Neuroprotection, Plasticity and Compensation: What about Speech?

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Disclosures

Dr. Fox receives lecture honorarium and has ownership interest in LSVT Global, Inc; she receives lecture honorariums from various other medical and Parkinson organizations.

STATEMENT ON DISCLOSURE AND CONFLICT: All members of this researcl team have fully disclosed any conflict of interest and their conflict of interest management plan has been approved by the Office of Conflict of Inter and Commitment at the University of Colorado, Boulder.

Objectives of Presentation

Describe the concepts of Neuroprotection, Plasticity, and Compensation

Discuss these concepts as they relate to speech and Parkinson disease

Propose a conceptual framework integrating these concepts in speech and DBS, with a focus on rehabilitation

Introduce animal models of basal ganglia and vocal motor dysfunction

Neuroprotection - therapies that can slow, stop, or reverse the degenerative process of Parkinson disease

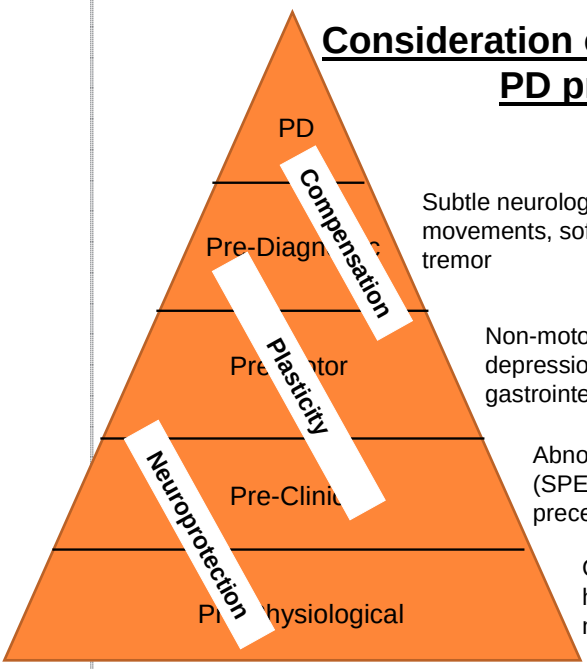
Plasticity - the adaptive capacity of the central nervous system

Activity-dependent neuroplasticity - modifications within the central nervous system in response to physical activity

Compensation – form of plasticity that utilizes alternative neural mechanisms to accomplish a behavioral goal (when primary mechanism fails)

Kleim, Jones, and Schallert, 2003; Petzinger et al, 2010

Consideration of these concepts in PD progression



Subtle neurological features: small, slow movements, soft, monotone voice, tremor

Non-motor features: olfactory loss, depression, cardiac, visual, gastrointestinal function, REM disorder

Abnormalities on imaging markers (SPECT); imaging abnormalities precede neural symptoms

Genetic mutations
high risk for PD; no motor or non-motor features of PD

Adapted from the Parkinson's Associated Risk Syndrome (PARS) Study
Stern MB, Siderowf A., 2010; Stephenson, R., 2008

Neuroprotection: Speech Early detection

Pre-diagnostic phase:

Evidence for early voice/speech dysfunction
(Aronson, 1990; Harel et al, 2004; Little, et al, 2008; Skodda, et al, 2009; Stewart et al, 1995)

-Individuals perceived as bored, disinterested, apathetic

-"I've always been a soft talker"

Pre-Physiological Phase/Pre-Clinical Phase

Any correlation of genetic pre-disposition and early changes in speech/voice

Potential additive "predictive" value for eventual diagnosis of PD

Activity dependent Neural Plasticity: Speech

"Brain Health"

(Cotman & Berchtold, 2002)

Activity linked neurotrophic factor expression
Neurogenesis
Synaptogenesis
Pre-synaptic/post-synaptic modulation
Glucose utilization
Immune system changes
Angiogenesis

Advances in neuroscience suggest that exercise may modify disease progression

Tillerson JL, Cohen AD, Philhower J, Miller GW, Zigmond MJU, Schallert T (2001) Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. J Nrsc 21(12):4427-4435

Tillerson JL, Cohen AD, Caudle WM, Zigmond MJ, Schallert T, Miller GW (2002) Forced nonuse in unilateral parkinsonian rats exacerbates injury. J Nrsc 22(15):6790-6799

Cohen AD, Tillerson JL, Smith AD, Schallert T, Zigmond MJ (2003) Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF. J Neurochem 85:299-305

Tillerson, JL, Caudle, WM, Reveron,& Miller, GW. (2003). Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. J Nrsc (119): 899-911.

Kleim, JA, Jones, TA, & Schallert, T. (2003). Motor enrichment and the induction of plasticity before or after brain injury. Neurochemical Research, (28): 1757-1769.

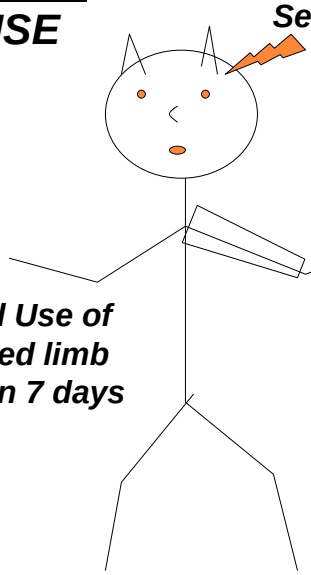
Fisher, Petzinger, Nixon, Hogg, Bremmer, Meshul, & Jankowec (2004). Exercise-induced behavoral recovery and neuroplasticity in the 1-Methyl-4-Phenyl1,2,3,6-Tetrahydropyridine-Lesioned Mouse Basal Ganglia. Journal of Neuroscience Research, 77, 378-390.

Smith AD, Zigmond MJ (2003). Can the brain be protected through exercise? Lessons from an animal modeo of parkinsonism. Exper Neurol 184:31-39

Anstrom KK, Schallert T, Woodlee MT, Shattuck A, Roberts DCS Repetitive vibrissae-elicited forelimb placing before and immediately after unilateral 6-hydroxydopamine improves outcome in a model of Parkinson's disease. Behav Brain Res 2007;179:183-191

Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, Turnquist P, Vuckovic M, Fisher BE, Togasaki DM, Jakowec MW Effects of treadmill exercise on

Experiment 1
Forced USE



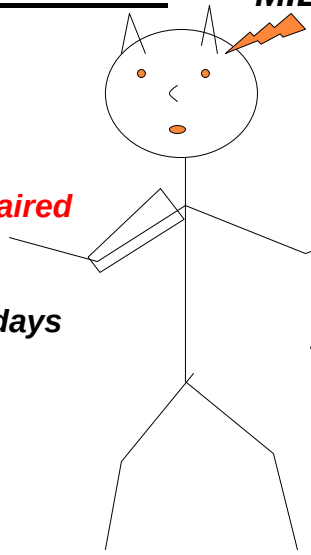
Severe unilateral injection 6-OHDA

Cast on non-impaired limb

Forced Use of impaired limb Duration 7 days

Early Onset Exercisers (Day 1 or Day 3) vs. Late Onset Exercisers (Day 7)

Experiment 2
Forced NON USE
Rats



MILD unilateral injection 6-OHDA

Cast on impaired limb

Duration 7 days

Inactivity began on Day 1 post lesion

Summary Exercise in PD

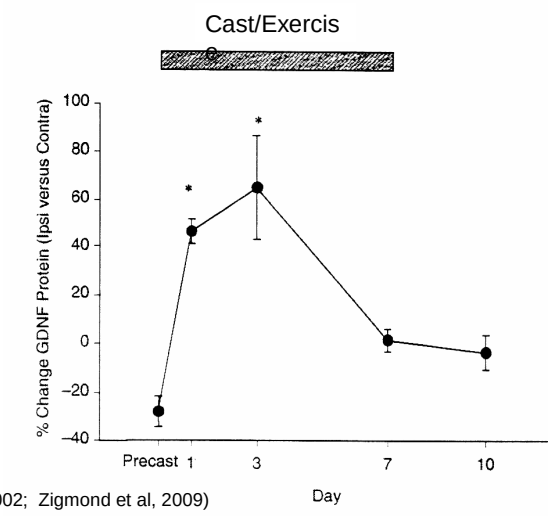
Exercise may slow the progression of PD and help the brain repair itself

- *by protecting the remaining DA neurons*
- *by restoring connections, signaling pathways*
- *by increasing reliance on undamaged systems (compensation)*

In an animal model lack of exercise exacerbates

- *behavioral asymmetry*
- *DA loss*

Mechanism: Exercise results in an increase in a neurotrophin (GDNF) in striatum may initiate a cascade of cellular events responsible for protecting vulnerable but not dead neurons



Tillerson et al, 2002; Zigmond et al, 2009)

Key principles that are important to optimize neural plasticity have emerged

(Dobkin et al, 2004; Fisher et al, 2004; Kleim & Jones, 2008; Kliem et al, 2003; Liepert, 2006; Petzinger et al, 2007)

Study neurobiological phenomenon related to functional recovery and to identify fundamental principles that may help to guide the optimization of rehabilitation

(Kleim and Jones, 2005)

Principles of Neural Plasticity

Intensity matters

Intensive practice is important for maximal plasticity (frequency, effort, force/resistance, and accuracy)

Complexity matters

Complex movements or environmental enrichment have been shown to promote greater structural plasticity

Repetition Matters

Induction of plasticity requires sufficient repetition (Kliem et al, 2004)
Acquisition not sufficient, need continued performance of skill for long-term structural

Salience matters

Practicing rewarding tasks (success/emotionally salient) activates basal ganglia circuitry

Timing matters

Injury creates fertile field for plasticity - need behavior to make it happen
Slow progression to non-impaired side

(Alexander et al., 1990; Fox et al., 2002; Graybiel 1998; Kliem et al., 2003; Kleim and Jones, 2005; Jones et al. 1999; Saint-Cyr JA, 2003; Tillerson et al., 2002; Vergara-Aragon et al., 2003; Black et al. 1990; Comery 1995; Fisher et al, 2004; Kleim et al., 2001; 1996; Perez et al. 2004; Pisani et al., 2005 Plautz et al., 2000)

Compensation: Speech?

Cellular compensation – changes in cellular function early in disease process

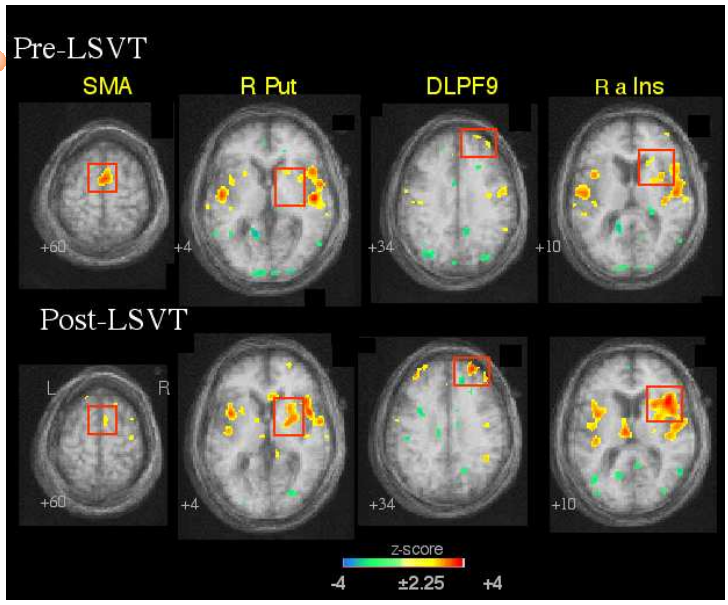
Behavioral compensation – changes in motor patterns (e.g., use of non-dominant, non-impaired limb)

Neurobehavioral compensation - changes in neural function related to behavioral compensation

-Undirected (potential for undesirable patterns)
-Directed (e.g., behavioral intervention)

Compensation: Speech?

Liotti, Ramig, et al, 2003



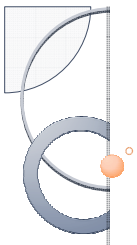
Conclusions: Imaging

Narayana, Fox, Ramig, et al, 2009

Top down modulation

- *The primary effect of LSVT LOUD consist of tw major components:*
  1. *effects on speech motor regions*
  2. *effects on multimodal association areas*

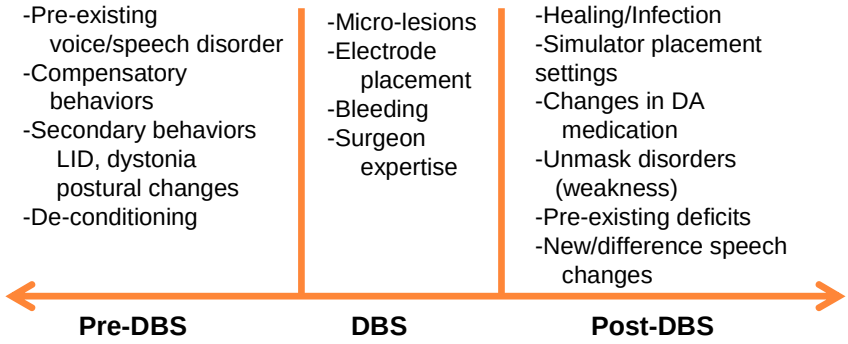
- *Right sided shift in motor, premotor and multim sensory integration areas*



Neuroprotection, Plasticity, Compensation and Speech:

What about in DBS?

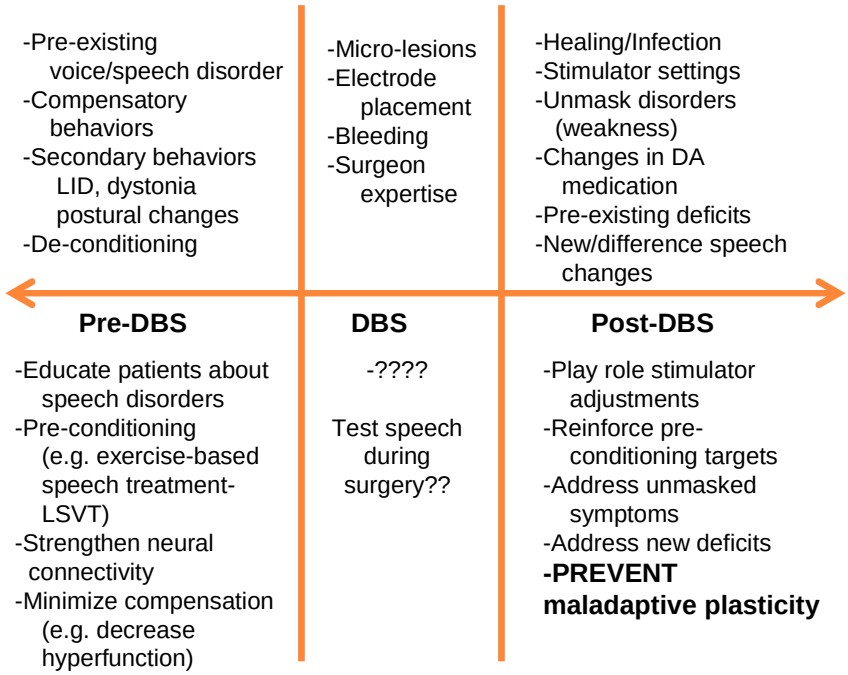
Typical/natural course for DBS



Opportunity – when to intervene?

Before?
During?
After?

Typical/natural course for DBS



Opportunity – WHEN to intervene post-surgery?

<u>Timing</u> "Injury creates fertile field for plasticity - need behavior to make it happen"

Opportunity to "imprint" normal or improved movement patterns in conjunction with STN-DBS immediately

(Kliem et al, 2003Shan, Zhu, Mungall, Johnson, 2003; Trost et al

Unique Opportunity to Maximize plasticity

Use behavioral intervention to "guide" neural plasticity and/or behavioral functioning in response to high frequency stimulation with STN-DBS

Combination of therapies:

-pharmacological therapies

-neurosurgical interventions

-behavioral interventions

(Adkins-Muir & Jones, 2003; Daffau, 2006; Ramie, Emerick, Bollnow, O'Brien, Tsai, Kartje, 2006; Boyd, Vidoni, Daly, 2007)

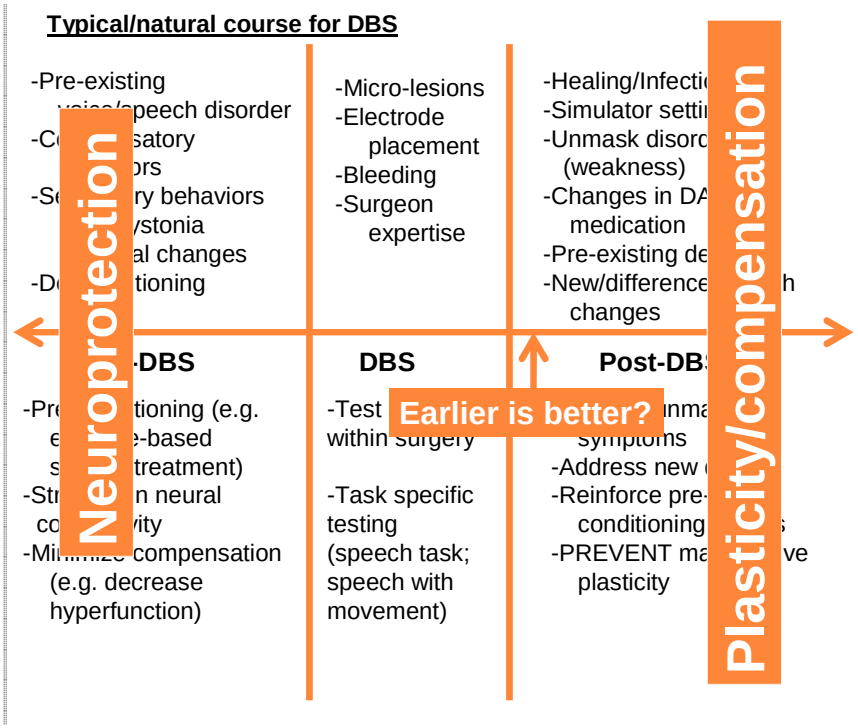
Paradigm Shift

Do not wait for manifestation of declines in speech

-chronic stimulation

-further disease progression

Engage in early behavioral intervention and perhaps prevent or delay onset of these later symptoms



Animal models of vocal motor deficits in PD

-Used in many aspects of studying PD

- Inherent limitations, but valuable

- Previously no models for voice deficits

- Three developing models:

Rat Model
Bird Model
Mice

Rat phonation in 6-0HDA models of Parkinson disease GOALS:

Is ultrasonic vocalization
(an index of rat communication)
a dopamine (DA) mediated/sensitive behavior in laboratory rats?

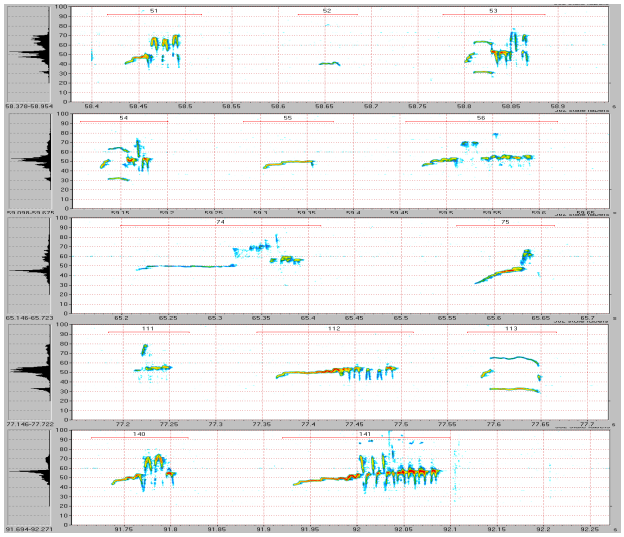
Are there changes in functioning with intensive vocal exercise in 6-OHDA rats?

Collaboration with Schallert Lab, University of Austin, Texas: Tim Schallert, Teh-Sheng Ma, Michelle Ciucci, Cynthia Fox, Lori Ramig

Continuation in Ciucci Lab: University of Wisconsin, Madison

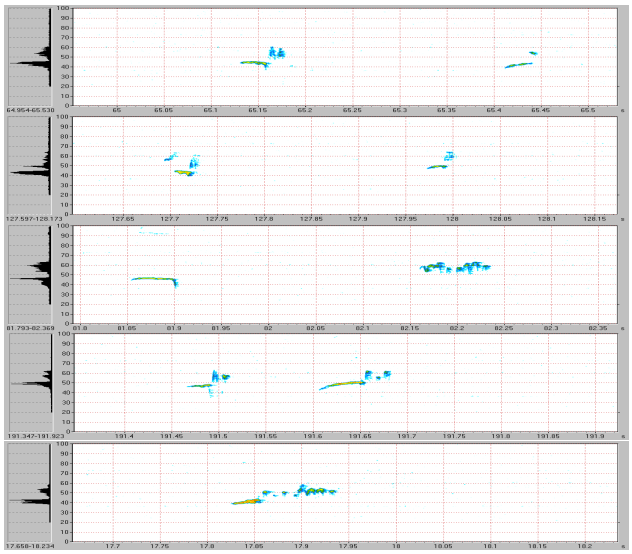
Vocalizations vulnerable to dopamine synaptic transmission alteration (Ciucci *et al*., 2007; Ciucci *et al.*, 2008)

Control Rat

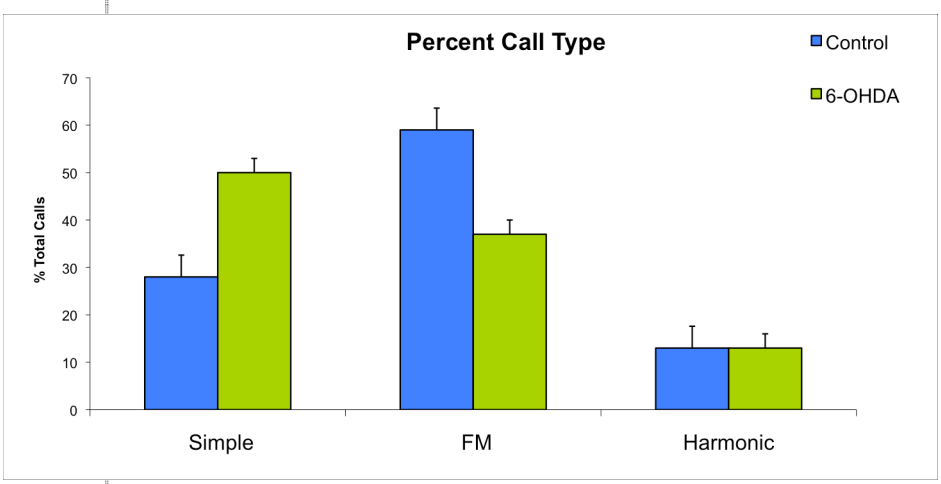


Vocalizations vulnerable to dopamine synaptic transmission alteration (Ciucci *et al*., 2007; Ciucci *et al.*, 2008)

6-OHDA Rat

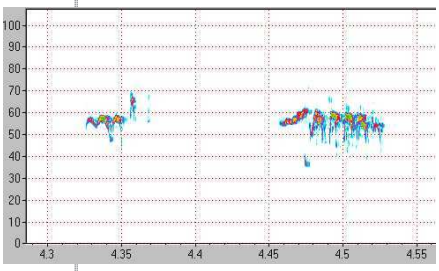


6-OHDA Effects on Call Type

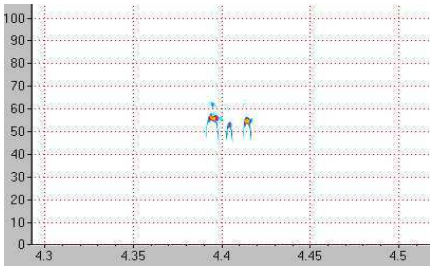


Ciucci, M. R., Ma, T. S., Fox, C., Kane, J. R., Ramig, L., & Schallert, T. (2007). Qualitative changes in ultrasonic vocalization in rats after unilateral dopamine depletion or haloperidol. Behavioral Brain Research, 182, 284–289.

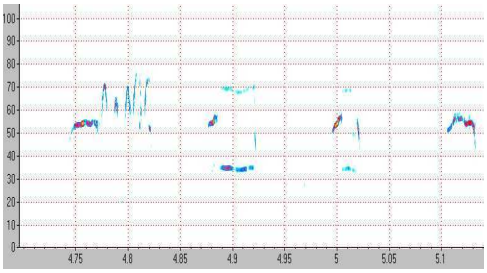
Pre-Surgery



Pre-Treatment

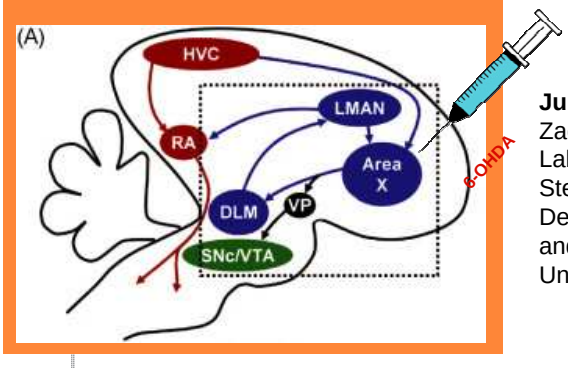


Post-Treatment



Ciucci, M. R., et al. A translational approach to vocalization deficits and neural recovery after behavioral treatment in Parkinson disease. Journal of Communication Disorders (2010), in press

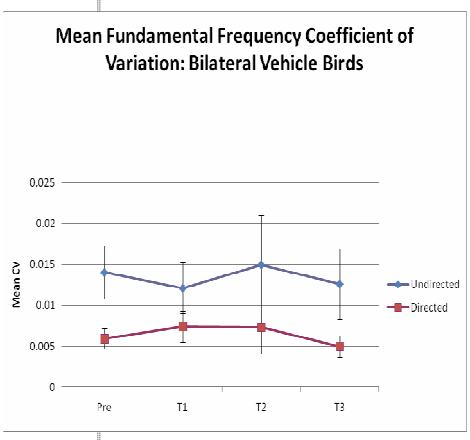
How to make a Parkinsonian zebra finch

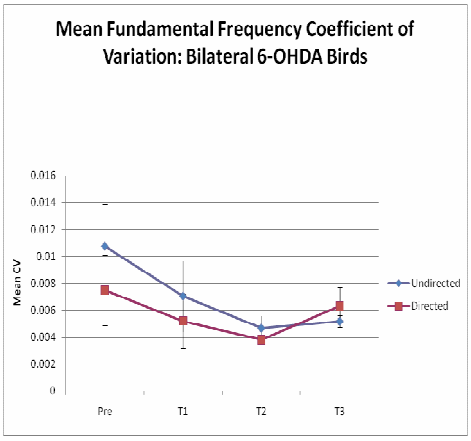


Julie Miller, PhD
Zack Burkett
Laboratory of :
Stephanie White, PhD
Department of Integrative Biology and Physiology
University of California Los Angeles

Figure modified from Gale & Perkel, 2009

Bilateral injection of 6-OHDA into basal ganglia song nucleus decreases variability in syllable fundamental frequency (Miller, Burkett, White, UCLA unpublished data)



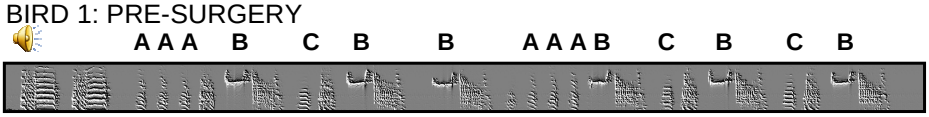


UNDIRECTED =
MALE 'PRACTICES' SOLO

DIRECTED =
MALE 'PERFORMS'
TO FEMALE

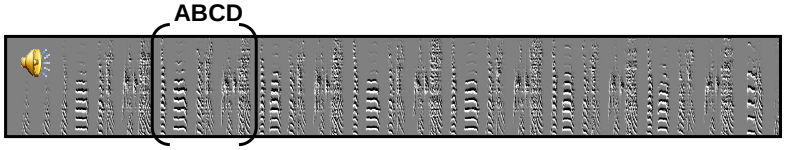
6-OHDA INJECTED BIRDS SHOW SONG DEFICITS DURING PRACTICE

BIRD 1: PRE-SURGERY



POST-SURGERY, T1

BIRD 2: PRE-SURGERY



POST-SURGERY, T1

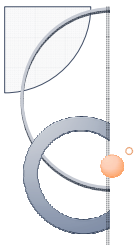
Ultrasonic vocalization in Transgenic Mice

Laboratory: Marie-Francoise Chesselet
Department of Neurology, David Geffen School of Medicine, UCLA.

Collaborators: Franziska Richter DVM, PhD,
Julie Miller PhD, Cynthia Fox PhD, Michelle Ciucci PhD

Transgenic mice
Over express human wild type alpha synuclein

These mice show a progressive PD like phenotype with early non-motor and progressively worsening motor dysfunction and loss of dopamine.



Summary

Neuroprotection, Plasticity, and Compensation play a role in management of speech disorders in PD

Continued research in these areas will helps us optimize speech treatment outcomes

Timing of interventions in patients who receive DBS needs to be examined

Animal models may offer insights into vocal motor pathophysiology as well as treatment-related change