The Basis and Basics of Common Neurological Diseases/Disorders

By Nathan Allen

With the population of the world now exceeding 7 billion people, there exist 7 billion people (even taking into account identical twins) who are genetically, and therefore biologically, unique (Casselman, 2008). And yet despite this extreme variation, who can say that they are neither related to, or know, someone who suffers from a neurological disease or disorder? Indeed, confining the neurological ailments strictly to Alzheimer's disease (AD), Parkinson's disease (PD), and Major Depressive Disorder (MDD) doesn't greatly diminish that number. Alzheimer's alone accounts for ~70% of dementia cases and approximately 1 in 9 older Americans suffer from Alzheimers (Alz. Assoc., 2014). Approximately 60,000 people in the United States are diagnosed with Parkinson's every year, and around 6.9% of U.S. adults experience at least one major depressive episode each year (Major Depress., 2012). Due to the ubiquity of these problems nearly every person either is or has the potential to be, effected by these diseases at some point in their life and thus knowledge of the symptoms is critical. Additionally, understanding the complexity of these problems allows one to see why these are dilemmas that are not so easily solved, and thus why they are still so prevalent.

What is/are the neurological basics and basis of Alzheimer's?

Interestingly, symptoms of AD, like PD and MDD, are more well-known then their method of disruption in the CNS (central nervous system) and PNS (peripheral nervous system). The CNS incorporates the nervous system of the brain and spinal cord and the PNS everything else outside of these two domains; namely, the nerve fibers that come from the spinal cord and reach out to all other parts of the body. Alzheimer's is an extensive disease and its symptoms are as well known: short-term memory loss, social withdrawal, spatial and temporal confusion, difficulty completing common tasks, and mood disruption such as apathy and depression (Park. Stats., 2013). Alzheimer's Disease is thought to have both genetic and non-genetic risk factors, as Alzheimer's Disease that is prevalent before the age of 65, known

as early-onset Alzheimer's Disease, has been found to be genetically linked; whereas regular Alzheimer's has not (Campion 1999).

At the neuronal level, Alzheimer's disease is characterized by a loss of neurons and synapses in the cerebral cortex of the brain which leads to degradation of the temporal and parietal lobes as well as the frontal cortex (Wenk et al., 2003). Neurons, which are the specialized cells of the nervous system, form connections with other neurons called synapses that allow these cells to talk to each other. It is these cells that are packed into the often-seen wrinkly outer layer of the brain, the aforementioned cerebral cortex.

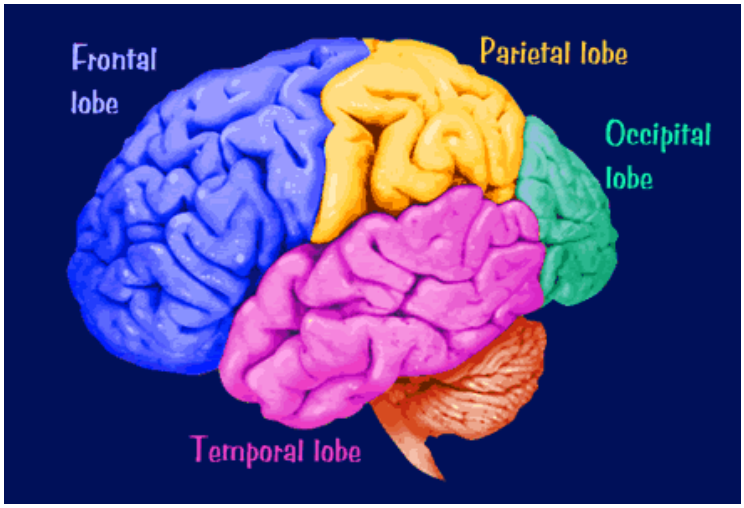

Fig 1. The four lobes of the brain. The wrinkly outer surface with bumps and grooves seen here is the cerebral cortex, which contains billions of neurons (from http://morphonix.com/software/education/science/brain/game/specimens/images/cerebral_cortex_lobes.gif.).

In addition to general brain changes, Alzheimer's Disease is characterized by a malfunction of certain proteins called amyloid plaques and neurofibrillary tangles. Proper protein function and structure is critical to health as proteins are the building blocks of the body, and these amyloid plaques are clumps of a specific protein called beta-amyloid which are a result of a protein function gone awry. In AD these plaques interfere with the communication between neurons and can cause inflammation. Neurofibrillary tangles occur when another protein called tau has its structure changed by a chemical in the body, and

forms tangles with other tau proteins. Originally, these proteins structurally strengthen microtubules, which act like the skeleton of the cell, and are commonly found in the axons of neurons (see picture).

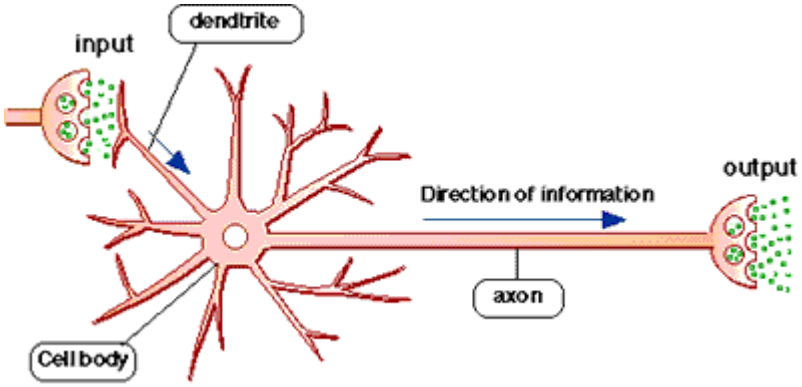

Fig 2. A general view of a neuron. The long skeleton-like microtubules extend the length of the axon like thin wires and tau proteins reinforce them, sort of the mortar between bricks. The green dots represent neurotransmitter released from circular vesicles (from http://www.med.nagoya-u.ac.jp/Yakuri/projects_e/projects_e03-01.gif)

Again, this causes cell communication disruption and inflammation. Since a neuron's form of communication is transmitted by traveling down the axon, its stability is essential, and both the microtubules and tau reinforce this. While these tangles and amyloid plaques are found in the brains of patients who suffer from AD, it is not currently certain how these factors accelerate or begin the progression of the disease.

What is/are the neurological basics and basis of Parkinson's?

Many are already familiar with the several physical impairments of Parkinson's from exposure to celebrities such as Michael J. Fox and Muhammad Ali. These include: tremors of the hand and limbs, taut and stiff muscles, alterations in speech fluency and speed, and overall slowed movement (Park. Stats., 2013). Parkinson's Disease, much like Alzheimer's, has an unknown direct cause. Fortunately, the physical effects of PD have been correctly attributed to the death of neurons that produce the neurotransmitter dopamine, called dopaminergic neurons, in the substania nigra of the brain (Kandel, 2013). Neurotransmitters are the chemical compounds manufactured in the body that are transferred across the synapse; specifically, neurotransmitters are released from storage compartments called vesicles

in one neuron onto the synaptic cleft that bridges two neurons together (see Fig 2). The effect on the post-synaptic neuron, the neuron that is being showered with neurotransmitter, depends on the type of neurotransmitter being released.

Unfortunately, the cause of death of these critical dopaminergic neurons is unknown; although, inclusions of structures called Lewy bodies are often found in the substantia nigra of patients who have suffered from PD, where they disrupt vital functions such as cell transport and membrane trafficking (Kandel, 2013). Lewy bodies form from a cluster of the protein α-synuclein, which are typically soluble (dissolvable) parts of the cell; however, in those with PD it becomes insoluble and forms a spherical shape. As mentioned, the cause of PD is unknown and continues to be highly debated; although, most researchers agree that PD, like Alzheimers, has both a genetic and environmental risk factor. Constant exposure to pesticides has been shown to cause Parkinson's-like effects in mice; e.g., the common pesticide Rotenone is used in laboratories for inducing a Parkinson's-like model in the animal for testing, and thus much caution should be used when dealing with, or being exposed to, pesticides (Carboni et al., 2004).

Due to the knowledge of the dopamine deficiency in PD patients, L-DOPA treatments for sufferers has been widely and successfully used for the characteristic motor effects in PD. L-DOPA is a precursor to dopamine in dopaminergic neurons in the body, and, much like having more batter to make more cake, supplying more L-DOPA to dopaminergic cells assists them in making more dopamine. This allows the dopaminergic neurons which have survived in PD patients to produce more dopamine to help counter the effect of having less of these dopamine-producing neurons.

What is/are the neurological basics and basis of MDD?

Depression is one of the most widespread diseases in the world and thus symptoms are variable but most often include: recurring sad feelings, lack of motivation, fatigue, loss of interest in previously enjoyable activities, insomnia, suicidal thoughts, and either overeating or a lack of appetite (Major

Depress., 2012). While it has become commonplace to call someone depressed who may only be having a bout of melancholy, those with major depressive disorder suffer from extreme changes in their neuronal structures and balance that are both genetically and environmentally driven. One supported cause of major depressive disorder is altered levels of three integral neurotransmitters: serotonin, dopamine, and norepinephrine (Nutt, 2008). Serotonin is associated with feelings of happiness or pleasure, dopamine with motivational, motor, and reward systems, and norepinephrine with one's level of alertness. Many treatments for depression have therefore used symptom-specific therapies that dictate which neurotransmitter should be modified; i.e., if a patient reports lowered levels of motivation, the used therapy would target dopamine synthesis or up-regulation.

SSRIs, selective serotonin reuptake inhibitors, are medications often used in the treatment of depression. These work by prolonging the effect of serotonin at the synaptic cleft. All neurotransmitters have some method of removal from the synaptic cleft, whether it be through macroglia known as astrocytes which recycle the neurotransmitters back into the neuron, or through transport proteins that "reuptake" the neurotransmitters back into the presynaptic neuron, as in the case of SSRIs. The SSRIs inhibit, or block, the transport action of the proteins responsible for "cleaning up" the serotonin at the synaptic cleft, thereby increasing serotonin's effect in the brain.

What's next for common neurological diseases/disorders

As can be gathered from the discussion above, identifying root causes of these common diseases and disorders is difficult as they all have both genetic and non-genetic factors; however, advanced methods of experimentation and brain analytical techniques allow progress to occur much quicker.

Recently, researchers successfully generated pluripotent stem cells from deceased Alzheimer's patient's tissues, allowing them to observe what occurs to the cells as the diseases progresses within them (NYSCF, 2014). Pluripotent stem cells are unique in that they can develop into any type of cell that's found in the body. Additionally, experimenters in the National Academy of Science enhanced dopamine

release in mice by increasing the expression of the gene VMAT2, vesicular monoamine transporter 2. This transporter is responsible for packing the monoamine neurotransmitters into the storage-like vesicles, allowing safe release at the synaptic cleft. They found that, exclusive to the monoamine transmitters (so disregarding amino acid transmitters such as glycine and glutamate), increasing the VMAT2 gene in mice caused higher synthesis of the transport proteins, which increased the size of the vesicles and therefore the amount of dopamine available for release by each vesicle (Lohr et al. 2014). While still at the animal stage, this process could prove invaluable for increasing neurotransmitter release for the deficient. In the scope of PD, sufferers may have their symptoms alleviated by medical marijuana, as a study from 2014 found that inhaled cannabis greatly assisted in the control of tremors, rigidity, and bradykinesia (Lotan et al., 2014).

As analysis techniques become more refined and the education of these disorders more widespread, so too will the treatment and success rate of dealing with Alzheimers, Parkinsons, and Major Depressive Disorder. Understanding the root of, and complexity within, each of these diseases is key to understanding the diseases themselves, and also paints a larger picture as to why these diseases and disorders have gone so long uncured. It is only through education, such as pesticide exposure being a potential cause of Parkinsons, and research, such as increasing VMAT2 expression, that some of these ailments could be prevented and in some instances, cured.

Works Cited

Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 10, Issue 2.

Caboni P, Sherer TB, Zhang N, Taylor G, Na HM, Greenamyre JT, Casida JE. Rotenone, deguelin, their metabolites, and the rat model of Parkinson's disease. Chem Res Toxicol. 2004 Nov;17(11):1540-8. PubMed PMID: 15540952.

Campion, Dominque (1999). "Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum.". *American Journal of Human Genetics* **65** (3): 664–670.

Kandel, E. (2013). *Principles of neural science* (5th ed.). New York: McGraw-Hill.

Lohr KM, Bernstein AI, Stout KA, Dunn AR, Lazo CR, Alter SP, Wang M, Li Y, Fan X, Hess EJ, Yi H, Vecchio LM, Goldstein DS, Guillot TS, Salahpour A, Miller GW. Increased vesicular monoamine transporter enhances dopamine release and opposes Parkinson disease-related neurodegeneration in vivo. Proc Natl Acad Sci U S A. 2014 Jul 8;111(27):9977-82. doi: 10.1073/pnas.1402134111. Epub 2014 Jun 16. PubMed PMID: 24979780; PubMed Central PMCID: PMC4103325.

Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clin Neuropharmacol. 2014 Mar-Apr;37(2):41-4. doi: 10.1097/WNF.0000000000000016. PubMed PMID: 24614667.

Major Depression with Severe Impairment, 2012, http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-with-severe-impairment-among-adults.shtml

Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. J Clin Psychiatry. 2008;69 Suppl E1:4-7. Review. PubMed PMID: 18494537.

NYSCF SCIENTISTS MAKE LIVING BRAIN CELLS FROM DECEASED ALZHEIMER'S PATIENTS BIOBANKED BRAIN TISSUE, 2014, http://nyscf.org/pdfs/NYSCF%20PR%202014-01-07%20Acta%20Neuropathologica%20-%20Alzheimers%20Dura%20Matter.pdf

Statistics on Parkinsons, 2013, http://www.alz.org/downloads/Facts_Figures_2014.pdf.

Wenk GL. Neuropathologic changes in Alzheimer's disease. J Clin Psychiatry. 2003;64 Suppl 9:7-10. Review. PubMed PMID: 12934968.

Zou K, Gong JS, Yanagisawa K, Michikawa M (June 2002). "A novel function of monomeric amyloid beta-protein serving as an antioxidant molecule against metal-induced oxidative damage". *J. Neurosci.* **22** (12): 4833–41.