AAS	Zn deficiency especially in young age may contribute to ASD severity. Correlation with Phenotype for Pb, Hg, Mg and Se observed.	19
	Cu/Zn ↑	Serum	Not specified		20
	Al, Cd, Pb ↑	Urine			21
Phelan McDermid Syndrome	Zn ↓	Blood	AAS	Zn deficiency associated with increased incidence of seizures.	22
Epilepsy	Zn, Cr ↓ Cu ↑	Serum		No changes in brain metal ions after seizure induction in rodent model hints that metal ion dysregulation might be causal.	23
ADHD	Zn ↓	Blood, nutrient intake	colorimetric, ELISA	Zn deficiency might contribute to ADHD etiology by Zn mediated regulation of the dopamine transporter.	24–26
	Fe (ferritin) ↑	Serum	GFAAS	Fe deficiency might contribute to ADHD by its impact on dopamine and catecholamines.	27
	Mn ↑	Hair	GFAAS	Accumulation in dopaminergic neurons via the presynaptic dopamine transporter	28
	Pb ↑	Blood	ICP		29–33
Mood Disorders	Zn ↓	Serum	AAS	Zn levels inversely correlated with severity of symptoms.	34–37
	Ca, Fe, Se ↓ Pb ↑	Blood	AAS, colorimetric		38,39
Schizophrenia	Zn ↓	Brain			40
	Ca, Zn ↓ Cu, Cd ↑	Hair	AAS		41
Parkinson's Disease	Ag, Cd, Co, Fe, Se ↓ Al, Ca, Cu, Cr, Hg, Mg, Mn, Pb ↑	Serum	ICP		42
	Cu ↓	Serum	AAS		43
	Fe ↑	Brains	WB, MRM	Increase in Fe and decrease in free Fe sequestering Neuromelamin might mediate neuronal toxicity and free Fe might contribute to αS aggregation.	44
Amyotrophic Lateral Sclerosis	Pb* ↑	CSF, plasma, spinal ventral horn tissue	AAS, NAA	Seems to result as a consequence of disease progression instead of being causal.	45–49
	Hg* ↑	Blood, urine	AAS, NAA	Partially conflicting reports complicate the analysis of metal ion homeostasis in ALS	50,51
	Se* ↑	Diet	-	Partially conflicting reports complicate the analysis of metal ion homeostasis in ALS	52–54
	Fe, Mn ↑	CSF	EPR, ICP, ELISA, AAS, colorimetric, immunonephelometry		55,56

	Fe (L-ferritin)	Plasma	EPR, ICP, ELISA	Correlation of L-ferritin level increase with survival time of patients	[57,49,58]
Huntington's Disease	Fe, Mn ↑	Brain	AAS		[59]
Prion Diseases	Mn ↑ Cu ↓	Blood, brain, frontal cortex and liver Frontal cortex tissue	ICP		[60,61]
Gaucher	Fe ↑	Liver, serum	MRE, colorimetric		[62,63]
Wilson's Disease	Cu ↑	Systemic	EDX		[55,55]
Menke's Disease	Cu ↓	Systemic			[64]
Friedreich's ataxia	Fe ↑	Brain, Myocard	XRF		[55,64]
	Zn ↓	Hair	AAS		[65]
Spinocere-bellar ataxia type 2	Zn ↓	CSF	AAS		[66]

Table S2: Identification of common motifs of alterations in biometals across neurological disorders. (AD: Alzheimer's Disease; ASD: Autism Spectrum Disorder; ALS: Amyotrophic Lateral Sclerosis; MD: Mood Disorders; HD: Huntington's Disease; E: Epilepsy; PD: Parkinson's Disease; SCZ: Schizophrenia). AD is shown in a separate table given the more complex alterations of trace metals depending on the regional distribution of metals and senile plaques within the brain, which creates rather local than systemic changes.

Metal A	Metal B	Diseases
Zn ↓	Cu ↑	ASD (hair, nails), D (hair, serum), E (hair, serum),
	Cu ↔	ADHD (serum, plasma, hair)
Zn ↑	Cu ↔	PD (hair)
Zn ↓	Fe ↑	E (hair)
	Fe ↓	ASD (hair, nails), D (serum, blood)
Zn ↑	Fe ↓	PD (hair)
Zn ↓	Se ↓	ASD (hair, nails), MD (serum, blood)
Zn ↑	Se ↔	PD (hair)
Zn ↓	Mn ↑	ADHD (serum, plasma, hair)
	Mn ↓	ASD (hair, nails)
Zn ↓	Pb ↑	ASD (hair, nails), ADHD (serum, blood), MD (serum,
Zn ↓	Hg ↑	ASD (hair, nails), ADHD (serum, plasma)
Cu ↑	Zn ↓	ASD (hair, nails, serum), D (hair, serum), E (serum,
Cu ↓	Fe ↑	PD (hair)
Cu ↑	Fe ↑	E (hair)
	Fe ↓	ASD (hair, nails), PD (serum)
Cu ↓	Se ↓	PD (serum)
Cu ↑	Se ↓	ASD (hair, nails)
Cu ↓	Mn ↑	PD (serum) Prion Disease (blood, brain, frontal cortex
Cu ↑	Mn ↓	ASD (hair, nails)
Cu ↑	Pb ↑	ASD (hair, nails), PD (serum)
Cu ↑	Hg ↑	ASD (hair, nails), PD (serum)
Fe ↓	Zn ↑	PD (hair)
	Zn ↓	ASD (hair, nails), D (serum, blood)
Fe ↑	Zn ↓	E (hair)
Fe ↓	Cu ↑	ASD (hair, nails), PD (serum)
	Cu ↔	ADHD (serum, plasma)
	Cu ↓	PD (hair)
Fe ↑	Cu ↑	E (hair)
Fe ↓	Se ↓	ASD (hair,nails), MD (blood), PD (serum)
Fe ↓	Mn ↑	PD (serum)
	Mn ↓	ASD (hair, nails)
Fe ↑	Mn ↑	ALS (CSF), HD (brain), ADHD (plasma)
Fe ↓	Pb ↑	ASD (hair, nails), MD (blood), PD (serum)
Fe ↑	Pb ↑	ADHD (serum, blood), ALS (plasma)
Fe ↓	Hg ↑	ASD (hair, nails), PD (serum)
Fe ↑	Hg ↑	ALS (plasma, blood)
Se ↓	Zn ↓	ASD (hair, nails), MD (serum, blood)
Se ↓	Cu ↑	ASD (hair, nails)
	Cu ↓	PD (serum)
Se ↓	Fe ↓	ASD (hair,nails), MD (blood), PD (serum)
Se ↓	Mn ↑	PD (serum)
	Mn ↓	ASD (hair, nails)
Se ↓	Pb ↑	ASD (hair, nails), MD (blood), PD (serum)
Se ↓	Hg ↑	ASD (hair, nails), PD (serum)
Mn ↓	Zn ↓	ASD (hair, nails)
Mn ↑	Zn ↓	ADHD (serum, plasma, hair)
Mn ↓	Cu ↑	ASD (hair, nails)
Mn ↑	Cu ↓	PD (serum) Prion Disease (blood, brain, frontal cortex
Mn ↓	Fe ↓	ASD (hair, nails)
Mn ↑	Fe ↑	ALS (CSF), HD (brain), ADHD (plasma)
	Fe ↓	PD (serum)
Mn ↓	Se ↓	ASD (hair, nails)
Mn ↑	Se ↓	PD (serum)
Mn ↓	Pb ↑	ASD (hair, nails)
Mn ↑	Pb ↑	PD (serum), ALS (CSF), ADHD (serum, plasma)
Mn ↓	Hg ↑	ASD (hair, nails)
Mn ↑	Hg ↑	PD (serum)
Hg ↑	Zn ↓	ASD (hair, nails), ADHD (serum, plasma)
Hg ↑	Cu ↑	ASD (hair, nails), PD (serum)
Hg ↑	Fe ↑	ALS (plasma, blood)
	Fe ↓	ASD (hair, nails), PD (serum)
Hg ↑	Se ↓	ASD (hair, nails), PD (serum)
Hg ↑	Pb ↑	ASD (hair, nails), PD (serum), ALS (plasma, blood)
Hg ↑	Mn ↑	PD (serum)
	Mn ↓	ASD (hair, nails)
Pb ↑	Zn ↓	ASD (hair, nails), ADHD (serum, blood), MD (serum,
Pb ↑	Cu ↑	ASD (hair, nails), PD (serum)
Pb ↓	Fe ↑	ADHD (serum, blood), ALS (plasma)
Pb ↑	Fe ↓	ASD (hair, nails), MD (blood), PD (serum)
Pb ↑	Se ↓	ASD (hair, nails), MD (blood), PD (serum)
Pb ↑	Hg ↑	ASD (hair, nails), PD (serum), ALS (plasma, blood)
Pb ↑	Mn ↑	PD (serum), ALS (CSF), ADHD (serum, plasma)
	Mn ↓	ASD (hair, nails)

Metal A	Metal B	Alzheimer's disease (AD)
Zn ↓	Cu ↓	AD (serum)
Zn ↑	Cu ↑	AD (senile plaques, neuropil, substantia nigra)
Zn ↑	Fe ↑	AD (senile plaques, neuropil, substantia nigra)
Zn ↑	Mn ↑	AD (senile plaques, neuropil, substantia nigra)
Cu ↓	Zn ↓	AD (serum)
Cu ↑	Zn ↑	AD (senile plaques, neuropil, substantia nigra)
Cu ↑	Fe ↑	AD (senile plaques, neuropil, substantia nigra)
Cu ↑	Mn ↑	AD (senile plaques, neuropil, substantia nigra)
Fe ↑	Zn ↑	AD (senile plaques, neuropil, substantia nigra)
Fe ↑	Cu ↑	AD (senile plaques, neuropil, substantia nigra)
Fe ↑	Mn ↑	AD (senile plaques, neuropil, substantia nigra)
Mn ↑	Zn ↑	AD (senile plaques, neuropil, substantia nigra)
Mn ↑	Cu ↑	AD (senile plaques, neuropil, substantia nigra)
Mn ↑	Fe ↑	AD (senile plaques, neuropil, substantia nigra)

Table S3: Identification of alterations in the behavioural phenotypes of rodent models for trace metal deficiency or overload.

Metal	Over-load	Defi-ciency	Timepoint	Behavior	General health/Other	Publication
Al	•		adult	spatial memroy deficits in Morris water maze	nerve degeneration	67
Al	•		adult	reduced locomotor activity, hypoactivity	dose dependent increase in localized fur loss	68
Al	•		adult, prenatal	adult & prenatal: reduced locomotor activity; prenatal: more time in light box (light/dark box test)		69
Al	•		perinatal	reduced locomotor activity, learning capability, and cognitive behavior	dose-dependent growth retardation in offspring; delays in opening of eyes, appearance of body hair fuzz; deficits in sensory motor reflexes of the pups	70
Al	•		perinatal	at weaning, forelimb grasp strength influenced by Al exposure; negative geotaxis was influenced by lactation exposure; hindlimb grasp and temperature sensitivity were influenced by both gestation and lactation exposure	growth retardation in offspring	71
Al	•		prenatal	reduction in the rate of ultrasonic volcaization by pups; shift in the timing of peak calling; no change in pup retrieval test	growth retardation in offspring	72
Al	•		prenatal	reduced maternal behavior, no chnage in pup retrieval	reduced birth weight	73
Hg	•		adult	reduced activity in open field, changes in locomotor behavior (footprint analysis and vertical pole test)		74
Hg	•		adult	reduced motor coordination and balabce in Rotarod, foorptint analysis and vertical pole test; reduced activity in open filed test;		75
Hg	•		prenatal	adults show deficits in motor abilities, coordination, and overall activity, as measured by rotarod, footprint analysis and open field; impaired reference memory in Morris water maze		76
Hg	•	**Se •**	prenatal	reduced activity of the mice (open filed test) in presence of Se deficiency		77
Hg	•		prenatal	differences in a 2-way active avoidance shuttle box and in a punishment situation; no alterations in an open field test, a water escape runaway and a conditioned suppression paradigm	pups display decreased weight after birth and through weaning	78
Hg	•		prenatal & perinatal	open field tests of the offspring showed an increase and decrease in voluntary activity in male and female mice, respectively; Morris water maze tests showed a delay in the latency to reach the platform in males		79
Hg	•		prenatal & perinatal	significant decrease in activity (open filed test), no change in ultrasonic vocalizations,	a total of 131 genes were differentially-regulated in pup brains	80
Hg	•		prenatal & perinatal	decreased exploratory activity in male mice, especially at young age; disturbances in reference memory in male mice. Predisposition to depressive-like behavior in male offspring (forced swimming test), no motor coordination deficits	no behavioral changes in female mice	81
Hg	•		prenatal & perinatal	less locomotion when the open field was new; impaired working memory in females in a modified T maze; no motor coordination deficits		82
Pb	•		adult	increased aggression	age dependent effects	83
Pb	•	**Fe •**	adult	iron-deficient mice treated with lead had more and longer seizures than controls treated with lead. Mice not exposed to lead did not seize. Changes in activity in the open field as a function of exposure to lead.	lower rates of body-weight gain over the 3-months treatment period and lower hemoglobin values	84

Pb	•		adult	no change in locomotor behavior, reduced social behavior, increased anxiety (plus maze)	elevated corticosterone blood levels affecting the level of stress responsivity of the offspring	85
Pb	•		perinatal	hyperactivity	impaired motor behavior, peripheral ataxia in the hind limb and spryed gait	86
Pb	•		perinatal	social and sexual investigation behavior is significantly lower in both sexes;	no effect on body weight	87
Pb	•		perinatal & adult	altered jumping behavior in the open field		88
Pb	•		prenatal	early exposure may contribute to distubances both in circadian rhythmicity, and general reactivity to environmental changes		89
Pb	•		prenatal & perinatal	reduction in the duration of social interaction (juvenile and adult mice)		90
Pb	•		prenatal & perinatal	male-specific decreased spontaneous motor activity, increased amphetamine-induced motor activity, and decreased rotarod performance in one year old mice	year-old male but not female mice exhibited late-onset obesity	91
Pb	•		prenatal & perinatal	significant alterations in exploratory behavior and water maze performance; rotarod performance was not affected; males displayed violent behavior towards their cage mates, but not to a stranger in the resident-intruder assay.	gene expression data pointed to evidence of neuroinflammation in the brain of both female and male mice	92
Pb	•		prenatal & perinatal & adult	increased aggression	age dependent effects in hyperactivity test	93
Mg		•	adult	enhanced anxiety-related behavior in a battery of established anxiety tests	Mg deficiency caused an enhanced set-point of the HPA axis	94
Mg		•	adult	enhanced depression-like behavior sensitive to chronic antidepressant treatment.		95
Mg		•	adult	increased anxiety- and depression-like behavior		96
Mg		•	adult	increased immobility time in the forced swim test, indicating enhanced depression-like behavior. Partial Mg-depletion increased anxiety-related behavior in the light/dark and open field test, while locomotor activity or motor coordination was not influenced.		97
Mg	•	□	adult	intraperitoneally (i.p) injection of $MgCl_2$ has antinociceptive effects (hot plate, tail flick)	Cu and Zn similarly induced antinociceptive effects, only Mg and Cu showed effects in an activity cage test for spontaneous behavior	98
Mg		•	adult (males only)	reduced conditional freezing behavior, reduced CLS (conditioned lick suppression). Spatial learning was normal		99
Mg		•	adult (males only)	impairments in contextual and cued fear conditioning. No changes in locomotor activity, exploration, or pain sensitivity.		100
Mg		•	adult (rat)	hyperaggressiveness increased with magnesium deficiency severity.		101
Mg		•	adult (rat)	a severe magnesium deprivation induces an interspecific aggressive behavior (muricidal behavior, MB) in different strains of rats.		102
Mg	•	□	adult postpartum depression induced mice	improves depressive symptoms and anxiety-like behaviors: significantly decreased immobility time in forced swim test, increased the percentage of both time spent in- and entries to open arms in the elevated plus-maze	administration of Mg, Zn and Vit B1	103
Se	•	□	adult	facilitation of formation of long-term object recognition memory	systemic administration of Diphenyl diselenide	104

Se		•	prenatal & perinatal	less locomotor activity (open field), more defecation, and less entry to the center square areas. Morris water maze: significant impairment during the initial phase of the trials (females only)		105
Fe	•		adult	initial hypoactivity followed by a later hyperactivity		106
Fe	□	•	adult	increases in wake time in the 4-h period prior to lights-on; both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep were reduced	Fe deficient mice may provide a potentially useful animal model for Restless Legs Syndrome	107
Fe	•		juvenile & adult	In the radial arm maze, the Days 10-12 treatment group evidenced significantly both more errors in arm choices and longer latencies to acquire all eight pellets; these mice showed also a severe trial-to-trial retention deficit as indexed by retention quotients.	behavioral deficits were observed also in animals treated with Fe during postnatal Days 3-5, but the effects were less pronounced, indicating the higher susceptibility of the brain for Fe-induced damage during Days 10-12 postpartum.	108
Fe	•	□	juvenile & adult	hypokinesia for locomotion, rearing and total activity during the first two 20-min periods in the activity test chambers but were more active during the final 20 min. More errors and longer latencies on the final three radial arm maze trials.		109
Fe	•	□	juvenile & adult	marked deficits in radial arm maze learning and retention performance		110
Fe		•	prenatal	significantly higher number of reference memory errors		111
Fe		•	prenatal & adult	reduction in grip strength	persistently lowered body weights	112
Fe		•	prenatal & adult	reduction in grip strength		113
Zn		•	adult	aggressive behavior (resident intruder)		114
Zn		•	adult	zinc deficiency induces depression and anxiety-like behavior		115
Zn	•		adult	zinc deficiency, but not zinc overload was observed in hippocampus, especially in the mossy fiber-CA3 pyramid synapse.	significant reduction in GPR39 and BDNF protein expression in the frontal cortex. Decreased expression levels of NR2A, NR2B, GluR1, PSD-93 and PSD-95 in hippocampus, with significant loss of dendritic spines.	116
Zn		•	adult	increased immobility time in the Forced Swim test (depression-like behavior)		117
Zn		•	adult	zinc deprivation induced "pro-depressive" behavior (forced swim test)	enhanced serum corticosterone concentration	118
Zn		•	adult	zinc deprivation induced "pro-depressive" behavior (tail suspension test)		119
Zn		•	adult	enhanced depression-like behavior in both the forced swim and tail suspension tests. No change in homecage and open field activity		120
Zn	•		adult (rat)	increased number of entries into the open arms in the elevated plus maze. Increased number of punished crossings in the four-plate test and attenuated stress-induced hyperthermia (SIH).		115
Zn		•	adult (rat)	Inferior learning		121
Zn		•	adult (rat)	deficits in short-term memory (water maze)	cyclic anorexia, decreased weight gain	122

Zn		•	juvenile	increased aggressive behavior (resident-intruder test)		123
Zn	•	□	prenatal (rat)	significant memory improvement (Morris water maze and a T-maze)		124
Zn		•	prenatal & adult	prenatal Zn deficiency induced "autism like behavior" (impaired ultrasonic vocalization, less maternal care), increased aggressivity (resdient intruder test). Acute Zn deficiency induced hyperresponsivity	decreased expression levels of NR1, NR2B, GluR1, in prenatal Zn deficient mice	22
Zn		•	MT-3 KO mice	normal movemet (open field), normal learning (shuttle box), normal spatial learning in the Morris water maze	more susceptible to seizures induced by kainic acid and subsequently exhibited greater neuron injury in the CA3 field of hippocampus.	125
Zn		•	MT-3 KO mice	social interactions were significantly shorter. The acoustic startle response showed diminished prepulse inhibition (PPI) at all prepulse intensities. Normal circadian rhythm, activity, and habituation to a novel environment. Normal memory in novel object recognition test.		126
Zn		•	ZnT3 knock out	ZnT3KO mice were normal in initial learning in the standard water maze but had difficulty finding a second platform location. The mutants showed increased social interaction but were deficient in social and object recognition memory.		127
Cu		•	adult	no significantl effects on behavior (open field, pole, predatory aggression, and habituation/dishabituation smell tests).	altered concentration of the other tested metal ions in the main organs as well as in the brain: reduction of Fe, Al, Zn, and Ca in brain	128
Cu		•	adult (rat)		no apparent effect on growth, ingestive behavior or short-term intake of preferred taste stimuli	129
Cu		•	perinatal (rat)	lasting impairment in motor function (rotarod)	lower brain Cu and Fe levels	130
Cu	•		perinatal	mildly impaired in the rotarod and cylinder test, unable to acquire spatial memory in the Morris water maze	Cu accumulated in striatum and hippocampus of “toxic milk” mice	131
Cd	•		adult (rat)	parameters of aggressiveness were not altered by either Cd or induced stress. Cd plus stress may lead to increased aggressiveness in rats.		132
Cd	•		adult (rat)	impaired cognition and enhanced anxiety-like behavior displayed by Cd-intoxicated rats	increase and decrease of AChE and Na+,K+-ATPase activities, respectively	133
Cd	•		APP/PS1 mice adult	Cd treatment worsened the learning ability of the APP/PS1 transgenic mice (Morris water maze)	Cd treatment increased the levels of free Zn	134
Cd	•		prenatal		fetal growth retardation	135
Mn	•		adult	decreased locomotor behavior, decreases in horizontal movement (grid crossing in open field) with no effect on rearing, swimming, grip strength, or grip fatigue		136
Mn	•		adult	decrease in spontaneous motor activity		137
Mn	•		adult (mice and rats)	movement abnormalities (single pellet reaching test, beam-walking test)	significant loss of substantia nigra compacta (SNc) dopaminergic neurons and dopamine depletion	138
Mn	•		adult & juvenile		a significant increase of Fe was observed in juvenile mice exposed to Mn	139
Mn	•	□	perinatal	no difference in the elevated plus maze or Morris water maze and the radial arm maze.		140
Mn	•		prenatal	no differences in motor resistance and coordination, or in learning at the passive avoidance test		141

Table S4: Comprehensive overview of the underlying genetics of the discussed neurological diseases and their possible link to the observed alterations in trace metals.

Disorder	Genetics	Relation to trace metal homeostasis
Alzheimer's disease	APP, PS1, PS2, risk factors: APOEε4, BIN1, CLU, PICALM, CR1	PS1 and PS2 participate in cellular Cu and Zn turnover; Amyloid-Beta peptide binds Zn as well as Cu and Fe
Autism Spectrum disorders	polygenic; some candidate genes are part of pathways regulating metal homeostasis (ZnT5, MTs, MTF1, COMMD1)	ZnT5: Zn transport; MTs: Metallothioneins (metal binding/buffering proteins); MTF1: Zn activated transcription factor regulating expression of MTs and several ZnTs; COMMD1: protein involved in Cu excretion
Attention deficit and hyperactivity disorder	polygenic; (one candidate gene NOS1 involved in Zn signalling)	NOS1 generates NO participating in intracellular Cu and Zn release
Mood Disorders and Schizophrenia	polygenic	-
Parkinson's disease	Alpha-Synuclein, LRRK2	Alpha-Synuclein binds Cu and Fe
Amyotrophic Lateral Sclerosis	C9orf72, SOD1, TDP-43, FUS, ANG, ALS2, SETX, VAPB	SOD1 and ANG bind Zn and Cu, TDP-43 binds Zn
Huntington's disease	monogenic (HTT)	HTT binds Cu
Prion diseases	PrP	PrP binds Cu and is involved in Fe homeostasis; PrP might also be involved in Zn transport
Lysosomal storage disorders	polygenic; TRPML1 (Mucolipidosis Type IV)	TRPML1 transports Ca, Fe and Zn
Menke's disease	ATP7A	ATP7A regulates Cu import
Wilson's disease	ATP7B	ATP7B regulates Cu export

Supplementary References

1 G. M. Bishop, S. R. Robinson, Q. Liu, G. Perry, C. S. Atwood, and M. A. Smith, Iron: a pathological mediator of Alzheimer disease?, *Dev. Neurosci.*, 2002, **24**, 184–7, DOI: 10.1002/mus.21625.

2 J. Collingwood and J. Dobson, Mapping and characterization of iron compounds in Alzheimer's tissue, *J. Alzheimers. Dis.*, 2006, **10**, 215–22, DOI: 10.1002/mus.21625.

3 J. R. Connor, B. S. Snyder, J. L. Beard, R. E. Fine, and E. J. Mufson, Regional distribution of iron and iron-regulatory proteins in the brain in aging and Alzheimer's disease, *J. Neurosci. Res.*, 1992, **31**, 327–35, DOI: 10.1002/jnr.490310214.

4 A. C. Leskovjan, A. Kretlow, A. Lanzirotti, R. Barrea, S. Vogt, and L. M. Miller, Increased brain iron coincides with early plaque formation in a mouse model of Alzheimer's disease, *Neuroimage*, 2011, **55**, DOI: 32–8, 10.1002/mus.21625.

5 M. . Lovell, J. . Robertson, W. . Teesdale, J. . Campbell, and W. . Markesbery, Copper, iron and zinc in Alzheimer's disease senile plaques, *J. Neurol. Sci.*, 1998, **158**, 47–52, DOI: 10.1016/S0022-510X(98)00092-6.

6 L. M. Miller, Q. Wang, T. P. Telivala, R. J. Smith, A. Lanzirotti, and J. Miklossy, Synchrotron-based infrared and X-ray imaging shows focalized accumulation of Cu and Zn co-localized with beta-amyloid deposits in Alzheimer's disease, *J. Struct. Biol.*, 2006, **155**, 30–7, DOI: 10.1016/j.jsb.2005.09.004.

7 D. Strozyk, L. J. Launer, P. A. Adlard, R. A. Cherny, A. Tsatsanis, I. Volitakis, K. Blennow, H. Petrovitch, L. R. White, and A. I. Bush, Zinc and copper modulate Alzheimer Abeta levels in human cerebrospinal fluid, *Neurobiol. Aging*, 2009, **30**, 1069–77, DOI: 10.1016/j.neurobiolaging.2007.10.012.

8 M. A. Deibel, W. D. Ehmann, and W. R. Markesbery, Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: possible relation to oxidative stress *, J. Neurol. Sci.*, 1996, **143**, 137–42.

9 D. Religa, D. Strozyk, R. A. Cherny, I. Volitakis, V. Haroutunian, B. Winblad, J. Naslund, and A. I. Bush, Elevated cortical zinc in Alzheimer disease, *Neurology*, 2006, **67**, 69–75, DOI: 0.1212/01.wnl.0000223644.08653.b5.

10 H. Basun, L. G. Forssell, L. Wetterberg, and B. Winblad, Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease, *J. Neural Transm. Park. Dis. Dement. Sect.*, 1991, **3**, 231–58.

11 L. Baum, I. H. S. Chan, S. K.-K. Cheung, W. B. Goggins, V. Mok, L. Lam, V. Leung, E. Hui, C. Ng, J. Woo, H. F. K. Chiu, B. C.-Y. Zee, W. Cheng, M.-H. Chan, S. Szeto, V. Lui, J. Tsoh, A. I. Bush, C. W. K. Lam, and T. Kwok, Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability, *Biometals*, 2010, **23**, 173–9, DOI: 10.1007/s10534-009-9277-5.

12 G. J. Brewer, S. H. Kanzer, E. A. Zimmerman, D. F. Celmins, S. M. Heckman, and R. Dick, Copper and ceruloplasmin abnormalities in Alzheimer's disease, *Am. J. Alzheimers. Dis. Other Demen.*, 2010, **25**, 490–7, DOI: 10.1177/1533317510375083.

13 B. R. Roberts, T. M. Ryan, A. I. Bush, C. L. Masters, and J. a Duce, The role of metallobiology and amyloid-β peptides in Alzheimer's disease, *J. Neurochem.*, 2012, **120 Suppl** , 149–66, DOI: 10.1111/j.1471-4159.2011.07500.x.

14 E. Blaurock-Busch, O. R. Amin, H. H. Dessoki, and T. Rabah, Toxic Metals and Essential Elements in Hair and Severity of Symptoms among Children with Autism, *Mædica*, 2012, **7**, 38–48.

15 A. Fido and S. Al-Saad, Toxic trace elements in the hair of children with autism, *Autism*, 2005, **9**, 290–8, DOI: 10.1177/1362361305053255.

16 H. Yasuda, K. Yoshida, Y. Yasuda, and T. Tsutsui, Infantile zinc deficiency: association with autism spectrum disorders, *Sci. Rep.*, 2011, **1**, 129, DOI: 10.1038/srep00129.

17 H. Yasuda, M. Kobayashi, Y. Yasuda, and T. Tsutsui, Estimation of autistic children by metallomics analysis, *Sci. Rep.*, 2013, **3**, 1199, DOI: 10.1038/srep01199.

18 L. Y. Al-Ayadhi, Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia *, Neurosciences (Riyadh).*, 2005, **10**, 213–8.

19 M. D. Lakshmi Priya and A. Geetha, Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism, *Biol. Trace Elem. Res.*, 2011, **142**, 148–58, DOI: 10.1007/s12011-010-8766-2.

20 S. Faber, G. M. Zinn, J. C. Kern, and H. M. S. Kingston, The plasma zinc/serum copper ratio as a biomarker in children with autism spectrum disorders, *Biomarkers*, 2009, **14**, 171–80, DOI: 10.1080/13547500902783747.

21 J. B. Adams, T. Audhya, S. McDonough-Means, R. A. Rubin, D. Quig, E. Geis, E. Gehn, M. Loresto, J. Mitchell, S. Atwood, S. Barnhouse, and W. Lee, Toxicological status of children with autism vs. neurotypical children and the association with autism severity, *Biol. Trace Elem. Res.*, 2013, **151**, 171–80, DOI: 10.1007/s12011-012-9551-1.

22 S. Grabrucker, L. Jannetti, M. Eckert, S. Gaub, R. Chhabra, S. Pfaender, K. Mangus, P. P. Reddy, V. Rankovic, T. M. Boeckers, M. J. Schmeisser, M. R. Kreutz, and A. M. Grabrucker, Zinc deficiency dysregulates the synaptic ProSAP / Shank scaffold and might contribute to autism spectrum disorders, *Brain*, 2013, DOI: 10.1093/brain/awt303.

23 R. W. Wojciak, E. Mojs, M. Stanislawska-Kubiak, and W. Samborski, The serum zinc, copper, iron, and chromium concentrations in epileptic children, *Epilepsy Res.*, 2013, **104**, 40–4, DOI: 10.1016/j.eplepsyres.2012.09.009.

24 J. Y. Kiddie, M. D. Weiss, D. D. Kitts, R. Levy-Milne, and M. B. Wasdell, Nutritional status of children with attention deficit hyperactivity disorder: a pilot study, *Int. J. Pediatr.*, 2010, **2010**, 767318, DOI: 10.1155/2010/767318.

25 M. M. Mahmoud, A.-A. M. El-Mazary, R. M. Maher, and M. M. Saber, Zinc, ferritin, magnesium and copper in a group of Egyptian children with attention deficit hyperactivity disorder, *Ital. J. Pediatr.*, 2011, **37**, 60, DOI: 10.1186/1824-7288-37-60.

26 C. Scassellati, C. Bonvicini, S. V Faraone, and M. Gennarelli, Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses *J. Am. Acad. Child Adolesc. Psychiatry*, 2012, **51**, 1003–1019.e20, DOI: 10.1016/j.jaac.2012.08.015.

27 A. C. Farias, A. Cunha, C. R. Benko, J. T. McCracken, M. T. Costa, L. G. Farias, and M. L. Cordeiro, Manganese in children with attention-deficit/hyperactivity disorder: relationship with methylphenidate exposure, *J. Child Adolesc. Psychopharmacol.*, 2010, **20**, 113–8, DOI: 10.1089/cap.2009.0073.

28 R. Nicolescu, C. Petcu, A. Cordeanu, K. Fabritius, M. Schlumpf, R. Krebs, U. Krämer, and G. Winneke, Environmental exposure to lead, but not other neurotoxic metals, relates to core elements of ADHD in Romanian children: performance and questionnaire data, *Environ. Res.*, 2010, **110**, 476–83, DOI: 10.1016/j.envres.2010.04.002.

29 C. W. Levenson, Zinc: The New Antidepressant?, *Nutrition Reviews*, 2006, 39–42, DOI: 10.1111/J.1753-4887.2006.tb00171.X.

30 E. C. Cope and C. W. Levenson, Role of zinc in the development and treatment of mood disorders, *Curr. Opin. Clin. Nutr. Metab. Care*, 2010, **13**, 685–9, DOI: 10.1097/MCO.0b013e32833df61a.

31 I. J. McLoughlin and J. S. Hodge, Zinc in depressive disorder, *Acta Psychiatr. Scand.*, 1990, **82**, 451–3.

32 G. Nowak and B. Szewczyk, Mechanisms contributing to antidepressant zinc actions, *Pol. J. Pharmacol.*, 2002, **54**, 587–92.

33 J. Wójcik, D. Dudek, M. Schlegel-Zawadzka, M. Grabowska, A. Marcinek, E. Florek, W. Piekoszewski, R. J. Nowak, W. Opoka, and G. Nowak, Antepartum/postpartum depressive symptoms and serum zinc and magnesium levels, *Pharmacol. Rep.*, 2006, **58**, 571–6.

34 L. M. Bodnar and K. L. Wisner, Nutrition and depression: implications for improving mental health among childbearing-aged women, *Biol. Psychiatry*, 2005, **58**, 679–85, DOI: 10.1016/j.biopsych.2005.05.009.

35 W. W. Manser, M. A. Khan, and K. Z. Hasan, Trace element studies on Karachi population. Part IV: Blood copper, zinc, magnesium and lead levels in psychiatric patients with depression, mental retardation and seizure disorders, *J. Pak. Med. Assoc.*, 1989, **39**, 269–74.

36 M. E. Pick, M. Edwards, D. Moreau, and E. A. Ryan, Assessment of diet quality in pregnant women using the Healthy Eating Index, *J. Am. Diet. Assoc.*, 2005, **105**, 240–6, DOI: 10.1016/j.jada.2004.11.028.

37 E. J. Corwin, L. E. Murray-Kolb, and J. L. Beard, Low hemoglobin level is a risk factor for postpartum depression, *J. Nutr.*, 2003, **133**, 4139–42.

38 K. Kimura and J. Kumura, Reports on the Metabolism of Trace Elements in Neuro Psychiatric Diseases. 1. Zinc in Schizophrenia, *Proc. Jpn. Acad.*, 1965, 943.

39 T. Mclardy, Hippocampal Zinc in Chronic Alcoholism and Schizophrenia, *IRCS Med. Sci.*, 1973, **2**, 1010.

40 A. Rahman, M. A. K. Azad, I. Hossain, M. M. A. S. Qusar, W. Bari, F. Begum, S. M. I. Huq, and A. Hasnat, Zinc, manganese, calcium, copper, and cadmium level in scalp hair samples of schizophrenic patients, *Biol. Trace Elem. Res.*, 2009, **127**, 102–8, DOI: 10.1007/s12011-008-8230-8.

41 S. S. S. J. Ahmed and W. Santosh, Metallomic profiling and linkage map analysis of early Parkinson's disease: a new insight to aluminum marker for the possible diagnosis, *PLoS One*, 2010, **5**, e11252, DOI: 10.1371/journal.pone.0011252.

42 S. Younes-Mhenni, M. Aissi, N. Mokni, A. Boughammoura-Bouatay, S. Chebel, M. Frih-Ayed, A. Kerkeni, M. Bost, G. Chazot, M. T. Sfar, and M. H. Sfar, Serum copper, zinc and selenium levels in Tunisian patients with Parkinson's disease, *Tunis. Med.*, 2013, **91**, 402–5.

43 C. M. Tolleson and J. Y. Fang, Advances in the mechanisms of Parkinson's disease, *Discov. Med.*, 2013, **15**, 61–6.

44 G. D. Kanias and E. Kapaki, Trace elements, age, and sex in amyotrophic lateral sclerosis disease*, Biol. Trace Elem. Res.*, 1997, **56**, 187–201, DOI: 10.1007/BF02785392.

45 A. Ignjatović, Z. Stević, D. Lavrnić, A. Nikolić-Kokić, D. Blagojević, M. Spasić, and I. Spasojević, Inappropriately chelated iron in the cerebrospinal fluid of amyotrophic lateral sclerosis patients, *Amyotroph. Lateral Scler.*, 2012, **13**, 357–62, DOI: 10.3109/17482968.2012.665929.

46 P. M. Roos, S. Lierhagen, T. P. Flaten, T. Syversen, O. Vesterberg, and M. Nordberg, Manganese in cerebrospinal fluid and blood plasma of patients with amyotrophic lateral sclerosis, *Exp. Biol. Med. (Maywood).*, 2012, **237**, 803–10, DOI: 10.1258/ebm.2012.011396.

47 R. M. Mitchell, Z. Simmons, J. L. Beard, and H. E. Stephens, Plasma biomarkers associated with ALS and their relationship to iron homeostasis, *Muscle Nerve*, 2010, 95–103, DOI:10.1002/mus.21625.

48 Y. Nadjar, P. Gordon, P. Corcia, G. Bensimon, and L. Pieroni, Elevated Serum Ferritin Is Associated with Reduced Survival in Amyotrophic Lateral Sclerosis, PLoS ONE, 2012, **7**, 2–7, DOI:10.1371/journal.pone.0045034.

49 A. B. Bowman, G. F. Kwakye, E. H. Hernández, and M. Aschner, Role of manganese in neurodegenerative diseases, *NIH-PA Author Manuscr.*, 2012, **25**, 191–203, DOI: 10.1016/j.jtemb.2011.08.144.Role.

50 M. Vinceti, I. Bottecchi, A. Fan, Y. Finkelstein, and J. Mandrioli, Are environmental exposures to selenium, heavy metals, and pesticides risk factors for amyotrophic lateral sclerosis?, *Rev. Environ. Health*, 2012, **27**, 19–41.

51 B. Callaghan, D. Feldman, K. Gruis, and E. Feldman, The association of exposure to lead, mercury, and selenium and the development of amyotrophic lateral sclerosis and the epigenetic implications, *Neurodegener. Dis.*, 2011, **8**, 1–8, DOI: 10.1159/000315405.

52 T. W. Rhoads, N. I. Lopez, D. R. Zollinger, J. T. Morre, B. L. Arbogast, C. S. Maier, L. DeNoyer, and J. S. Beckman, Measurung Copper and Zinc Superoxide Dismutase from Spinal Cord Tissue using Electrospray Mass Spectrometry, *NIH-PA Author Manuscr.*, 2012, **415**, 52–58, DOI: 10.1016/j.ab.2011.03.029.Measuring.

53 A. P. Smith and N. M. Lee, Role of zinc in ALS, *Amyotroph Lateral Scler.*, 2007, 131–143, DOI: 10.1080/17482960701249241.

54 K. A. Trumbull and J. S. Beckman, A role for copper in the toxicity of zinc-deficient superoxide dismutase to motor neurons in amyotrophic lateral sclerosis, *Antioxid. Redox Signal.*, 2009, **11**, 1627–39, DOI:10.1080/17482960701249241.

55 P. Dusek, J. Jankovic, and W. Le, Iron dysregulation in movement disorders, *Neurobiol. Dis.*, 2012, **46**, 1–18, DOI: 10.1016/j.nbd.2011.12.054.

56 E. A. Malecki, A. G. Devenyi, J. L. Beard, and J. R. Connor, Existing and emerging mechanisms for transport of iron and manganese to the brain, *J. Neurosci. Res.*, 1999, **56**, 113–22.

57 D. R. Brown, Prions and manganese: A maddening beast, *Metallomics*, 2011, **3**, 229–38, DOI: 10.1039/c0mt00047g.

58 D. Slivarichová, E. Mitrová, M. Ursínyová, I. Uhnáková, S. Koscová, and L. Wsólová, Geographic accumulation of Creutzfeldt-Jakob disease in Slovakia--environmental metal imbalance as a possible cofactor, *Cent. Eur. J. Public Health*, 2011, **19**, 158–64.

59 H. Hayashi, A. Hattori, Y. Tatsumi, K. Hayashi, Y. Katano, J. Ueyama, S. Wakusawa, M. Yano, and H. Goto, Various copper and iron overload patterns in the livers of patients with Wilson disease and idiopathic copper toxicosis, *Med. Mol. Morphol.*, 2013, **46**, 133–40, DOI: 10.1007/s00795-013-0015-2.

60 W. Cerpa, L. Varela-Nallar, A. E. Reyes, A. N. Minniti, and N. C. Inestrosa, Is there a role for copper in neurodegenerative diseases?, *Mol. Aspects Med.*, 2005, **26**, 405–20, DOI: 10.1016/j.mam.2005.07.011.

61 D. J. Waggoner, T. B. Bartnikas, and J. D. Gitlin, The role of copper in neurodegenerative disease, *Neurobiol. Dis.*, 1999, **6**, 221–30, DOI: 10.1006/nbdi.1999.0250.

62 A. Mekinian, J. Stirnemann, N. Belmatoug, D. Heraoui, B. Fantin, O. Fain, A. Charpentier, and C. Rose, Ferritinemia during type 1 Gaucher disease: mechanisms and progression under treatment, *Blood Cells. Mol. Dis.*, 2012, **49**, 53–7, DOI: 10.1016/j.bcmd.2012.04.002.

63 A. E. Bohte, L. van Dussen, E. M. Akkerman, A. J. Nederveen, R. Sinkus, P. L. M. Jansen, J. Stoker, and C. E. M. Hollak, Liver fibrosis in type I Gaucher disease: magnetic resonance imaging, transient elastography and parameters of iron storage, *PLoS One*, 2013, **8**, e57507, DOI: 10.1371/journal.pone.0057507.

64 A. H. Koeppen, R. L. Ramirez, D. Yu, S. E. Collins, J. Qian, P. J. Parsons, K. X. Yang, Z. Chen, J. E. Mazurkiewicz, and P. J. Feustel, Friedreich's ataxia causes redistribution of iron, copper, and zinc in the dentate nucleus, *Cerebellum*, 2012, **11**, 845–60, DOI: 10.1007/s12311-012-0383-5.

65 D. Shapcott, R. Giguère, and B. Lemieux, Zinc and taurine in Friedreich's ataxia, *Can. J. Neurol. Sci.*, 1984, **11**, 623–5.

66 L. Velázquez-Pérez, J. Rodríguez-Chanfrau, J. C. García-Rodríguez, G. Sánchez-Cruz, R. Aguilera-Rodríguez, R. Rodríguez-Labrada, J. C. Rodríguez-Díaz, N. Canales-Ochoa, D. A. Gotay, L. E. Almaguer Mederos, J. M. Laffita Mesa, M. Porto-Verdecia, C. G. Triana, N. R. Pupo, I. H. Batista, O. D. López-Hernandez, I. D. Polanco, and A. J. Novas, Oral zinc sulphate supplementation for six months in SCA2 patients: a randomized, double-blind, placebo-controlled trial, *Neurochem. Res.*, 2011, **36**, 1793–800, DOI: 10.1007/s11064-011-0496-0.

67 N. Kaneko, J. Takada, H. Yasui, H. Sakurai, Memory deficit in mice administered aluminum-maltolate complex, *Biometals*, 2006, **19**, 83-9.

68 M. S. Golub, J. M. Donald, M. E. Gershwin, C. L. Keen, Effects of aluminum ingestion on spontaneous motor activity of mice, *Neurotoxicol Teratol*, 1989, **11**, 231-5, DOI: 10.1007/s10534-005-6965-7.

69 H. Erazi, W. Sansar, S. Ahboucha, H. Gamrani, Aluminum affects glial system and behavior of rats, *C R Biol*, 2010, **333**, 23-7.

70 G. M. Abu-Taweel, J. S. Ajarem, M. Ahmad, Neurobehavioral toxic effects of perinatal oral exposure to aluminum on the developmental motor reflexes, learning, memory and brain neurotransmitters of mice offspring, *Pharmacol Biochem Behav*, **2012**, 101, 49-56.

71 M. S. Golub, C. L. Keen, M. E. Gershwin, Neurodevelopmental effect of aluminum in mice: fostering studies, *Neurotoxicol Teratol*, 1992, **14**, 177-82,, DOI: 10.1016/0892-0362(92)90013-Z.

72 J. Rankin, A. Manning, Alterations to the pattern of ultrasonic calling after prenatal exposure to aluminium sulfate, *Behav Neural Biol*, 1993; **59**, 136-42.

73 J. Rankin, K. Sedowofia, R. Clayton, A. Manning, Behavioural effects of gestational exposure to aluminium, *Ann Ist Super Sanita*, 1993, **29**, 147-52.

74 S. Bellum, K. A. Thuett, B. Bawa, L. C. Abbott, The effect of methylmercury exposure on behavior and cerebellar granule cell physiology in aged mice, *J Appl Toxicol*, 2013, **33**, 959-69, DOI: 10.1002/jat.2786.

75 S. Bellum, K. A. Thuett, R. Grajeda, L. C. Abbott, Coordination deficits induced in young adult mice treated with methylmercury, *Int J Toxicol*, 2007, **26**, 115-21.

76 K. S. Montgomery, J. Mackey, K. Thuett, S. Ginestra, J. L. Bizon,L. C. Abbott, Chronic, low-dose prenatal exposure to methylmercury impairs motor and mnemonic function in adult C57/B6 mice, *Behav Brain Res*, 2008, **191**, 55-61, DOI: 10.1016/j.bbr.2008.03.008.

77 C. Watanabe, K. Yin, Y. Kasanuma, H. Satoh, In utero exposure to methylmercury and Se deficiency converge on the neurobehavioral outcome in mice, *Neurotoxicol Teratol*, 1999, **21**, 83-8.

78 J. A. Hughes, Z. Annau, Postnatal behavioral effects in mice after prenatal exposure to methylmercury, *Pharmacol Biochem Behav*, 1976, **4**, 385-91.

79 M. Yoshida, M. Suzuki, M. Satoh, A. Yasutake, C. Watanabe, Neurobehavioral effects of combined prenatal exposure to low-level mercury vapor and methylmercury, *J Toxicol Sci*, 2011, **36**, 73-80.

80 C. N. Glover, D. Zheng, S. Jayashankar, G. D. Sales, C. Hogstrand, A. K. Lundebye, Methylmercury speciation influences brain gene expression and behavior in gestationally-exposed mice pups, *Toxicol Sci*, 2009, **110**, 389-400, DOI: 10.1093/toxsci/kfp105.

81 N. Onishchenko, C. Tamm, M. Vahter, T. Hökfelt, J. A. Johnson, D. A. Johnson, S. Ceccatelli, Developmental exposure to methylmercury alters learning and induces depression-like behavior in male mice, *Toxicol Sci*, 2007, **97**, 428-37.

82 S. Goulet, F. Y. Doré, M. E. Mirault, Neurobehavioral changes in mice chronically exposed to methylmercury during fetal and early postnatal development, *Neurotoxicol Teratol*, 2003, **25**, 335-47.

83 R. G. Burright, W. J. Engellenner, P. J. Donovick, Lead exposure and agonistic behavior of adult mice of two ages, *Physiol Behav*, 1983, **30**, 285-8.

84 O. Barzideh, R. G. Burright, P. J. Donovick, Dietary iron and exposure to lead influence susceptibility to seizures, *Psychol Rep*, 1995, **76**, 971-6.

85 F. E. Nieto-Fernandez, A. Ruiz, N. Ntukogu, L. Nodimelle, S. C. Pryor, Short term lead exposure induces a stress-like response in adult mice, *Med Sci Monit*, 2006, **12**, BR325-9.

86 E. K. Silbergeld, A. M. Goldberg, Hyperactivity: a lead-induced behavior disorder, *Environ Health Perspect*, 1974, **7**, 227-32.

87 M. G. Cutler, Effects of exposure to lead on social behaviour in the laboratory mouse, *Psychopharmacology*, 1977, **52**, 279-82.

88 R. T. Zimering, R. G. Burright, P. J. Donovick, Effects of pre-natal and continued lead exposure on activity levels in the mouse, *Neurobehav Toxicol Teratol*, 1982, **4**, 9-14.

89 L. J. Draski, R. G. Burright, P. J. Donovick, The influence of prenatal and/or postnatal exposure to lead on behavior of preweanling mice, *Physiol Behav*, 1989, **45**, 711-5.

90 J. M. Donald, M. G. Cutler, M. R. Moore, M. Bradley, Development and social behaviour in mice after prenatal and postnatal administration of low levels of lead acetate, *Neuropharmacology*, 1981, **20**, 1097-104.

91 J. L. Leasure, A. Giddabasappa, S. Chaney, J. E. Johnson, K. Pothakos, Y. S. Lau, D. A. Fox , Low-level human equivalent gestational lead exposure produces sex-specific motor and coordination abnormalities and late-onset obesity in year-old mice, *Environ Health Perspect*, 2008, **116**, 355-61, DOI: 10.1289/ehp.10862.

92 J. Kasten-Jolly, N. Pabello, V. J. Bolivar, D. A. Lawrence, Developmental lead effects on behavior and brain gene expression in male and female BALB/cAnNTac mice, *Neurotoxicology*, 2012, **33**, 1005-20, DOI: 10.1016/j.neuro.2012.04.017.

93 Z. S. Dolinsky, R. G. Burright, P. J. Donovick, Behavioral changes in mice following lead administration during several stages of development, *Physiol Behav*, 1983, **30**, 583-9.

94 S. B. Sartori, N. Whittle, A. Hetzenauer, N. Singewald, Magnesium deficiency induces anxiety and HPA axis dysregulation: modulation by therapeutic drug treatment, *Neuropharmacology*, 2012, **62**, 304-12, DOI: 10.1016/j.neuropharm.2011.07.027.

95 N. Whittle, L. Li, W. Q. Chen, J. W. Yang, S. B. Sartori, G. Lubec, N. Singewald, Changes in brain protein expression are linked to magnesium restriction-induced depression-like behavior, *Amino Acids*, 2011, **40**, 1231-48, DOI: 10.1007/s00726-010-0758-1.

96 A. Muroyama, M. Inaka, H. Matsushima, H. Sugino, Y. Marunaka, Y. Mitsumoto, Enhanced susceptibility to MPTP neurotoxicity in magnesium-deficient C57BL/6N mice, *Neurosci Res*, 2009, **63**, 72-5, DOI: 10.1016/j.neures.2008.09.009.

97 N. Singewald, C. Sinner, A. Hetzenauer, S. B. Sartori, H. Murck, Magnesium-deficient diet alters depression- and anxiety-related behavior in mice--influence of desipramine and Hypericum perforatum extract, *Neuropharmacology*, 2004, **47**, 1189-97.

98 B. I. Tamba, M. M. Leon, T. Petreus, Common trace elements alleviate pain in an experimental mouse model, *J Neurosci Res*, 2013, **91**, 554-61, 10.1002/jnr.23191.

99 M. E. Bardgett, P. J. Schultheis, A. Muzny, M. D. Riddle,J. R. Wagge, Magnesium deficiency reduces fear-induced conditional lick suppression in mice, *Magnes Res*, 2007, **20**, 58-65.

100 M. E. Bardgett, P. J. Schultheis, D. L. McGill, R. E. Richmond, J. R. Wagge JR, Magnesium deficiency impairs fear conditioning in mice, *Brain Res*, 2005, **1038**, 100-6.

101 P. Bac, M. German-Fattal, [Potentiation of Delta9-tetrahydrocannabinol (THC) effects by magnesium deficiency in the rat], *Ann Pharm Fr*, 2006, **64**, 207-13.

102 P. Bac, N. Pages, C. Herrenknecht, C. Dupont, P. Maurois, J. Vamecq, J. Durlach, THC aggravates rat muricide behavior induced by two levels of magnesium deficiency, *Physiol Behav*, 2002, **77**, 189-95.

103 S. Nikseresht, S. Etebary, M. Karimian, F. Nabavizadeh, M. R. Zarrindast, H. R. Sadeghipour, Acute administration of Zn, Mg, and thiamine improves postpartum depression conditions in mice, *Arch Iran Med*, 2012, **15**, 306-11, DOI: 012155/AIM.0012.

104 R. M. Rosa, D. G. Flores, H. R. Appelt, A. L. Braga, J. A. Henriques, R. Roesler, Facilitation of long-term object recognition memory by pretraining administration of diphenyl diselenide in mice, *Neurosci Lett*, 2003, **341**, 217-20.

105 C. Watanabe, H. Satoh, Effects of prolonged selenium deficiency on open field behavior and Morris water maze performance in mice, *Pharmacol Biochem Behav*, 1995, **51**, 747-52.

106 T. Archer, A. Fredriksson, Functional consequences of iron overload in catecholaminergic interactions: the Youdim factor, *Neurochem Res*, 2007, **32**, 1625-39.

107 T. Dean, R. P. Allen, C. P. O'Donnell, C. J. Earley, The effects of dietary iron deprivation on murine circadian sleep architecture, *Sleep Med*, 2006, **7**, 634-40.

108 A. Fredriksson, N. Schröder, P. Eriksson, I, Izquierdo, T. Archer, Maze learning and motor activity deficits in adult mice induced by iron exposure during a critical postnatal period, *Brain Res Dev Brain Res*, 2000, **119**, 65-74.

109 A. Fredriksson, N. Schröder, T. Archer, Neurobehavioural deficits following postnatal iron overload: I spontaneous motor activity, *Neurotox Res*, 2003; **5**, 53-76.

110 T. Archer, N. Schröder, A. Fredriksson, Neurobehavioural deficits following postnatal iron overload: II Instrumental learning performance, *Neurotox Res*, 2003, **5**, 77-94.

111 S. C. Ranade,A. Rose, M. Rao, J. Gallego, P. Gressens, S. Mani, Different types of nutritional deficiencies affect different domains of spatial memory function checked in a radial arm maze, *Neuroscience*, 2008, **152**, 859-66, DOI: 10.1016/j.neuroscience.2008.01.002.

112 E. S. Carlson, I. Tkac, R. Magid, M. B. O'Connor, N. C. Andrews, T. Schallert, H. Gunshin, M. K. Georgieff, A. Petryk, Iron is essential for neuron development and memory function in mouse hippocampus, *J Nutr*, 2009, **139**, 672-9, DOI: 10.3945/jn.108.096354.

113 C. L. Kwik-Uribe, M. S. Golubt, C.L. Keen, Behavioral consequences of marginal iron deficiency during development in a murine model, *Neurotoxicol Teratol*, 1999, **21**, 661-72.

114 A. Takeda, H. Iwaki, K. Ide, H. Tamano, N. Oku, Therapeutic effect of Yokukansan on social isolation-induced aggressive behavior of zinc-deficient and pair-fed mice, *Brain Res Bul*,l 2012, **87**, 551-5, DOI: 10.1016/j.brainresbull.2012.02.003.

115 A. Partyka, M. Jastrzębska-Więsek, B. Szewczyk, K. Stachowicz, A. Sławińska, E. Poleszak, U. Doboszewska, A. Pilc, G. Nowak, Anxiolytic-like activity of zinc in rodent tests, *Pharmacol Rep*, 2011, **63**, 1050-5.

116 Y. Yang, X. P. Jing, S. P. Zhang, R. X. Gu, F. X. Tang, X. L. Wang, Y. Xiong, M. Qiu, X. Y. Sun, D. Ke, J. Z. Wang, R. Liu, High dose zinc supplementation induces hippocampal zinc deficiency and memory impairment with inhibition of BDNF signaling, *PLoS One*, 2013, **8**, e55384, DOI: 10.1371/journal.pone.0055384.

117 K. Młyniec, B. Budziszewska, W. Reczyński, M. Sowa-Kućma, G. Nowak, The role of the GPR39 receptor in zinc deficient-animal model of depression, *Behav Brain Res*, 2013, **238**, DOI: 10.1016/j.bbr.2012.10.020.

118 K. Młyniec, C. L. Davies, B. Budziszewska, W. Opoka, W. Reczyński, M. Sowa-Kućma, U. Doboszewska, A. Pilc, G. Nowak, Time course of zinc deprivation-induced alterations of mice behavior in the forced swim test, *Pharmacol Rep*, 2012, **64**, 567-75.

119 K. Młyniec, G. Nowak, Zinc deficiency induces behavioral alterations in the tail suspension test in mice, Effect of antidepressants, *Pharmacol Rep*, 2012, **64**, 249-55.

120 N. Whittle, G. Lubec, N. Singewald, Zinc deficiency induces enhanced depression-like behaviour and altered limbic activation reversed by antidepressant treatment in mice, *Amino Acids*, 2009, **36**, 147-58, DOI: 10.1007/s00726-008-0195-6.

121 D. F. Caldwell, D. Oberleas, J. J. Clancy, A. S. Prasad, Behavioral impairment in adult rats following acute zinc deficiency, *Proc Soc Exp Biol Med*, 1970, **133**, 1417-21.

122 K. A. Keller, A. Grider, J. A. Coffield, Age-dependent influence of dietary zinc restriction on short-term memory in male rats, *Physiol Behav*, 2001, **72**, 339-48.

123 A. Takeda, H. Tamano, F. Kan, T. Hanajima, K. Yamada, N. Oku, Enhancement of social isolation-induced aggressive behavior of young mice by zinc deficiency, *Life Sci*, 2008, **82**, 909-14, DOI: 10.1016/j.lfs.2008.02.005.

124 A. Piechal, K. Blecharz-Klin, J. Pyrzanowska, E. Widy-Tyszkiewicz, Maternal zinc supplementation improves spatial memory in rat pups, *Biol Trace Elem Res*, 2012, **147**, 299-308, DOI: 10.1007/s12011-012-9323-y.

125 J. C. Erickson, G. Hollopeter, S. A. Thomas, G. J. Froelick, R. D. Palmiter, Disruption of the metallothionein-III gene in mice: analysis of brain zinc, behavior, and neuron vulnerability to metals, aging, and seizures, *J Neurosci*, 1997, **17**, 1271-81.

126 A. Koumura, K. Kakefuda, A. Honda, Y. Ito, K. Tsuruma, M. Shimazawa, Y. Uchida, I. Hozumi, M. Satoh, T. Inuzuka, H. Hara, Metallothionein-3 deficient mice exhibit abnormalities of psychological behaviors, *Neurosci Lett*, 2009, **467**, 11-4, DOI: 10.1016/j.neulet.2009.09.051.

127 G. Martel, C. Hevi, N. Kane-Goldsmith, G. P. Shumyatsky, Zinc transporter ZnT3 is involved in memory dependent on the hippocampus and perirhinal cortex, *Behav Brain Res*, 2011, **223**, 233-8, DOI:10.1016/j.bbr.2011.04.020.

128 S. Bolognin, F. Pasqualetto, C. Mucignat-Caretta, J. Scancar, R. Milacic, P. Zambenedetti, B. Cozzi, P. Zatta, Effects of a copper-deficient diet on the biochemistry, neural morphology and behavior of aged mice, *PLoS One*, 2012, **7**, e47063, DOI: 10.1371/journal.pone.0047063.

129 S. Greeley, K. Gniecko, Short-term taste behavior and copper/vitamin B-6 nutriture in Long-Evans rats, *Physiol Behav*, 1986, **38**, 765-71

130 J. G. Penland, J. R. Prohaska, Abnormal motor function persists following recovery from perinatal copper deficiency in rats, *J Nutr*, 2004, **134**, 1984-8.

131 D. Terwel, Y. N. Löschmann, H. H. Schmidt, H. R. Schöler, T. Cantz, M. T. Heneka, Neuroinflammatory and behavioural changes in the Atp7B mutant mouse model of Wilson's disease, *J Neurochem*, 2011, **118**, 105-12, DOI: 10.1111/j.1471-4159.2011.07278.x.

132 S. G. Terçariol, A. A. Almeida, A. F. Godinho, Cadmium and exposure to stress increase aggressive behavior, *Environ Toxicol Pharmacol*, 2011, **32**, 40-5, DOI: 10.1016/j.etap.2011.03.005.

133 J. F. Gonçalves, F. T. Nicoloso, P. da Costa, J. G. Farias, F: B. Carvalho, M. M. da Rosa, J. M. Gutierres,F. H. Abdalla, J. S. Pereira, G. R. Dias, N. B. Barbosa, V. L. Dressler, M. A. Rubin, V. M. Morsch, M. R. Schetinger, Behavior and brain enzymatic changes after long-term intoxication with cadmium salt or contaminated potatoes, *Food Chem Toxicol*, 2012, **50**, 3709-18, DOI: 10.1016/j.fct.2012.07.016.

134 X. Li, Y. Lv, S. Yu, H. Zhao, L. Yao, The effect of cadmium on Aβ levels in APP/PS1 transgenic mice, *Exp Ther Med*, 2012, **4**, 125-130.

135 W. S. Webster, Cadmium-induced fetal growth retardation in the mouse, *Arch Environ Health*, 1978, **33**, 36-42.

136 C. A. Dodd, D. L. Ward, B. G. Klein, Basal Ganglia accumulation and motor assessment following manganese chloride exposure in the C57BL/6 mouse, *Int J Toxicol*, 2005, **24**, 389-97.

137 E. J. Talavera, J. L. Arcaya, D. Giraldoth, J. Suárez, E. Bonilla, Decrease in spontaneous motor activity and in brain lipid peroxidation in manganese and melatonin treated mice, *Neurochem Res*, 1999, **24**, 705-8.

138 J. Sanchez-Betancourt, V. Anaya-Martínez, A. L. Gutierrez-Valdez, J. L. Ordoñez-Librado, E. Montiel-Flores, J. Espinosa-Villanueva, L. Reynoso-Erazo, M. R. Avila-Costa, Manganese mixture inhalation is a reliable Parkinson disease model in rats, *Neurotoxicology*, 2012, **33**, 1346-55.

139 J. A. Moreno, E. C. Yeomans, K. M. Streifel, B. L. Brattin, R. J. Taylor, R. B. Tjalkens, Age-dependent susceptibility to manganese-induced neurological dysfunction, *Toxicol Sci*, 2009, **112**, 394-404, DOI: 10.1093/toxsci/kfp220.

140 B. A. Pappas, D. Zhang, C. M. Davidson, T. Crowder, G. A. Park, T. Fortin, Perinatal manganese exposure: behavioral, neurochemical, and histopathological effects in the rat, *Neurotoxicol Teratol*, 1997, **19**, 17-25.

141 M. Torrente, M. T. Colomina, J. L. Domingo, Effects of prenatal exposure to manganese on postnatal development and behavior in mice: influence of maternal restraint, *Neurotoxicol Teratol*, 2002, **24**, 219-25.