

The Frozen Addicts Lesson Plan

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Piedmont Project Introductory Paragraph

I had known about the “frozen addicts” for over a decade now, and I was very comfortable discussing the molecular and chemical aspects of the story. A few years ago, I found the PBS NOVA special from 1986 which put the story of the addicts in context within the movement to consider environmental chemicals as influencing Parkinson’s disease susceptibility. Even then, I was still more comfortable thinking quite strictly about the neuroscience of Parkinson’s disease with my students. I used the context and techniques I learned from both the graduate and faculty Piedmont Project fellowships to take the students from a detached discussion of “toxins” to a more personal exploration of what toxins they can buy themselves. Further, by checking with their parents, students learn they’ve likely been exposed to many of these chemicals too. The powerful connection of the chemistry, neuroscience and personal experience makes this lesson much more effective.

Abstract

This lesson in the form of an interrupted case supports students while they explore the mystery of the summer of 1982 when seven California heroin users mysteriously and suddenly developed Parkinson’s disease. By watching the NOVA video about the mystery, and stopping briefly for class discussion and mini-lectures, the students explore the neurobiology of Parkinson’s disease symptoms along with the striking evidence that environmental toxins can contribute to Parkinson’s disease susceptibility. By extending the lesson to a second class period, the class explores pesticides and other chemicals in their environment and the possible impacts on their neurological systems due to the exposures. Further research and discussion brings the class to the current ideas about gene-environment interactions and considerations for current Parkinson’s treatments and research. Designed for two class periods of 2.5 hours each, this module is appropriate for advanced high school students or early undergraduate students.

Lesson Topics

Gene-environment interactions in disease development

Genetic influences on Parkinson’s disease development

Environmental influences on Parkinson’s disease development

Parkinson’s disease symptoms

Parkinson's disease pathology
Motor systems circuitry
Basal Ganglia influence on movement
Parkinson's disease treatments
Catecholamine biosynthesis and metabolism with focus on dopamine
Laws regulating drug synthesis and distribution with a focus on illegal drugs of abuse
Ethical and social influences on scientific and healthcare decisions

Resources for implementation

Required online resources

In-class video from WGBH streamed online:

The Frozen Addict, NOVA 1986

http://openvault.wgbh.org/catalog/V_474CF2C8A20B4173988486AC4C605A3C

Out of class video from PBS streamed online:

My Father, My Brother and Me, PBS FRONTLINE

<http://www.pbs.org/video/1082086931/>

Optional resources for instructors or students

Detailed account of the Frozen Addicts story told in non-technical language for a widely accessible summary with updates on current (2014) concepts and treatments-

The Case of the Frozen Addicts

Langston and Palfreman January 2014 264 pages IOS press.

<http://www.iospress.nl/book/the-case-of-the-frozen-addicts/>

First published peer-reviewed technical report on the MPTP patients-

Langston JW, Ballard P, Tetrad JW, Irwin I. 1983 *Science*. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Feb 25;219(4587):979-80.

<http://www.ncbi.nlm.nih.gov/pubmed/6823561>

Online textbook chapter on Basal Ganglia circuitry-

Chapter 18 "Circuits within the Basal Ganglia System" *Neuroscience*. 2nd Edition.

Purves D, Augustine GJ, Fitzpatrick D et al. editors. Sinauer Associates, 2001.

<http://www.ncbi.nlm.nih.gov/books/NBK10847/>

Online textbook chapter on Catecholamines-

Chapter 12 "Biosynthesis of Catecholamines" by Kuhar MJ, Couceyro PR, Lambert PD.

Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th Edition. Siegel GJ, Agranoff BW, Albers RW et al. editors. Lippincott-Raven, 1999.

<http://www.ncbi.nlm.nih.gov/books/NBK27988/>

Technical reviews of gene-environment interactions in Parkinson's disease-

Cannon JR and Greenamyre JT 2013 *Neurobiology of Disease*. Gene-environment interactions in Parkinson's disease: specific evidence in human and mammalian models. Sep;57:38-46.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3815566/>

Ritz BR, Paul KC, Bronstein JM 2016 *Current Environmental Health Reports*. Of pesticides and men: a California story of genes and environment in Parkinson's disease.

Mar;3(1):40-52.

<http://www.ncbi.nlm.nih.gov/pubmed/26857251>

Implementation Plan

Instruct the students to watch the video as if it were a case study. Ask them to take notes on terms and concepts creating a chart of two columns: “know” and “don’t know”. Remind them to choose ideas that interest them!

Play the video here:

http://openvault.wgbh.org/catalog/V_474CF2C8A20B4173988486AC4C605A3C

Begin at 0:00

Man in his 40s frozen.

Prisoner at local jail awakens frozen

JW Langston, MD

Wilson’s disease [copper accumulation] similar but quite different says JWL

Mentally normal

Can write some...

Case history reveals heroin addict

Bad batch of synthetic heroin

George and Juanita

PD symptoms touched on shallowly

Age of onset over 50, gradual onset

Other neurologist talking to other neurologist

Young brothers found frozen – video

Also heroin user

Bad heroin press conference

Video of Connie and Toby

5:52 stop here and have use these Discussion Questions:

Define the problem.

7 cases of heroin users with sudden Parkinson’s disease

Describe the symptoms of Parkinson’s disease (even though covered very briefly)

Burning sensation

Freezing up

Shaking in hand

Inability to speak

Occurs gradually in people over 50

How are the symptoms of this type of movement disorder similar and different to the types of problems with movement you’ve learned about before?

Compare and contrast with rigid paralysis, flaccid paralysis, SCI, reflexes...

Draw a diagram (as in stick figure) detailing what you know about the ‘motor system’ from a neuroscience – perhaps focus on ‘voluntary’ movement...

NMJ, spinal cord, motor cortex?

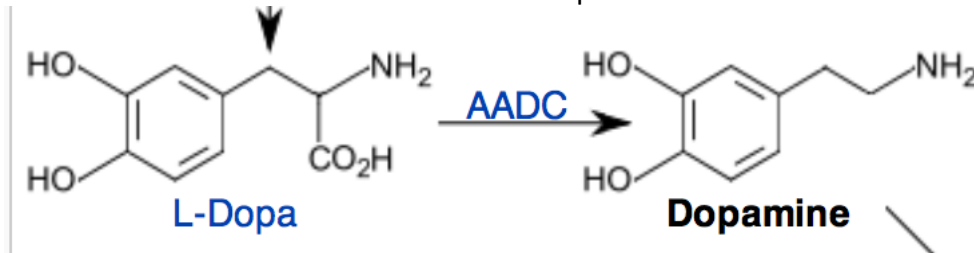
See appendix for what the class white board might look like after this discussion.

Begin again, lots of criminal and legal stuff.

Heroin from opium poppy
Synthetic opiates & designer drugs
Analytical chemistry and unknown substance
12:27 begin more Patient videos
LDOPA and effects around 15:50
Description of SN and disease

15:09 stop here. Discussion questions:

What is LDOPA and how does it relate to Dopamine?



Does taking LDOPA as a pill increase DA in the SN specifically or everywhere in the body?
If DA is increased everywhere, can you think of any unwanted side effects of this treatment?

Very Mini lecture touching on DA systems and connecting Basal Ganglia to Motor Cortex.

<http://www.ncbi.nlm.nih.gov/books/NBK10847/>

See appendix for example white board at this point in the discussion.

Begin the video again.

15:30 ish, article and description of drug synthesis and MPTP

If you need to save time, can skip to 27:00, but you must name MPTP since you've skipped the 'MPTP' discovery part.

Also around 17:30 see injections of rats with MPP+ (heads up for sensitive students)

Description of synthetic drug and PD

MPTP in rats show no effect, and role of primates and animal models in general

[25:15 ish: Can take a minute to emphasize role of models for disease study]

27:00 Clinical PD details and meet Connie in more detail.

Dyskinesias and side effects of LDOPA

Stop at 30:00 pause to build know/don't know lists

include MPTP details, questions about LDOPA side effects, and genetic vs. environment

Again, appendix includes a third example whiteboard image.

30:00 start again focusing on environmental exposures

Note that some of the evidence AGAINST genetic is dated and now the theory is much more about gene-environment interactions. This is specifically important to pair with the more modern story in the homework video "My Father, My Brother and Me."

42:00 ish minutes begins the herbicide and pesticide link

46:00 ish, discussion of protective effects of MAO inhibitors

50:00 ish, therapeutic ideas from the 80s

MAO inhibitors and PET imaging of DA systems

Cell transplants

52:40 laws at state and national level

53:00 caught the guy who spread the MPTP and was actually treated by Langston.

End at 55 minutes. Discussion ideas?

Generate a list of questions and concerns – scary thoughts!

Other things that might be interesting to bring up (not in the video):

Smoking inverse relationship

Caffeine inverse relationship

Men more common than women

Pesticide exposure, rural living, well water correlated with higher risk

Thoroughly discuss homework assignments.

Homework- check out the active ingredients in pesticides and herbicides you could buy for your home garden/lawn. Or call your parents and ask them to read you the active ingredients in the pesticides/herbicides at your house (what have you been exposed to???)! Find at least 3 different products and at least 3 different active ingredients. Try to find at least one that is 'all natural' or 'organic' but be sure to identify the active ingredient in each.

Homework- watch "My Father, My Brother, and Me" from PBS Frontline.

<http://www.pbs.org/video/1082086931/>

We now know PD certainly has genetic factors as well. Check out the sources on the Frontline website as well. Bring at least 3 comments/questions about the video to next class.

Next class, Day 2:

Recall discussion from last class. Review stick figure picture of motor systems.

Thinking about homework and environmental influences on disease. Contextualize – lots of things are toxic in high enough doses...Not killing pests can be an important health issue itself (malaria, west nile, etc)...insects are TINY and much more sensitive in general than mammals. Bioaccumulation and persistence in the environment is also important to consider- even if super toxic initially, what is exposure likely to be in practice?

Review and discuss active ingredients found by the students in their homework.

Some they found included:

Abamectin

Acephate (organophosphate) <http://www.biomedcentral.com/1471-2377/8/6> Hancock et al 2008. AChEI

Benefin

Tetramethrin (Pyrethroids v gated NaChannels)

Cypermethrin

Imiprothrin

Phenethyl propionate

Phenothrin
Phallethrin
Glyphosate (Roundup)
Sevin (AchEI)
Carbamates (AchEI)
Rosemary oil, cinnamon oil, etc?
DEET irritating odor and also AchEI

Major players to discuss-

AchEIs including Organophosphates, Carbamates, Sevin, DEET*

Vgated NaChannel effectors including Pyrethroids – natural and synthetic
Chrysanthemum flowers

Rotenone

Paraquat

Considering not everyone gets the PD even with these environmental insults, clearly genes are important too!

Discuss questions/comments from My Father, My Brother and Me.

In small groups, focus on the family and genes aspect of PD that this video added to what we saw with in the Frozen Addicts story. Goals to get them to consider

Genetic forms of PD – monogenetic causes.

Genetic influences on PD – susceptibility

Again, gene-environment interactions

In class jigsaw. Each student will be an expert in their home group of 3-4 students. In their 'working group' (4 groups of 5-6), each group will consider one of the major treatment strategies discussed in My Father, My Brother, and Me.

Pharmacology/Drug therapies

Exercise

Deep brain stimulation

Cell based therapies (stem cell, fetal cell)

In about 45 min of group research, create a google doc for each treatment strategy. Consider at least these issues:

Basic biological mechanisms of HOW this therapy works

Current status of this therapy (research only?, clinically available?)

Side effects, risks & benefits

Come together back in home group to consider a patient story. Present briefly to class.

Example patient stories in appendix.

Appendix

In class discussions as we stopped the movie, we added to the boards with questions, comments, and mini-lecture material. For each period of discussion, notes were added in different colored markers:

First break = purple

Second break = green on two boards

Third break = black

Fourth break = red on two boards

Main Board 1

Know

PD varies w/ geography prevalence

Symptoms: → look like PD >50 (55)

- Can't move
- Shaky (tremor)
- Can't talk
- Burning Sensation
- Sudden onset → PD slow onset 1-2 years before going to clinic
- "mind" seems okay
- mPTP → animal model to treat & cure
- all patients used heroin

akinesia
bradykinesia
stiffness
masked faces

local area of CA

Unknown drug - Not heroin
Drug must have affected SN
DA → L-DOPA evidence

Can't arrest bad chemist
SN degenerates in PD

Heroin is derived from opium poppies = opiate
morphine → heroin

MPTP Made by accident in quest for synthetic opiate
too much bad stuff

Not MPTP itself but MPP+ metabolite
MAO does this

MPP+ looks like herbicide + pesticides

Organic? better?

Don't know

L-DOPA test for PD?

Side effects if natural? Does heroin use for PD lead to PD?

What parts of CNS are affected in PD?

Has there always been PD? geographic? → & Heroin?

First time worse?

What chemical is it?

* Is L-DOPA treatment long term?

Does L-DOPA work better in these young people than PD?

Cell transplants

Motor Cortex

Substantia nigra

Motor neuron

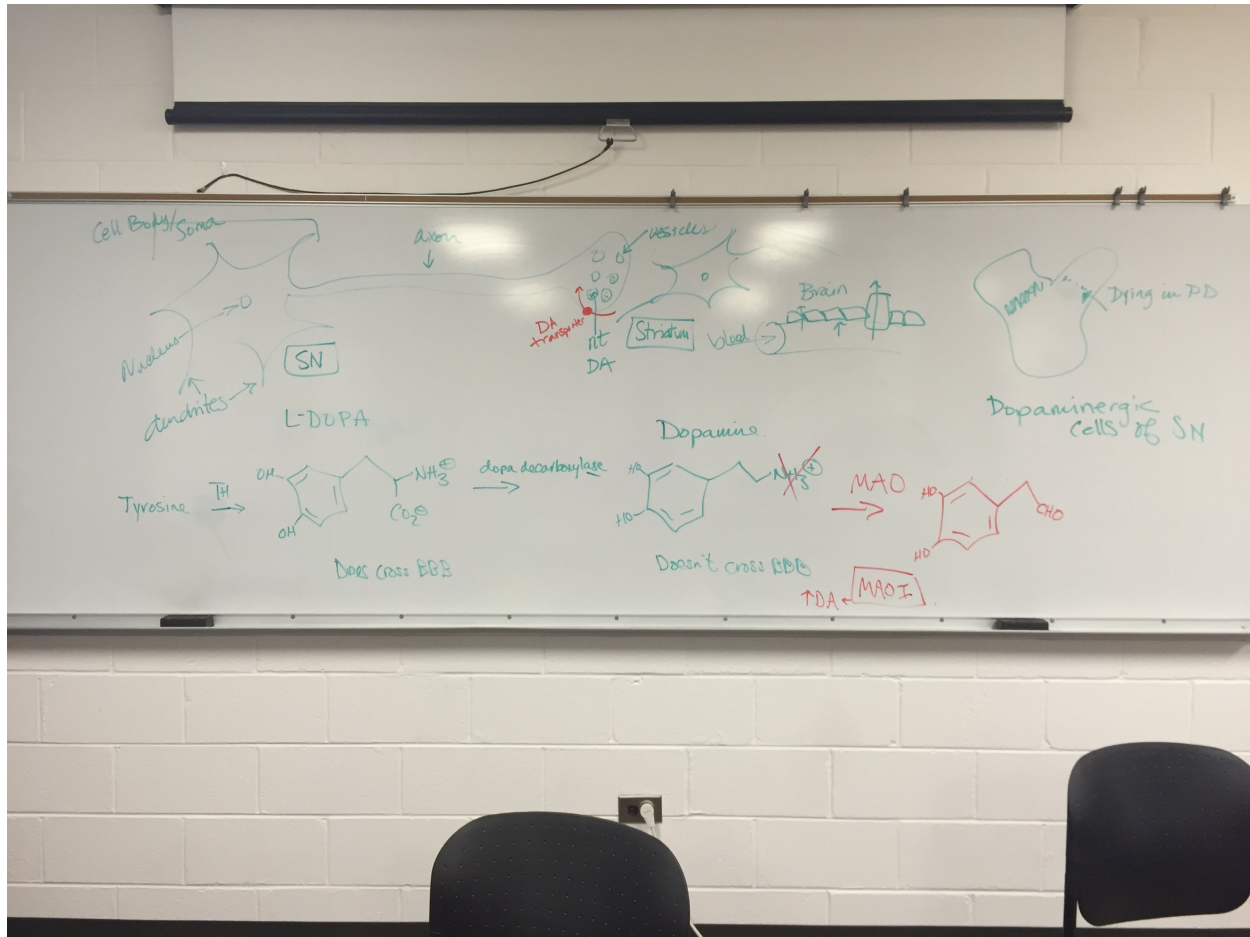
genes → environment

α-Syn: 100%
tau: 100%

PIPT: 100%

My father, My Brother Same

Side board 2



Example Patient Cases for consideration on Day 2:

Patient 1

Linda is a friend of your aunt and at Thanksgiving dinner, your aunt has asked you to help her understand what's going on with Linda. She tells you that Linda has been depressed for the last year or so and has been struggling to keep her depression in check. Just recently though, Linda's noticed mild tremors and stiffness in her muscles. Although mild, the symptoms are enough to make her see a physician. Linda is about 70 years old and has no family history of Parkinson's disease, but her physician suspects PD and has recommended that Linda see a neurologist right away. Your aunt wonders could this really be Parkinson's disease? What kinds of treatment options does Linda have? Your aunt wonders what to expect going forward.

Patient 2

Charlie is a friend of your Dad's from college. You've known him forever and your family regularly goes camping with his family, so you even know his kids. Charlie has a successful small business and is in the prime of his life. You remember that a while back Charlie was diagnosed with Parkinson's disease, but you've almost forgot since his therapies have been working quite well. He is now 50 years old and has had the disease for about 5 years, but now he's developing pretty severe side effects to the drug therapy that has been working well until now. Your dad is really worried about Charlie and he's asked you what you've learned about PD in your NBB class. Your dad tells you that Charlie's father and grandmother also had PD and everyone is worried about Charlie's kids. He's looking for a better understanding of what PD drug therapies are and what else Charlie might consider in order to stay active and involved in work and family. Will the drugs ever work again? Are there other drugs or other treatment options? Are Charlie's kids going to have PD too?

Patient 3

Reggie is your next-door neighbor and friend from church. He's 75 years old and he's been a great neighbor and fixture in your community your whole life. His 4 grown kids all live out of state, but they check in with your family whenever they come to visit. Reggie loves the neighborhood and he takes great pride in his beautiful house and yard, but his kids are concerned that he may have to move in order to be closer to them. Reggie has had PD for several years and although the drug therapies worked well for several years, the drugs are now very hard to manage and Reggie is having a lot of side effects. Reggie's son tells your dad that no one in the family has ever had PD and the family isn't sure how to cope or what to do next. Your dad's really worried about Reggie and wonders what to expect going forward. Are there other treatments that could help Reggie? Will he be able to live alone and keep up his home?