Metal toxicity is a global health concern. We summarize the evidence for metal interactions with the nervous system with an emphasis on synaptic transmission. The appropriate functioning of synaptic transmission is crucial for the information transfer in any neural network.

Presynaptically, metal ions modulate transmitter release through their interaction with neurotransmitter (NT) synthesis, fusion of synaptic vesicles, signaling cascades and ion channels. Ca$^{2+}$ entry through voltage-gated channels is impaired by Pb$^{2+}$, Cd$^{2+}$ or Zn$^{2+}$, therefore all processes which depend on Ca$^{2+}$, including NT release, will be affected. Furthermore, some metals interact with intracellular pathways e.g. Pb$^{2+}$ inhibits PKC enzymes through its catalytic domains, and Ni$^{2+}$ causes a decline in the transcription of two isoforms of PKC (prkcc and prkz) and two regulatory binding proteins (prkcbp1 and prkcdb) affecting most functions of PKC. Cd and Hg inhibit adenylate cyclase activity, while the extent of inhibition depends on exposure time and brain area. Exocytosis is impaired by Pb$^{2+}$ and Cu$^{2+}$, which interact with Synaptotagmin I.

Postsynaptically, processes associated with binding of NT to their receptors, activation of the channels and degradation of NT are changed by metal. Zn$^{2+}$, Pb$^{2+}$, Cu$^{2+}$, Cd$^{2+}$, Ni$^{2+}$, Co$^{2+}$, Li$^{3+}$, Hg$^{+}$ and methylmercury modulate NMDA, AMPA/Kainate and/or GABA receptor’s activity. These effects are more or less specific e.g. Zn$^{2+}$ and Cu$^{2+}$ modulate all three types of receptors, while Zn$^{2+}$ is more potent (IC50= 0.77μM) compared to Cu$^{2+}$ (IC50=15μM) at NMDA-Rs, but both have similar potencies at GABA-R. For the most part, metal interactions depend on the subunit composition of the NMDA-R, while less data are available for other targets, possibly underestimating their importance.

These modulations change the synaptic efficiency and therefore impair long-term potentiation (LTP). Consequently, metals such as Al, Pb or Cd result in various cognitive deficits. In addition the generation and maintenance of LTP is reduced by metal actions on phosphorylation of transcription factors like CREB as well as by reduction of nitric oxide synthase (NOS) that change retrograde signaling.

Overall, there are multiple effects of metals based on the forms of the metals, their concentrations and the types of neurons involved.