

# Contributions to Parkinson's Disease by Environmentally Relevant Mixtures of Metals

Randi Jones, Kasey Smith and Urvashi Khosla

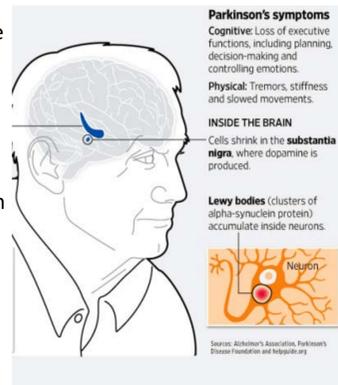
Dept. of Environmental and Occupational Health, California State University, Northridge

## ABSTRACT

Parkinson's disease is a known neurological disease that affects the substantia nigra of the brain. The substantia nigra produces dopamine, a neurotransmitter that controls muscle movement [1]. In Parkinson's disease, the brain cells that make dopamine degenerate or die. There are many theories, but no definite answer, to what causes these brain cells to die or degenerate. Several environmental pollutants have been implicated as possible contributors to Parkinson's disease. Those include iron, zinc, aluminum, manganese, copper, cobalt, cadmium and lead [2]. Studies have shown that there is a strong connection between environmental pollutants and Parkinson's disease. The current work explores the mechanisms by which these environmental pollutants are linked with Parkinson's disease and the aggregation of  $\alpha$ -synuclein and loss of dopamine [3]. The environmental pollutants will enter the brain through ingestion and inhalation. These pollutants aggregate the mis-folding of  $\alpha$ -synuclein, which then combine to form fibrils that make up Lewy bodies and the formation and release of peroxides ( $H_2O_2$ ) in the presence of iron [4]. This forms Reactive Oxidative Species (ROS), damages organelles and proteins, increases the protein aggregation of  $\alpha$ -synuclein, and creates fibrils that make up Lewy bodies [5]. The current work explores the possibility of environmental pollutants causing Parkinson's disease. The current research indicates that a mixture of environmental pollutants will make this connection even stronger. Additional research is needed to study the various environmental pollutants causing Parkinson's disease.

## INTRODUCTION

Neurodegenerative disorders are a familiar product of aging [6]. The etiology of certain health effects such as Parkinson's disease have yet to be definitively determined. Technology has advanced in the last decades to allow for medical research to advance in the detection of contributing factors. Parkinson's disease leads to a loss of cognitive and physical function [7]. Research shows that metal cations play a large role in Parkinson's disease by allowing the primary structure of the  $\alpha$ -synuclein protein to tangle by interfering with naturally repelling anions [8]. In particular, combinations of metals through routes of inhalation and ingestion have been shown to contribute to the development of neurodegenerative disorders [9]. The substantia nigra, lewy bodies, and dopamine synthesis are areas and functions of the brain proven to be affected in Parkinson's. Understanding that environmental factors play a role in most diseases, this allows for regulation and action to be implemented in order to protect human health.



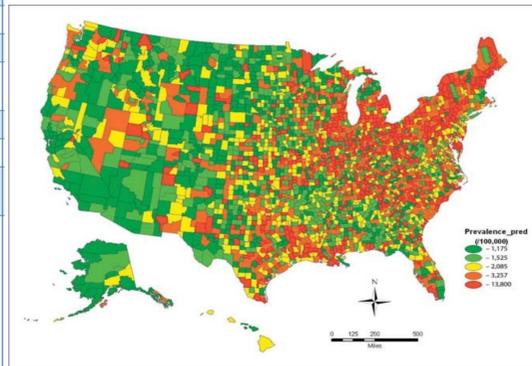
[10]

## EPIDEMIOLOGY

| Parameter                | Parkinson's                                                                                                                                                                                                                                       |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Typical Age Onset        | ~60 y.o.                                                                                                                                                                                                                                          |
| USA Cases                | 1 million                                                                                                                                                                                                                                         |
| Worldwide Cases          | 5-6 million                                                                                                                                                                                                                                       |
| Region of Brain Affected | Substantia nigra, critical for dopamine synthesis                                                                                                                                                                                                 |
| Neurodegenerative        | Yes                                                                                                                                                                                                                                               |
| Progressive Disease      | Yes                                                                                                                                                                                                                                               |
| Primary Symptoms         | Mainly movement disorder                                                                                                                                                                                                                          |
| Therapy Available        | Treatments include medication and surgery; Carbidopa/levodopa, Mirapex (pramipexole*), Requip (ropinirole*), Amantadine (Symmetrel*), Anticholinergic Drugs, COMT-inhibitors, MAO-B inhibitors. Other treatments include lifestyle modifications. |

11

County level Age- and Race-Standardized Prevalence of Parkinson's Disease

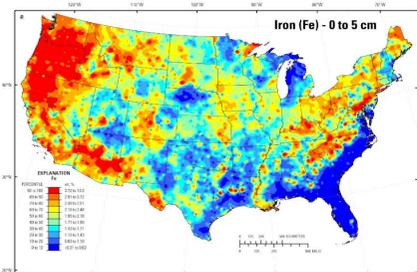


12

## ENVIRONMENTAL CONCENTRATIONS

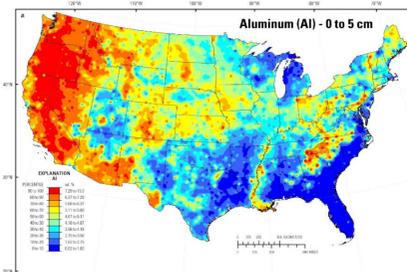
Two examples of metals that are commonly related to the onset of Parkinson's Disease. The concentrations of soil were analyzed taken  $\leq 5$  cm.

Concentration of Iron in Soil



13

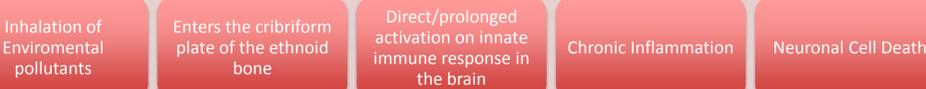
Concentration of Aluminum in Soil



13

## ROUTES OF EXPOSURE

### Inhalation



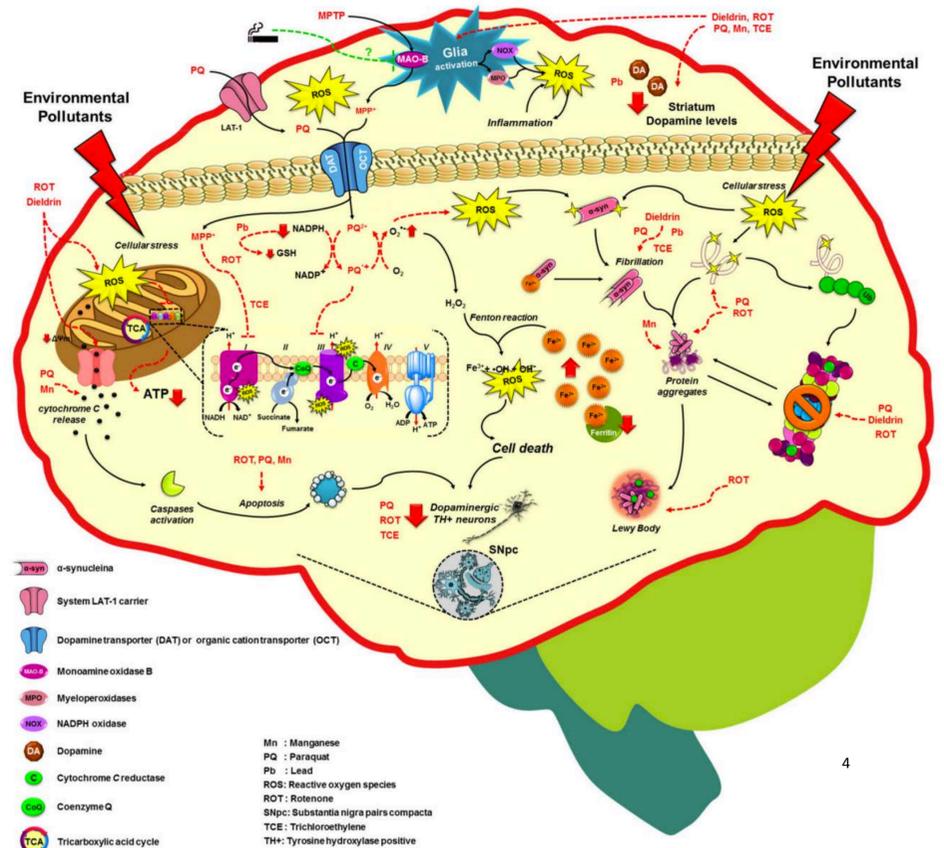
14

### Ingestion



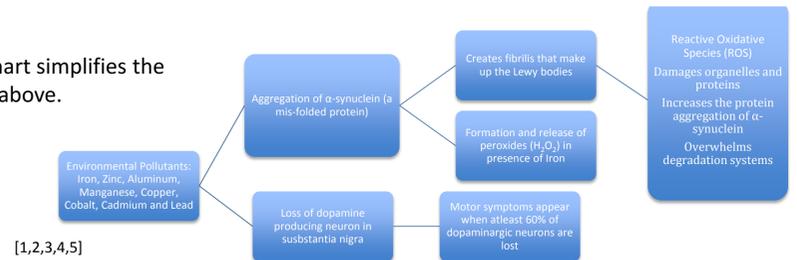
15

## MECHANISMS OF ACTION



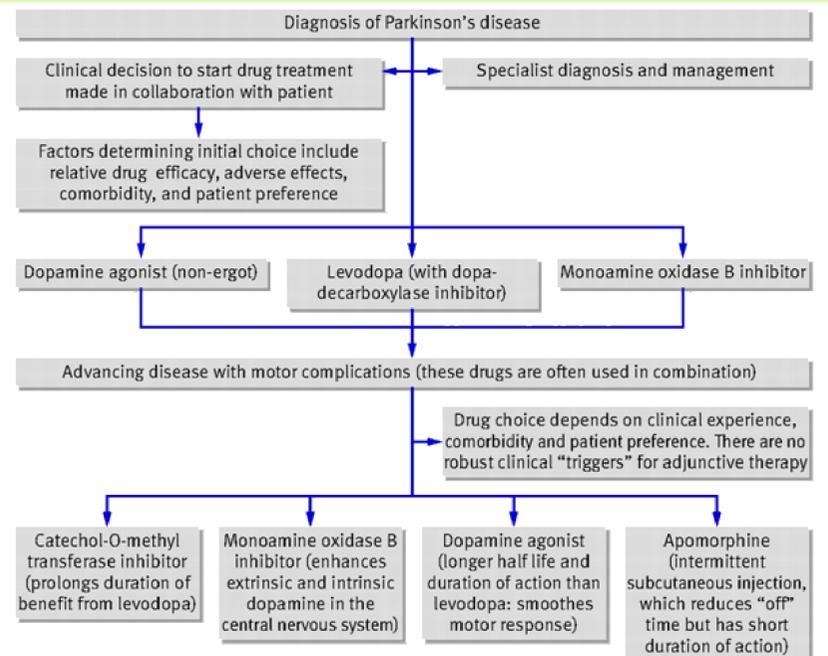
4

This flow chart simplifies the illustration above.



[1,2,3,4,5]

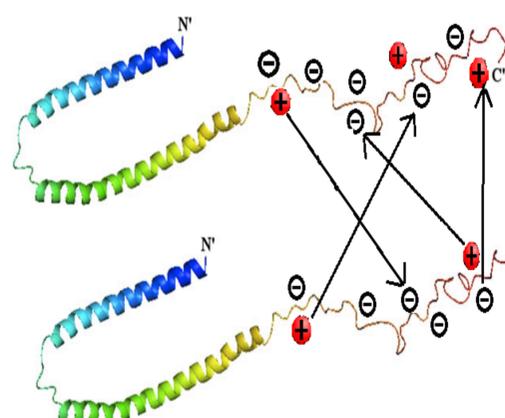
## DIAGNOSIS



[16]

## CONCLUSION

### Tangling of $\alpha$ -synuclein to Form Lewy Bodies



[8,18]

Present research relates environmentally relevant heavy metals to the development of neurodegenerative disorders such as Parkinson's disease. Metal cations such as iron, zinc, aluminum, manganese, copper, cobalt, lead, and cadmium aggregate the mis-folding of the  $\alpha$ -synuclein proteins. This result is most likely due to the ability of the metal cations to interfere with the naturally repelling, negatively charged, regions of the  $\alpha$ -synuclein protein, causing them to attract one another and become tangled. This effect, along with the ability of these metals to form ROS, leads to the formation of Lewy bodies. This further damages cell organelles and proteins leading to formation of more fibril containing Lewy bodies which are a key feature in Parkinson's disease [17].

## CITATIONS

- Agrawal, M., Biswas, A. (2015). Molecular diagnostics of neurodegenerative disorders. *Frontiers in Molecular Biosciences*. 2: 1-8. doi: 10.3389/fmolb.2015.00054
- Arita, A., Costa, M. (2009). Epigenetics in metal carcinogenesis: Nickel, Arsenic, Chromium and Cadmium. *Metallomics*. 1:222-228. doi: 10.1039/b903049b
- Migliore, L., Coppede, F. (2008). Environmental-induced oxidative stress in neurodegenerative disorders and aging. *Mutation Research*. 674: 73-84. doi:10.1016/j.mrgentox.2008.09.013
- Chin-Chan, M., Navarro-Yepes, J., Quintanilla-Vega, B. (2015). Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Frontiers in Cellular Neuroscience*. 9:1-15. doi: 10.3389/fncel.2015.00124
- Luong, K., Nguyen, L. (2013). Environmental factors in Alzheimer's and Parkinson's diseases. *J Alzheimer's Dis Parkinsonism*. 3: 1-12. doi: 10.4172/2161-0460.1000119
- Willis, A., Evanoff, B., Lian, M., Galarza, A., Wegzyn, A., Schootman, M., Racette, B. (2010). Metal emissions and urban incident Parkinson disease: A community health study of Medicare beneficiaries by using geographic information systems. *American Journal of Epidemiology*. 172: 1357-1363. doi: 10.1093/aje/kwq303
- White, A., Kanninen, K., Crouch, P. (2015). Editorial: Metals and neurodegeneration: restoring the balance. *Frontiers in Aging Neuroscience*. 7: 1-2. doi: 10.3389/fnagi.2015.00127
- Uversky, V., Li, J., Fink, A. (2001). Metal-triggered structural transformations, aggregation, and fibrillation of human  $\alpha$ -synuclein. *The Journal of Biological Chemistry*. 276: 44284-44296. doi: 10.1074/jbc.M105343200
- Mitra, J., Guerrero, E., Hegde, P., Wang, H., Boldogh, I., Rao, K., Mitra, S., Hegde, M. (2014). New perspectives on oxidized genome damage and repair inhibition by pro-oxidant metals in neurological diseases. *Biomolecules*. 4: 678-703. doi:10.3390/biom4030678
- Wang, S. (2010). How Parkinson's Alters the Brain. *The Wall Street Journal*. Retrieved from <http://www.wsj.com/articles/SB10001424052748703748904575411662795000790>
- Church, F. (2015). Overview of Neurodegenerative Disorders. *Journey with Parkinson's*. Retrieved from <http://journeywithparkinsons.com/category/research/>
- Willis, A., Evanoff, B., Lian, M., Criswell, S., Racette, B. (2010). Geographic and Ethnic Variation in Parkinson Disease: A Population-Based Study of US Medicare Beneficiaries. *Neuroepidemiology*. 34(3): 143-151. doi: 10.1159/000275491
- Smith, D.B., Cannon, W.F., Woodruff, L.G., Solano, Federico, and Ellefsen, K.J., 2014. *Geochemical and mineralogical maps for soils of the conterminous United States: U.S. Geological Survey Open-File Report 2014-1082*, 386 p., <http://dx.doi.org/10.3133/ofr20141082>.
- Campbell, A. (2005). Inflammation, Neurodegenerative diseases, and environmental exposures. *Annals of the New York Academy of Sciences*. 1035: 117-132. doi: 10.1196/annals.1332.008
- Klassen, Curtis D. "Absorption, Distribution, and Excretion of Toxicants." *Casarett and Doull's Toxicology: The Basic Science of Poisons*. 7th ed. New York: Mc Graw Hill, 2008. 132. Web. doi: 10.1036/0071470514
- Parkinson's disease. (2010). *Neurology*. Retrieved from <http://www.gp-training.net/protocol/neurology/parkinsons.htm>
- Montes, S., Rivera-Mancia, S., Diaz-Ruiz, A., Tristan-Lopez, L., Rios, C. (2014). Copper and iron proteins in Parkinson's disease. *Oxidative Medicine and Cellular Longevity*. 2014: 1-15. doi: 10.1155/2014/147251
- Ritchie, C., Thomas, P. (2012). Alpha-synuclein truncation and disease. *Health*. 4: 1167-1177. doi: 10.4236/health.2012.431175