Research Biosketch

Jesse C. DeSimone, M.Sc., Ph.D.

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Education & Positions

Education & Training

2012	B. Kin. (Honours), Brock University, St. Catharines, Canada
2014	M.Sc. Kinesiology, University of Western Ontario, London, Canada
2015	Visiting Research Scholar, University of Florida, Gainesville, USA
2019	Ph.D. Kinesiology, University of Florida, Gainesville, USA
2020	Post-doctoral Training, Radiology, UT Southwestern Medical Center, Dallas, USA

Other Positions/Training

National High Magnetic Field Laboratory Trainee & User

Trainee, Movement Disorders, National Institutes of Health T32 Training Program

Reviewer *Ad Hoc*, Movement Disorders

Personal Research Statement

I am a systems neuroscientist interested in understanding how cognitive, visual, and motor centers of the brain work in tandem to plan and execute motor movements based on standard (i.e., reflexive, automatic) and non-standard (i.e., top-down) task rules. My training includes expertise in sensorimotor neuroscience, design and implementation of multimodal neuroimaging paradigms, anatomy and physiology, and experimental design and statistics. A major research emphasis has been utilizing advanced brain imaging techniques to understand the disease-specific effects of movement disorders and neurotrauma on functional and microstructural neural pathways.

My doctoral level research was under the mentorship of Dr. David Vaillancourt at the University of Florida. During my Ph.D., I received advanced neuroimaging training at the National High Magnetic Field Laboratory, where I worked on NIH-funded studies using high-field functional and diffusion MRI to characterize disease-specific sensorimotor abnormalities in dystonia, Parkinson's disease, and essential tremor. I was also a trainee under the NIH T32 Training Program in Movement Disorders and Neurorestoration, a program dedicated to the development of expert scientists in the field of neurological movement disorders. I later completed a 1-year postdoc in Radiology under the mentorship of Dr. Joseph Maldjian at UT Southwestern Medical Center, where I leveraged my advanced neuroimaging training to lead a NIH-funded study on the effects of repetitive, non-concussive head impact exposure on default mode network functional connectivity patterns in youth football players.

I am an active member of the Society for Neuroscience and regularly serve as an Expert Reviewer for *Movement Disorders*.

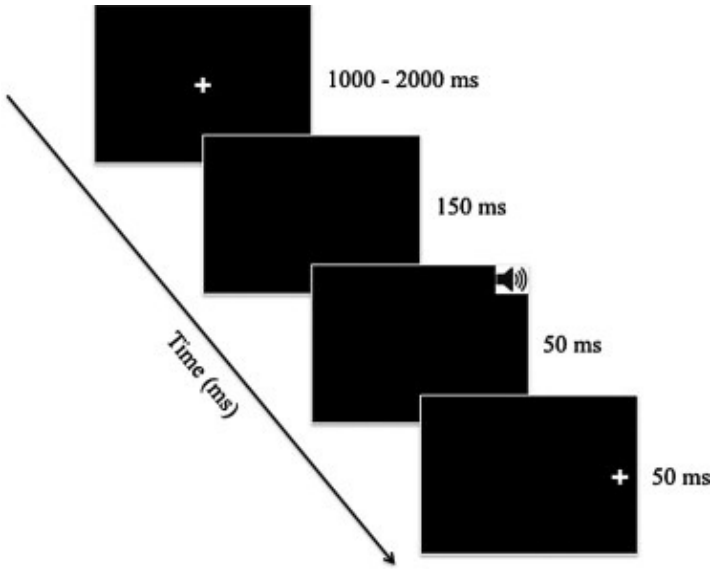
CONTRIBUTIONS TO SCIENCE

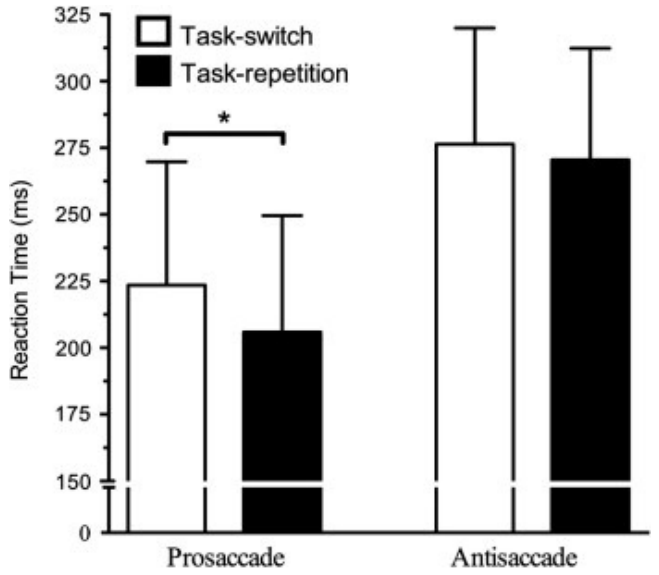
Top-Down Response Selection for Oculomotor and Manual Motor Control

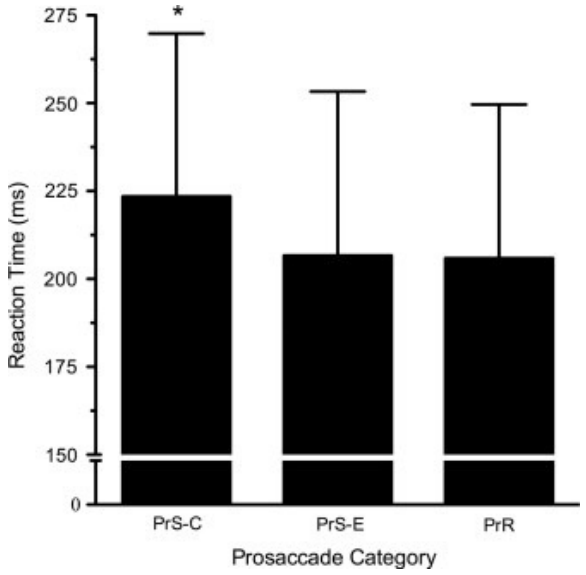
Non-standard tasks (e.g., antisaccade, antipoint) represent an important area of inquiry because they provide a framework for understanding how top-down cognitive control influences the brain's ability to efficiently and effectively execute a motor response. Unlike the standard saccade and point tasks, which require a direct spatial coupling between stimulus and response, the anti-saccade and –point tasks require the inhibition of a stimulus-driven response (i.e., response suppression) and visual remapping of that response by 180 degrees (i.e., vector inversion). A residual effect of this 'oculomotor pre-setting' is that the top-down and executive demands of response suppression and vector inversion engender a persistent inhibition of the oculomotor networks that mediate the planning of a to-be-completed stimulus-driven prosaccade (*the oculomotor inhibition hypothesis*). My research showed that the prosaccade switch cost is not related to explicit awareness of task goals. Instead, the residual inhibition of stimulus-driven oculomotor planning networks is the result of response suppression and vector inversion required for the completion of a spatially correct antisaccade response.

In subsequent work, I examined whether antisaccade and antipoint responses adhere to the *Remote Distractor Effect* – a phenomenon in which response planning times to a target are delayed by the presentation of a remote (i.e., contralateral) but not proximal (i.e., ipsilateral) distractor. For antisaccades, reaction times were increased independent of the distractor's spatial location, suggesting that a distractor increases uncertainty related to the evocation of the response-selection rule necessary for decoupling the stimulus-response relations. In contrast, my research showed comparable distractor-related effects for pro- and antipointing trials, wherein the visual properties of remote and proximal distractors respectively inhibited and facilitated target selection – a finding consistent with the *Lateral Inhibition Hypothesis*.

Unidirectional Prosaccade Switch Cost



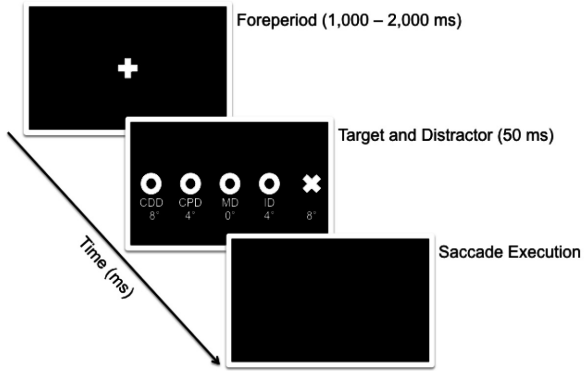


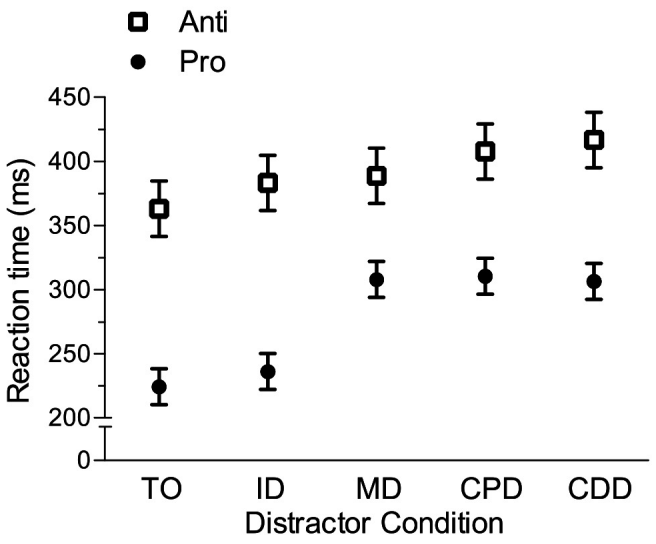


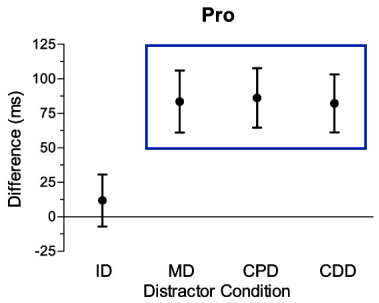
- Prosaccade latencies are longer when preceded by an antisaccade (i.e., switch-cost)
- Examined if correct vs. error antisaccades differently influence the switch-cost
- Correct, but not error, antisaccades elicit a switch ‘cost’
- Antisaccade response suppression and vector inversion impart a residual inhibition of oculomotor networks involved in planning of prosaccades

DeSimone et al., 2014 *Vision Res*

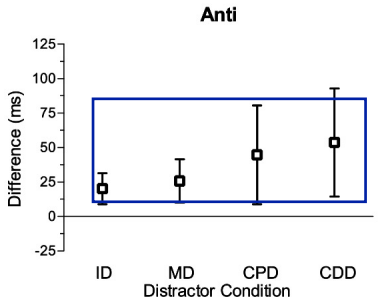
Distractor Related Effects on Top-down Oculomotor Response Selection



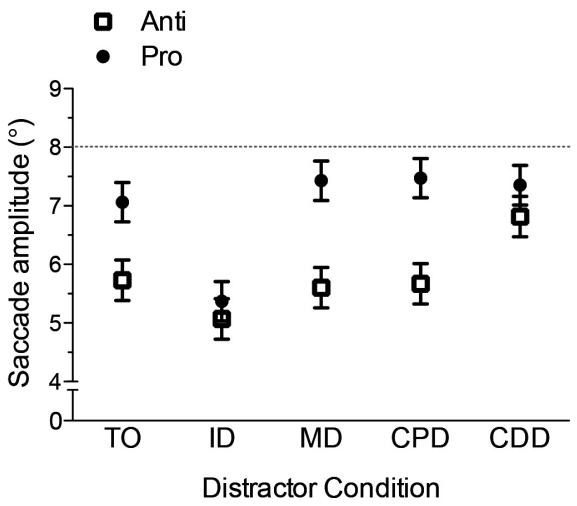


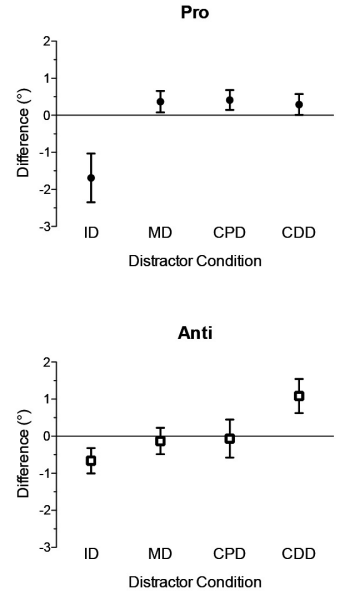


Remote distractor effect



Location-independent distractor effect

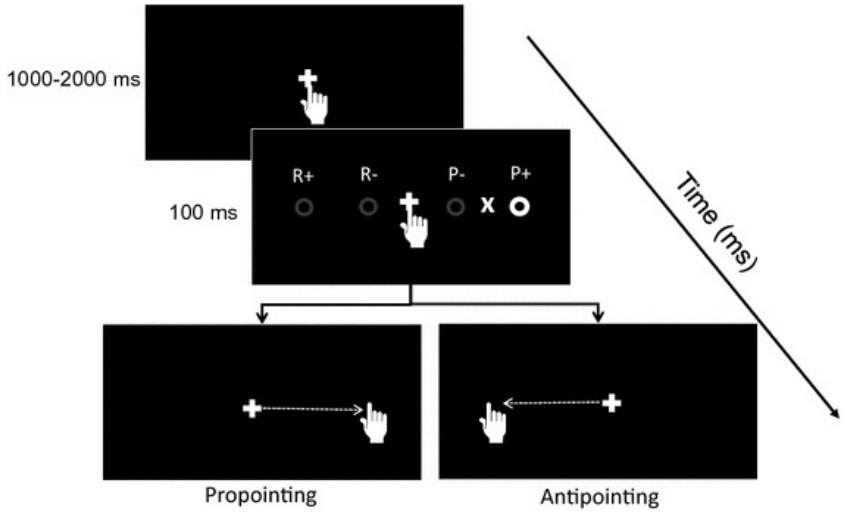


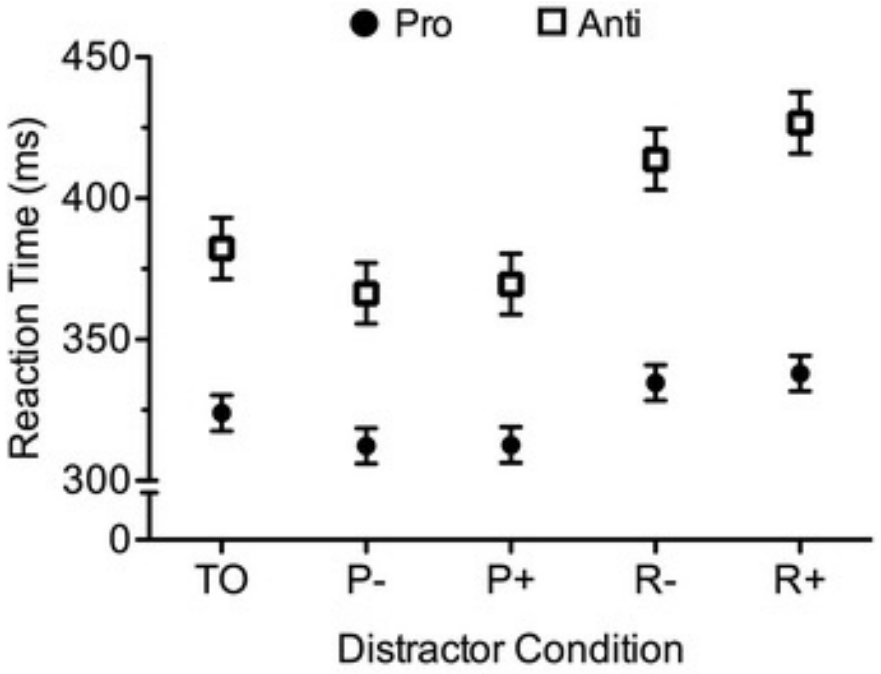


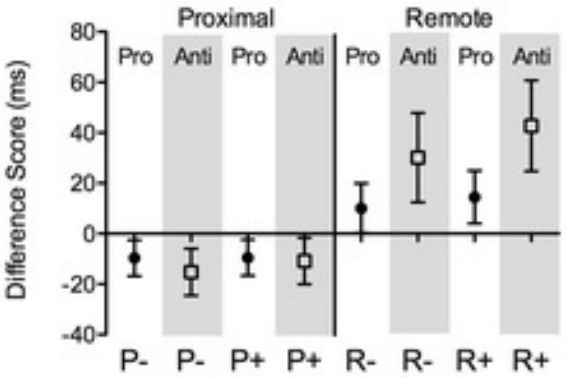
- Prosaccades adhere to RDE
- Antisaccade RTs were lengthened independent of the spatial location of the distractor
- Distractor-related antisaccade RT costs are not accounted for by a competitive integration between conflicting saccade generating commands
- Instead, a visual distractor increases uncertainty related to the evocation of the response-selection rule necessary for decoupling SR relations

DeSimone et al. 2015 *Plos One*

Distractor Related Effects on Top-down Manual Response Selection







- Remote and proximal distractors respectively increased (inhibited) and decreased (facilitated) reaching planning times Effects was consistent for both pro- and anti-pointing responses
- Results evince that the *remote distractor effect* and the facilitatory effects of a proximal distractor are effector independent
- Provides behavioral support for the contention that the SC serves as a general target selection mechanism and supports the *lateral inhibition hypothesis*

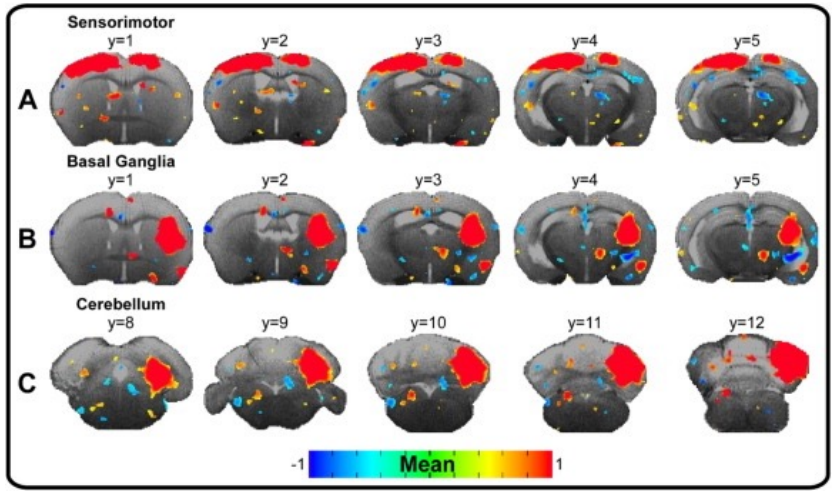
Heath & DeSimone, 2016 *Exp Brain Res*

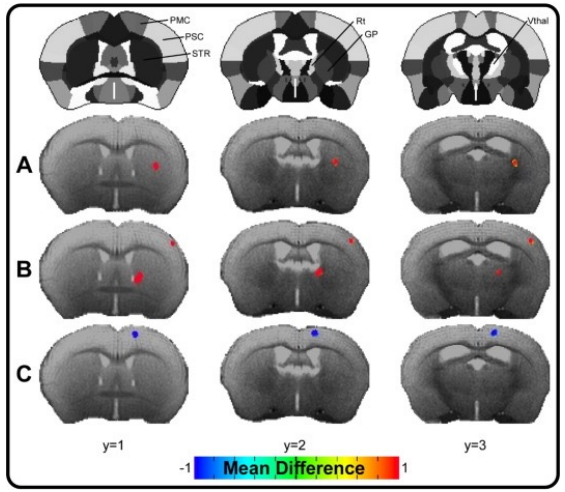
Functional and Microstructural MRI Characterization of DYT1 Loss-of-Function Mutation in Mouse Models of Dystonia

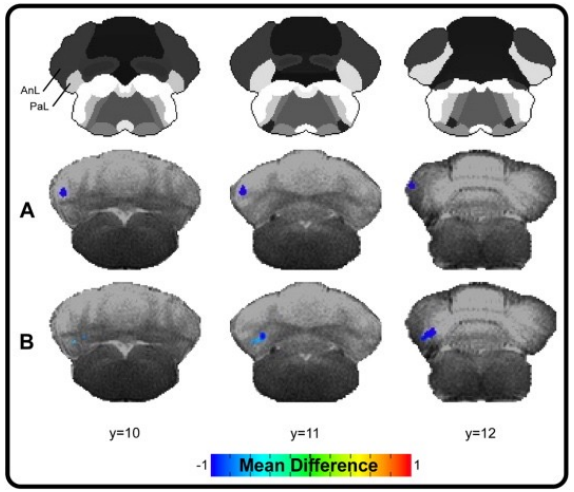
Leveraging advanced neuroimaging techniques and pre-clinical animal models, my doctoral dissertation work examined how cell-specific loss-of-function of the DYT1 gene encoding the dystonia disease protein torsinA influenced functional and microstructural pathways of the brain. The exact pathogenic mechanism by which ΔE-torsinA regulates phenotypic manifestation of dystonia is not yet clear. Developing quantifiable *in vivo* assays of brain function and microstructure related to cellular-localized lesions of torsinA is fundamental to understanding the neural substrates of dystonia and developing effective symptomatic and disease-modifying therapies. The following publications have provided improved understanding of the large-scale effects in brain function and connectivity caused by the GAG-Dyt1 mutation, as well as the loss of torsinA within specific cell types of the forebrain and striatum. Diffusion MRI findings have helped provide an *in vivo* readout of changes in brain microstructure characterizing these mouse models. A critical next step is to address the relationship between the loss of torsinA function in other cell types and associated systems-level changes in brain pathophysiology. Combined assays from current and future work will shape a perspective of the cell-specific functional hierarchy driving the expression of dystonia. This work will be important in developing and testing more effective symptomatic and disease-modifying therapies.

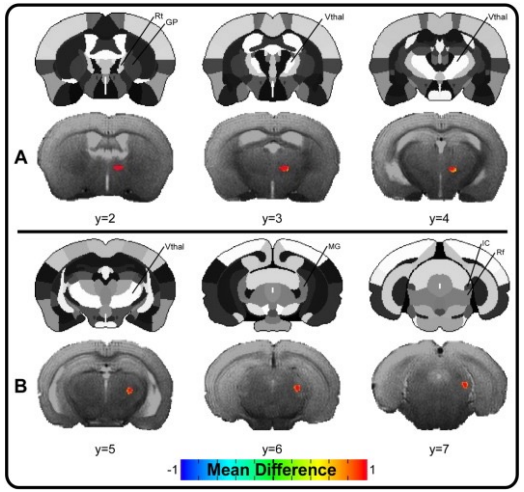
Functional Connectivity & Free-Water in Dystonia Model: ΔGAG-DYT1 Knock-In (Human Genetic Corollary)

Independent Component Analysis

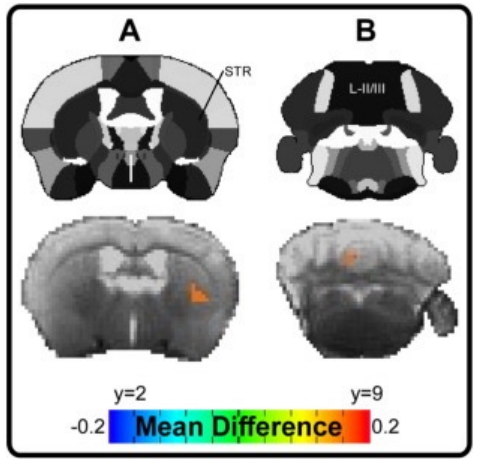








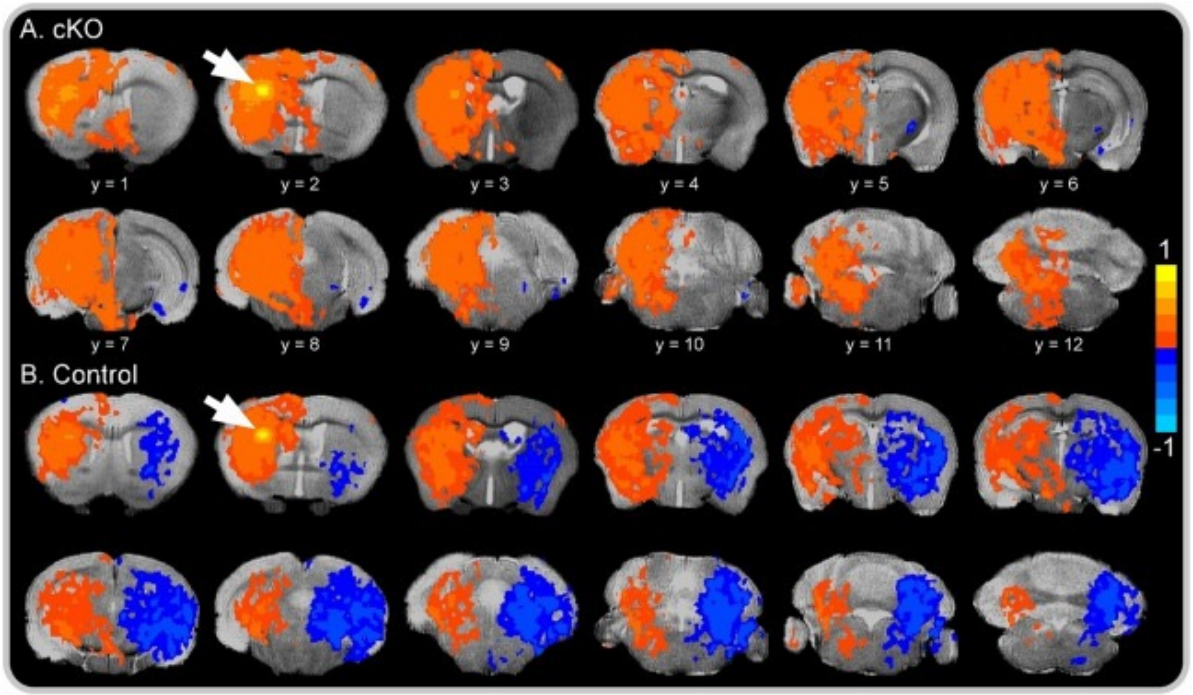
Free-water

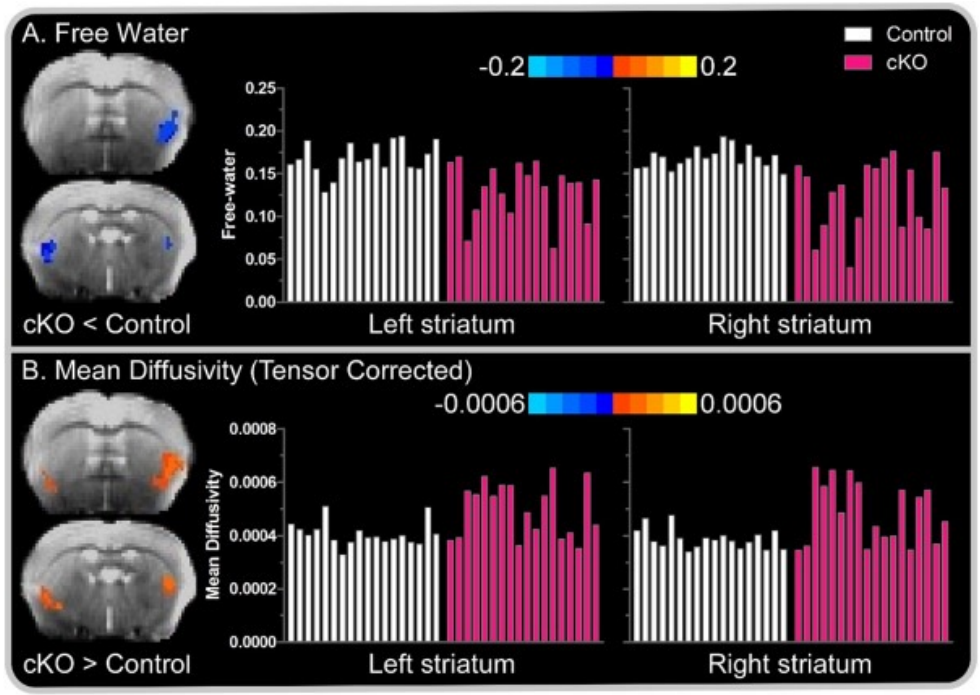


- Dyt1 KI mice elicit increased connectivity in the sensory cortex and basal ganglia
- Dyt1 KI mice show decreased connectivity in motor and cerebellar cortices
- Functional connectivity renders high area under the curve and genotype prediction
- Dyt1 KI mice have increased striatal and cerebellar free-water
- Striatal and cerebellar free-water correlates with functional connectivity

DeSimone et al. 2016 *Neurobiol Dis*

Functional Connectivity & Free-Water in Dystonia Model: Conditional Forebrain Cholinergic and GABAergic DYT1 KO Model (Symptomatic Model)

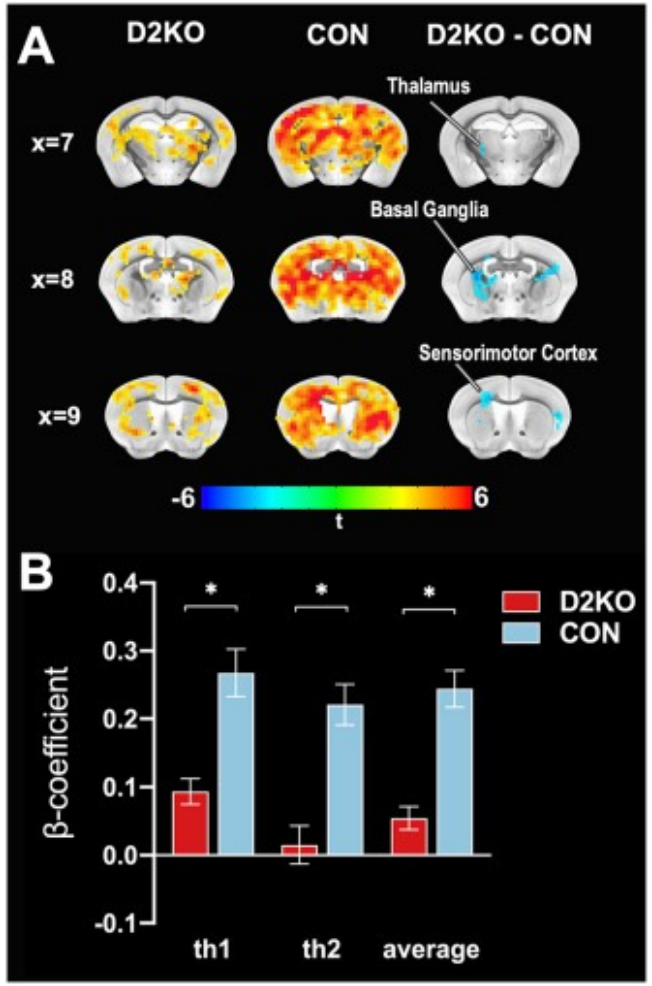


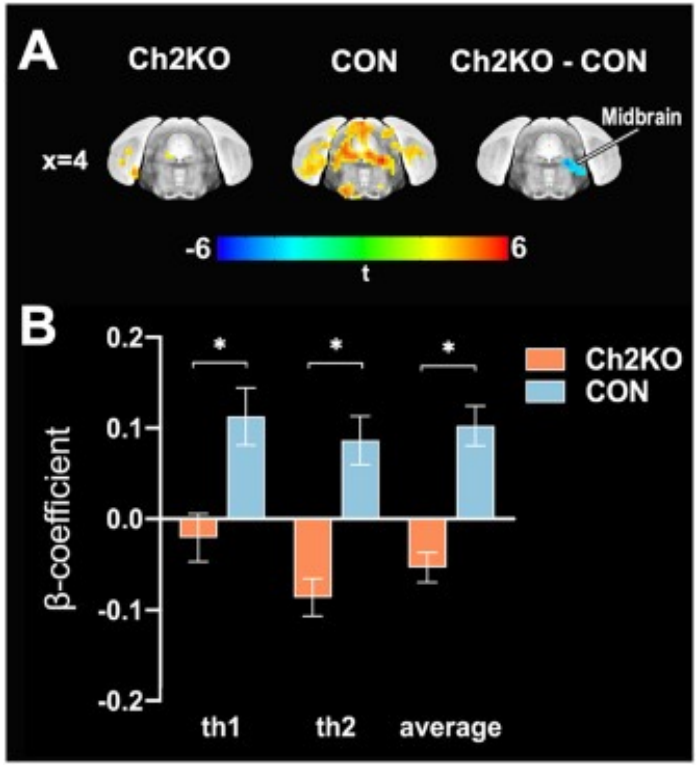


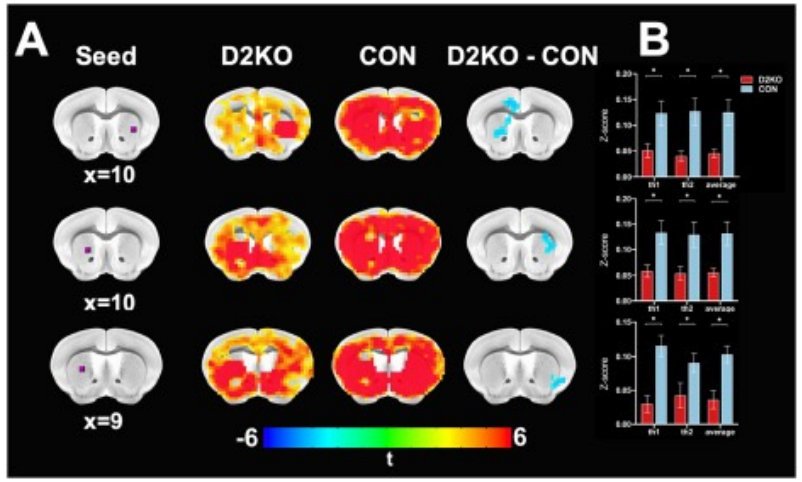
- Evaluated multimodal imaging assays in a symptomatic dystonia mouse model
- Forebrain torsinA deletion reduces striatal free-water values
- Diffusivity assays provide supplemental metric of striatal pathology
- Forebrain torsinA loss imparts whole-brain connectivity changes with striatum
- First in vivo support that direct pathological insult to forebrain can engage genetically normal hindbrain regions into an aberrant connectivity network

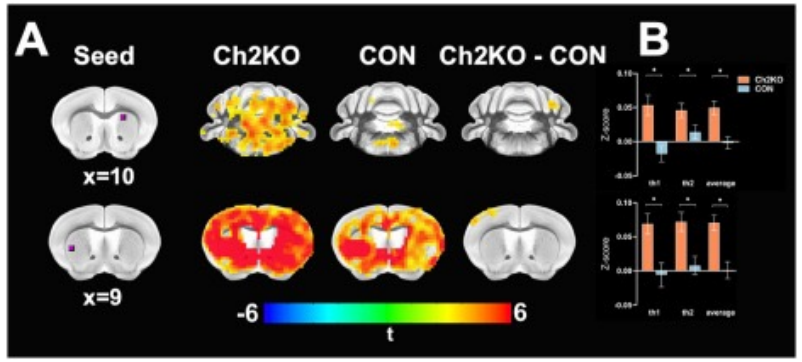
DeSimone et al. 2017 *Neurobiol Dis*

Cell-specific Effects of Dyt1 Knock-out on sensory processing, network-level connectivity





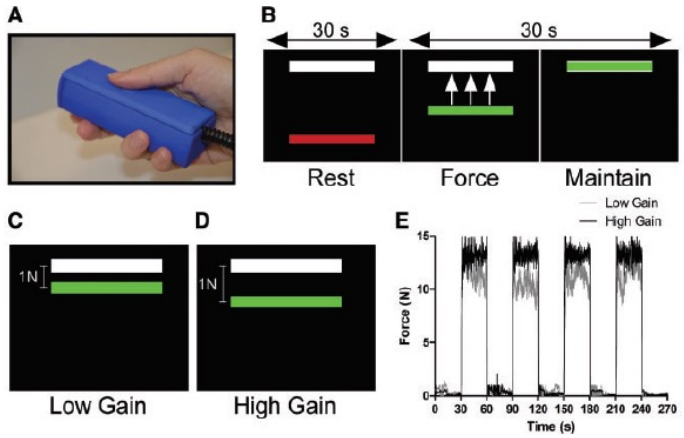


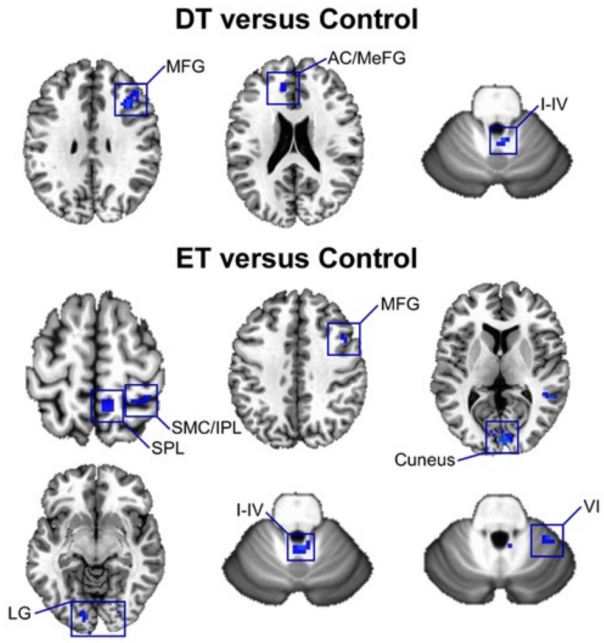


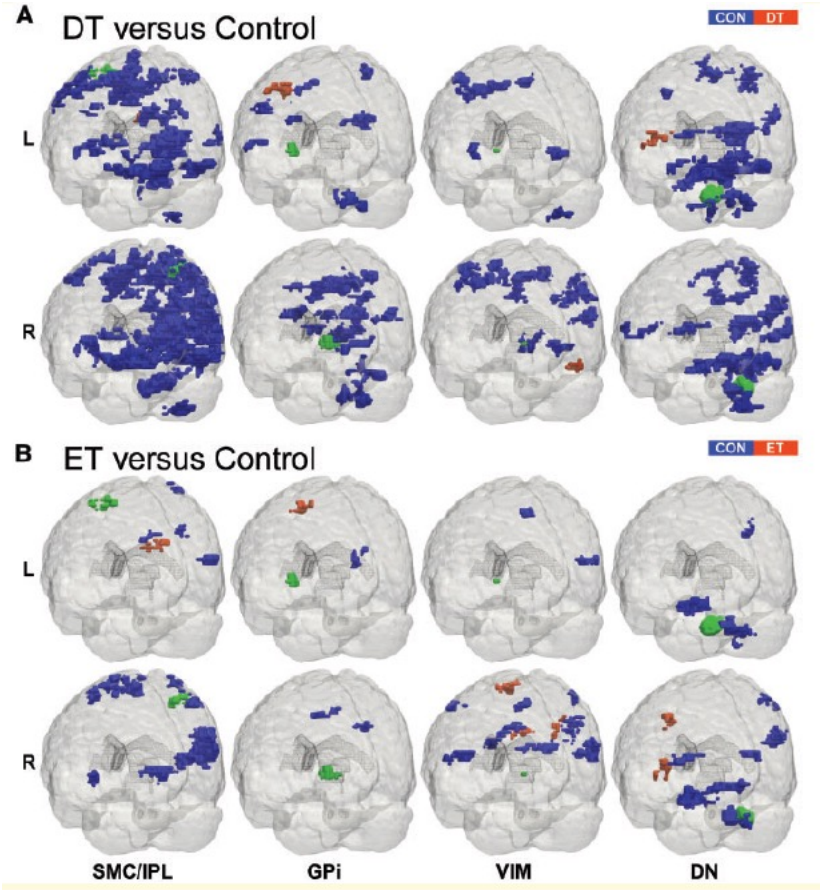
- D2KO mice showed greater impairment than Ch2KO mice, including reduced sensory-evoked brain activity in key regions of the sensorimotor network, and altered functional connectivity of the striatum that correlated with motor deficits
- TorsinA dysfunction of D2 neurons generate more profound deficits than dysfunction of cholinergic neurons alone

Wilkes, DeSimone et al. 2021 *Exp Neurol*

Functional Network Classification of Dystonic and Essential Tremor







CLASSIFICATION

Binary logistic regression with ROC & LOOCV

Variable(s)	AUC	Sensitivity	Specificity
Spectral power (tremor)	0.77	83%	65%
Functional Connectivity	0.89	78%	90%
Tremor + FC	0.94	78%	100%

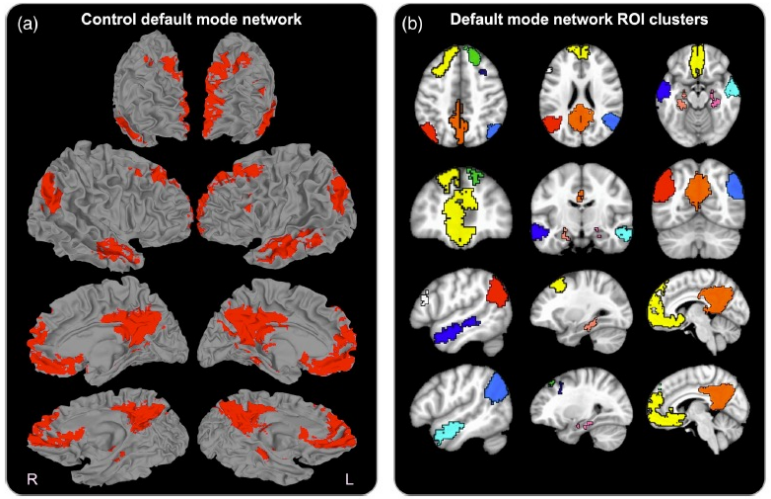
- DT and ET characterized by distinct functional activation signatures in higher-level cortical and visual regions, but common cerebellar impairments
- Magnitude of the FC delta effects are more widespread in DT group
- FC delta provided advantage over tremor in classifying DT and ET using binary logistic regression classification

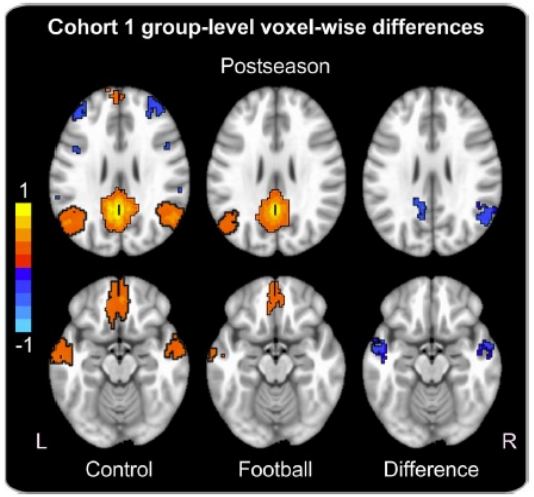
DeSimone et al. 2019 *Brain*

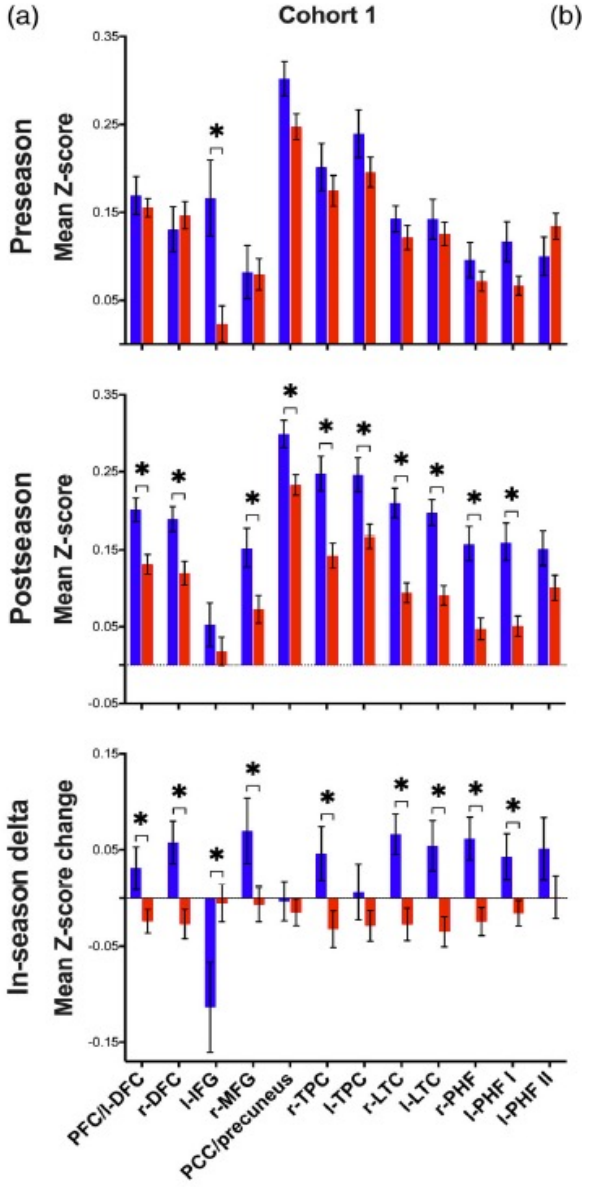
Functional Connectivity of the Default Mode Network following repetitive, non-concussive head impacts

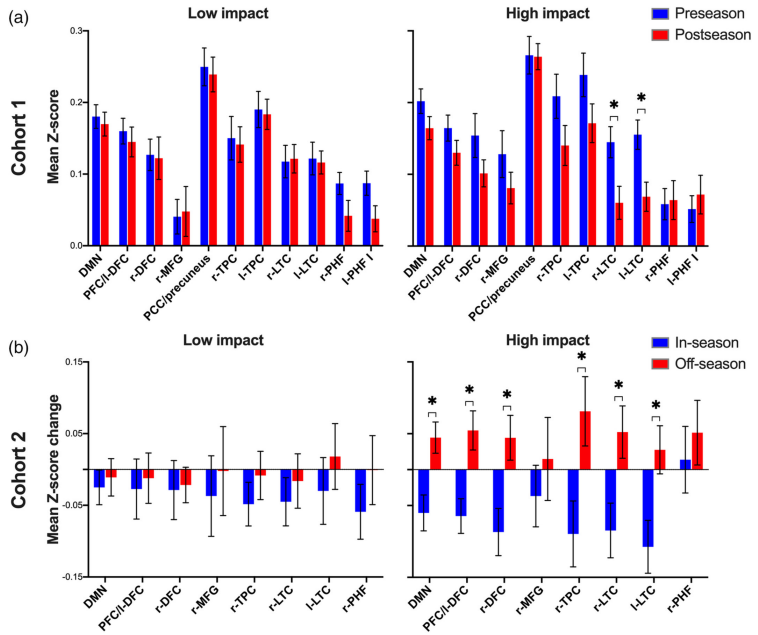
Repetitive head impact (RHI) exposure in collision sports may contribute to adverse long-term neurological outcomes, such as CTE. In contrast to a concussion, or mild traumatic brain injury, “subconcussive” RHIs represent a more frequent and asymptomatic form of exposure. It has been hypothesized that the frequent and repetitive nature of these so-called subconcussive head impacts may have more detrimental effects on brain function and neuropathology. Despite a growing body of work characterizing the effects of subconcussive head impacts on brain function, the neural network-level signatures characterizing subconcussive events in a youth collision sport cohort such as American Football are not known. To this end, I led a prospective and longitudinal cohort study to examine changes in rsfMRI FC of the DMN in youth tackle football players (n = 50; ages 8–14 years). I provided initial evidence in a high-risk youth collision-sport cohort that a single season of subconcussive head impact exposure in the absence of concussion causes reduced network-level FC of widespread DMN regions compared with non-collision sport controls. In the longitudinal analysis, in-season delta FC was characterized by a negative directional change between preseason and postseason, whereas an opposite, compensatory effect was observed for off-season delta FC between postseason and follow-up. Lastly, the number of experienced head impacts in youth football players proved to be a key contributing factor to FC alterations. These findings extend evidence from other neuroimaging modalities and advance our understanding of the underlying pathophysiology characterizing subconcussive head impact exposure in youth football players.

Mapping Subconcussive Head Impact Exposure in Youth Football









- RHIs in absence of concussion causes reduced network-level FC of widespread DMN regions
- In-season delta FC was characterized by a negative directional change between preseason and postseason, whereas an opposite, compensatory effect was observed for offseason delta FC between postseason and follow-up.
- Number of RHIs a key contributing factor to FC alterations

DeSimone et al. 2021 *Hum Brain Mapp*

Complete List of Published Work

https://www.ncbi.nlm.nih.gov/myncbi/collections/60930088/

Research & Technical Skills

Computational/Statistics

- Unix shell/bash/zsh
- SQL
- Python
- MATLAB
- R
- SPSS
- Prism

MRI Software Platforms

- AFNI
- FSL
- CONN Toolbox
- SPM
- ITK-SNAP
- Mango
- SUIT
- Group ICA Toolbox
- Brain Connectivity Toolbox
- BRAPH Toolbox

Neuroimaging Skills

- MRI acquisition & preprocessing
- BOLD activation processing & analysis
- Percent signal change processing & analysis
- Seed-based functional connectivity processing & analysis
- Graph-based connectivity processing & analysis
- Independent component processing & analysis
- Diffusion tensor image processing & analysis
- Free-water image processing & analysis
- NODDI processing & analysis

MRI Data Collection

- Agilent VnmrJ Pre-Clinical MRI
- 11 T/40 cm Bruker Advance III HD Horizontal (Magnex Scientific)
- 4.7 T/33 cm Agilent VNMRS