

Research Biosketch

Jesse C. DeSimone, B.Kin (Hons.), M.Sc., Ph.D.

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

- Trainee and Advanced User, National High Magnetic Field Laboratory
- 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. A major research focus has been

My training includes expertise in sensorimotor neuroscience, design and implementation of multimodal neuroimaging paradigms, anatomy and physiology, and experimental design, and computational programming 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.

I received my Ph.D. in motor neuroscience and neuroimaging from the University of Florida under the mentorship of Dr. David Vaillancourt. 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. A key theme of my research was using functional MRI and functional connectivity analysis to investigate the mechanisms underlying motor dysfunction in dystonia, Parkinson's disease, and essential tremor. I was 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 neuroradiology 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*.



The unidirectional prosaccade switch-cost: Correct and error antisaccades differentially influence the planning times for subsequent prosaccades



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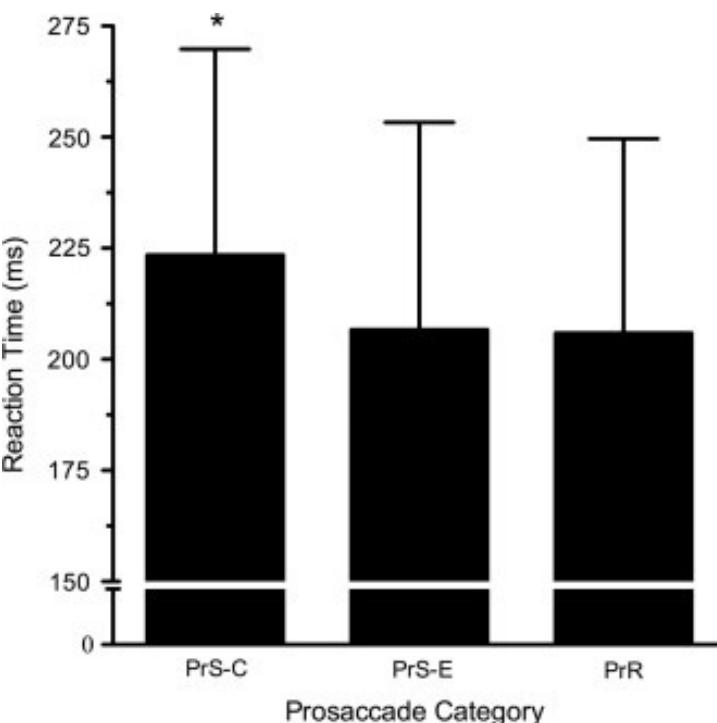
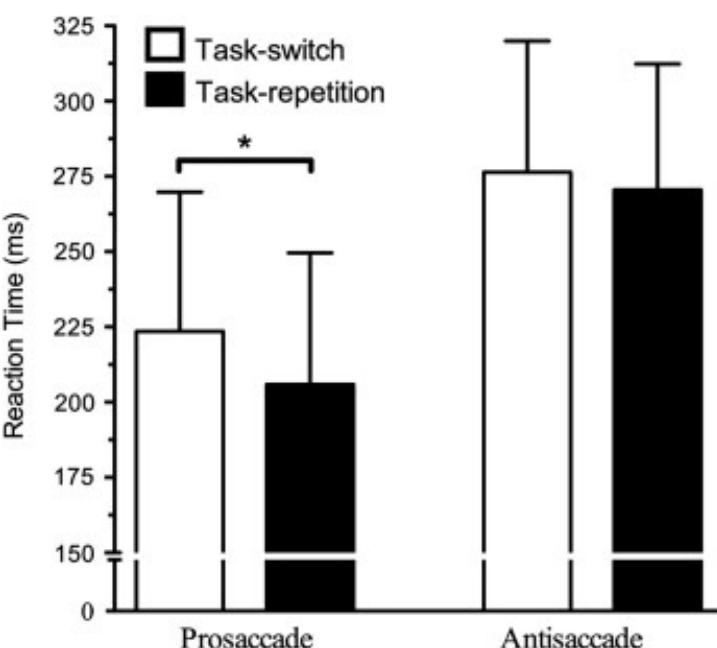
Saccade

Task-switching

ABSTRACT

Antisaccades produce longer reaction times (RT) than their prosaccade counterparts and this latency increase has been linked to an oculomotor ‘pre-setting’ that prevents the evocation of a stimulus-driven prosaccade. Moreover, a consequence of oculomotor pre-setting is a lengthening of the RTs associated with a subsequent prosaccade. The goal of the present study was to determine whether the constituent elements associated with planning a correct antisaccade (i.e., response suppression and vector inversion) imparts a residual delay that inhibits the planning of a subsequent prosaccade. To that end, participants alternated between pro- and antisaccades in a pseudo-randomized task-switching schedule (e.g., AAB-BAA...) and responses were cued via a paradigm that was designed to evoke frequent error antisaccades (i.e., a saccade initially, and incorrectly, planned to the target stimulus). Results showed that RTs for correct antisaccades were longer than error antisaccades and that prosaccades preceded by the former, but not the latter, trial-type were associated with a reliable increase in RT (i.e., prosaccade switch-cost). In other words, error antisaccades were associated with a failure to withhold a stimulus-driven prosaccade and did not delay the planning of a subsequent prosaccade. Based on these findings we propose that the prosaccade switch-cost is not related to an explicit awareness of task goals; rather, our results are consistent with the assertion that a consequence of response suppression and vector inversion is a residual inhibition of stimulus-driven oculomotor planning networks.

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RESEARCH ARTICLE

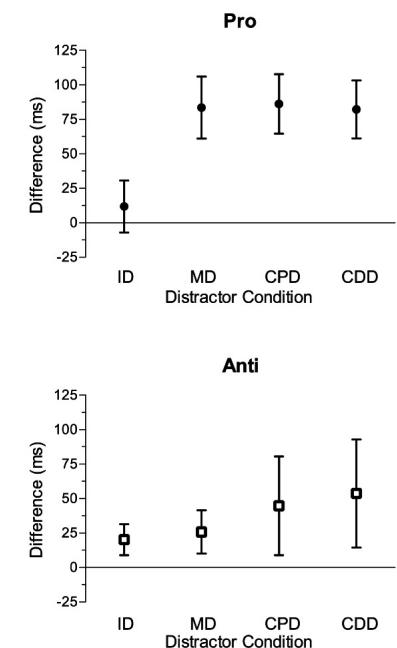
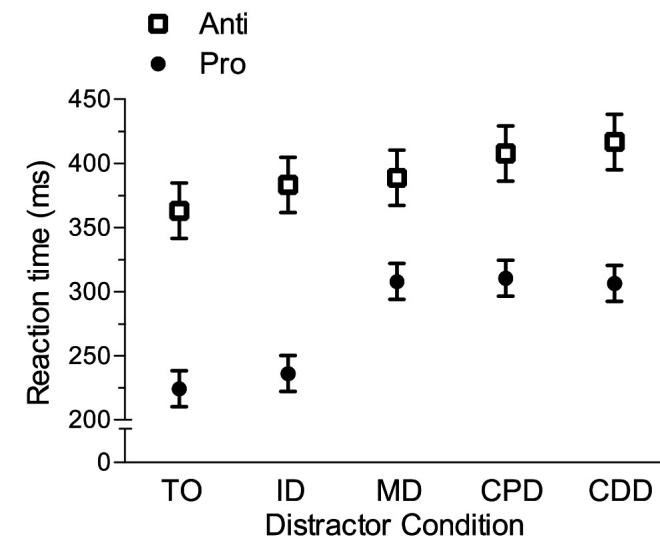
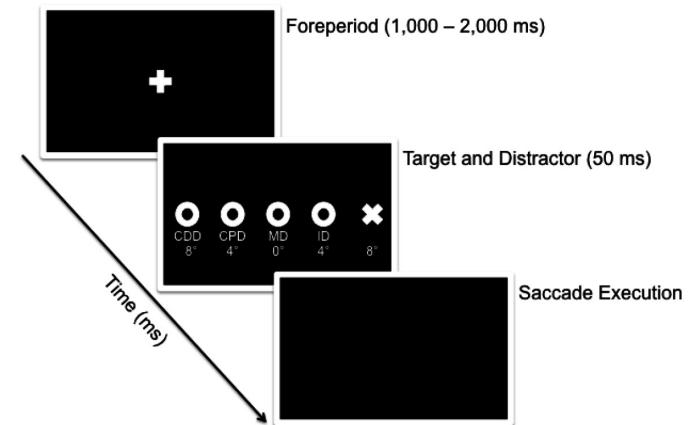
The Antisaccade Task: Visual Distractors Elicit a Location-Independent Planning ‘Cost’

Jesse C. DeSimone¹, Stefan Everling², Matthew Heath^{3*}

1 School of Kinesiology, University of Western Ontario, London, ON, Canada, **2** Department of Physiology and Pharmacology, Department of Psychology, Robarts Research Institute, and Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada, **3** School of Kinesiology and Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada

Abstract

The presentation of a remote – but not proximal – distractor concurrent with target onset increases prosaccade reaction times (RT) (i.e., the *remote distractor effect*: RDE). The competitive integration model asserts that the RDE represents the time required to resolve the conflict for a common saccade threshold between target- and distractor-related saccade generating commands in the superior colliculus. To our knowledge however, no previous research has examined whether remote and proximal distractors differentially influence antisaccade RTs. This represents a notable question because antisaccades require decoupling of the spatial relations between stimulus and response (SR) and therefore provide a basis for determining whether the sensory- and/or motor-related features of a distractor influence response planning. Participants completed pro- and antisaccades in a target-only condition and conditions wherein the target was concurrently presented with a proximal or remote distractor. As expected, prosaccade RTs elicited a reliable RDE. In contrast, antisaccade RTs were increased independent of the distractor’s spatial location and the magnitude of the effect was comparable across each distractor location. Thus, distractor-related antisaccade RT costs are not accounted for by a competitive integration between conflicting saccade generating commands. Instead, we propose that a visual distractor increases uncertainty related to the evocation of the response-selection rule necessary for decoupling SR relations.

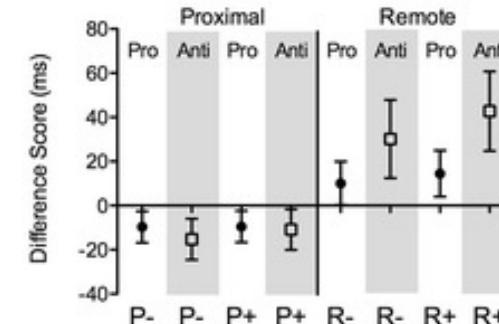
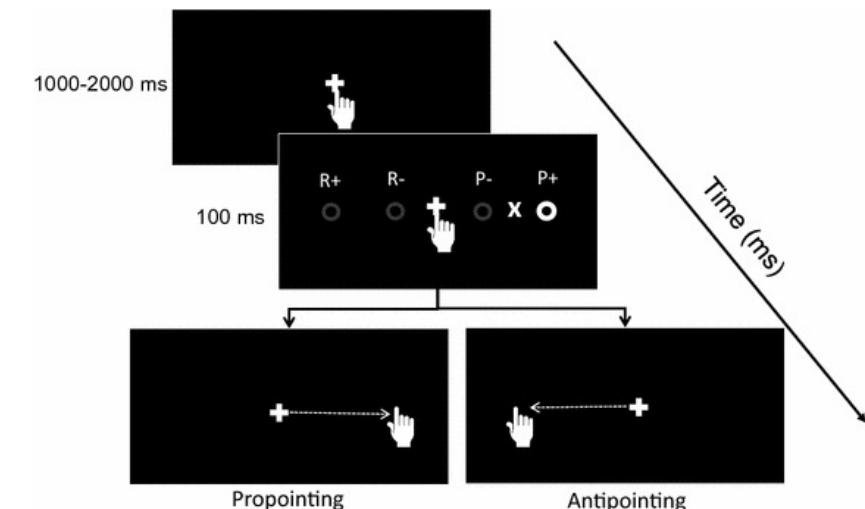
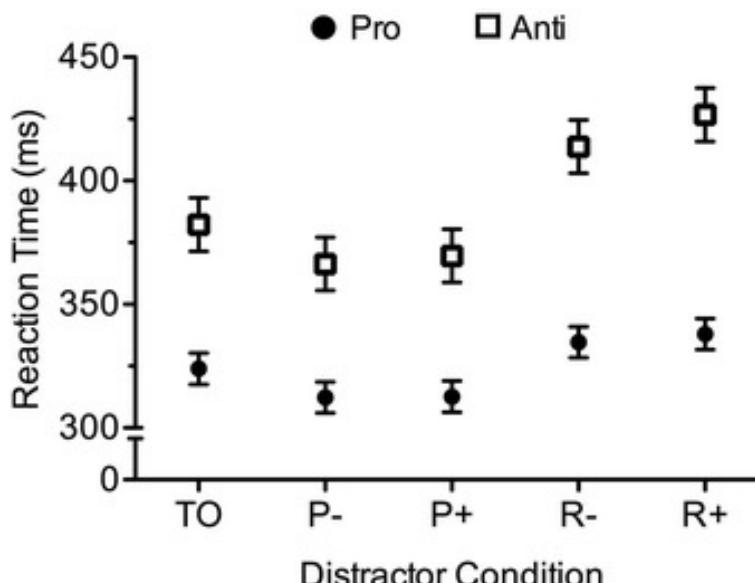


The visual properties of proximal and remote distractors differentially influence reaching planning times: evidence from pro- and antipointing tasks

Matthew Heath^{1,2} · Jesse C. DeSimone¹

Abstract The saccade literature has consistently reported that the presentation of a distractor remote to a target increases reaction time (i.e., the remote distractor effect: RDE). As well, some studies have shown that a proximal distractor facilitates saccade reaction time. The lateral inhibition hypothesis attributes the aforementioned findings to the inhibition/facilitation of target selection mechanisms operating in the intermediate layers of the superior colliculus (SC). Although the impact of remote and proximal distractors has been extensively examined in the saccade literature, a paucity of work has examined whether such findings generalize to reaching responses, and to our knowledge, no work has directly contrasted reaching RTs for remote and proximal distractors. To that end, the present investigation had participants complete reaches in target only trials (i.e., TO) and when distractors were presented at “remote” (i.e., the opposite visual field) and “proximal” (i.e., the same visual field) locations along the same horizontal meridian as the target. As well, participants reached to the target’s veridical (i.e., propointing) and mirror-symmetrical (i.e., antipointing) location. The basis for contrasting pro- and antipointing was to determine whether the distractor’s visual- or motor-related activity influence reaching RTs. Results demonstrated that remote and proximal distractors, respectively, increased and decreased reaching RTs and the effect was consistent for pro- and antipointing. Accordingly, results evince that the RDE and

the facilitatory effects of a proximal distractor are effector independent and provide behavioral support for the contention that the SC serves as a general target selection mechanism. As well, the comparable distractor-related effects for pro- and antipointing trials indicate that the visual properties of remote and proximal distractors respectively inhibit and facilitate target selection.



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. These readouts, combined with future work, will be critical to the development and testing of effective disease-modifying therapies for DYT1 dystonia.



In vivo imaging reveals impaired connectivity across cortical and subcortical networks in a mouse model of DYT1 dystonia



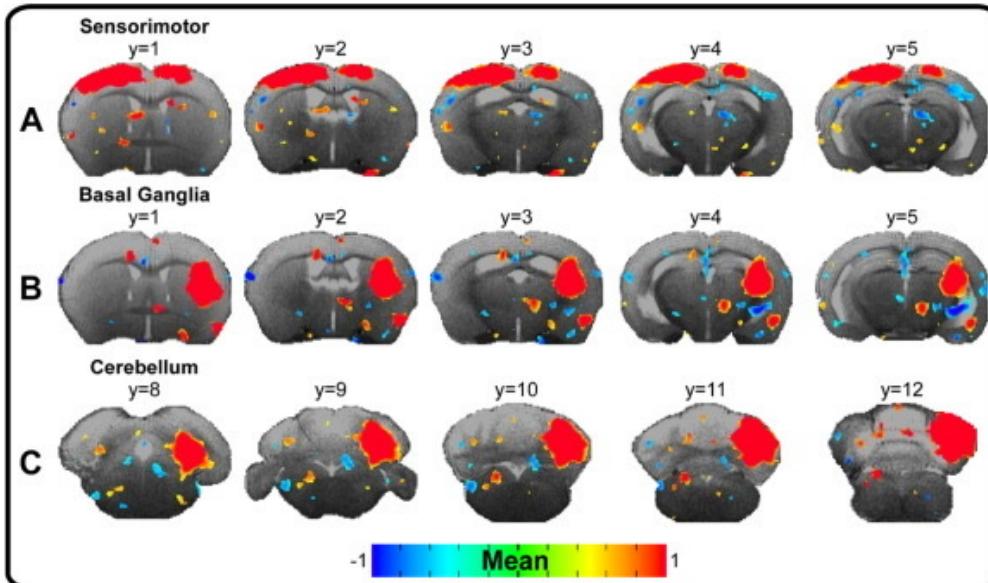
Jesse C. DeSimone^a, Marcelo Febo^b, Priyank Shukla^a, Edward Ofori^a, Luis M. Colon-Perez^b, Yuqing Li^c, David E. Vaillancourt^{a,c,d,*}

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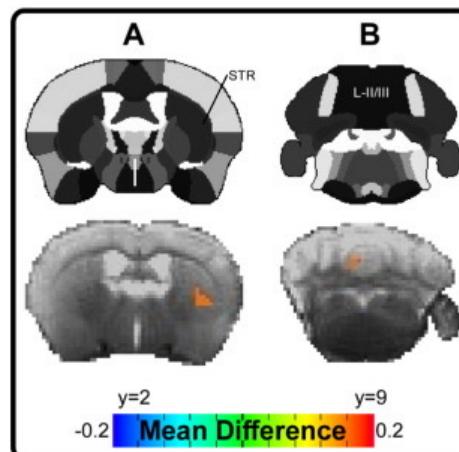
^d Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA



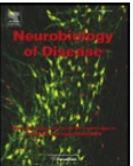
Independent Component Analysis

Developing in vivo functional and structural neuroimaging assays in Dyt1 Δ GAG heterozygous knock-in (Dyt1 KI) mice provide insight into the pathophysiology underlying DYT1 dystonia. In the current study, we examined in vivo functional connectivity of large-scale cortical and subcortical networks in Dyt1 KI mice and wild-type (WT) controls using resting-state functional magnetic resonance imaging (MRI) and an independent component analysis. In addition, using diffusion MRI we examined how structural integrity across the basal ganglia and cerebellum directly relates to impairments in functional connectivity. Compared to WT mice, Dyt1 KI mice revealed increased functional connectivity across the striatum, thalamus, and somatosensory cortex; and reduced functional connectivity in the motor and cerebellar cortices. Further, Dyt1 KI mice demonstrated elevated free-water (FW) in the striatum and cerebellum compared to WT mice, and increased FW was correlated with impairments in functional connectivity across basal ganglia, cerebellum, and sensorimotor cortex. The current study provides the first in vivo MRI-based evidence in support of the hypothesis that the deletion of a 3-base pair (Δ GAG) sequence in the Dyt1 gene encoding torsinA has network level effects on in vivo functional connectivity and microstructural integrity across the sensorimotor cortex, basal ganglia, and cerebellum.

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Free-water



Forebrain knock-out of torsinA reduces striatal free-water and impairs whole-brain functional connectivity in a symptomatic mouse model of DYT1 dystonia



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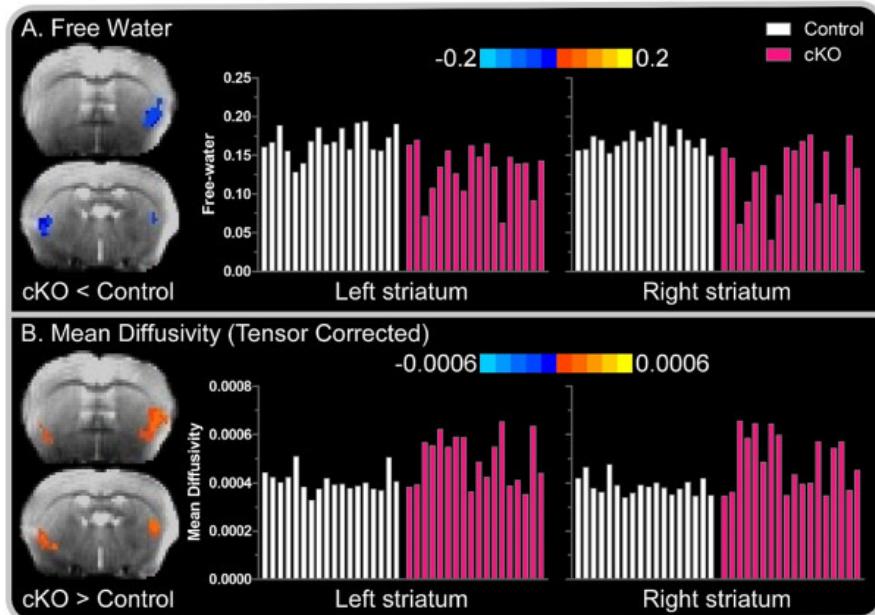
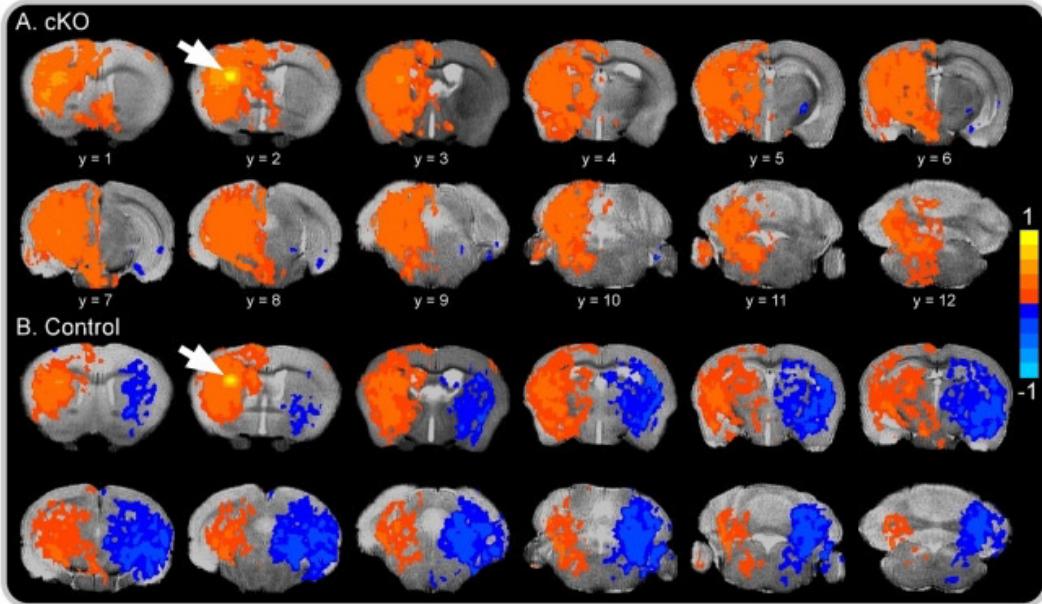
^f Department of Neurology, College of Medicine, University of Florida, Gainesville, FL 32610, USA

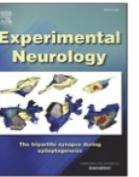
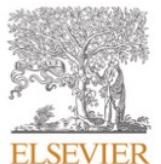
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ABSTRACT

Multiple lines of evidence implicate striatal dysfunction in the pathogenesis of dystonia, including in DYT1, a common inherited form of the disease. The impact of striatal dysfunction on connected motor circuits and their interaction with other brain regions is poorly understood. Conditional knock-out (cKO) of the DYT1 protein torsinA from forebrain cholinergic and GABAergic neurons creates a symptomatic model that recapitulates many characteristics of DYT1 dystonia, including the developmental onset of overt twisting movements that are responsive to antimuscarinic drugs. We performed diffusion MRI and resting-state functional MRI on cKO mice of either sex to define abnormalities of diffusivity and functional connectivity in cortical, subcortical, and cerebellar networks. The striatum was the only region to exhibit an abnormality of diffusivity, indicating a selective microstructural deficit in cKO mice. The striatum of cKO mice exhibited widespread increases in functional connectivity with somatosensory cortex, thalamus, vermis, cerebellar cortex and nuclei, and brainstem. The current study provides the first *in vivo* support that direct pathological insult to forebrain torsinA in a symptomatic mouse model of DYT1 dystonia can engage genetically normal hindbrain regions into an aberrant connectivity network. These findings have important implications for the assignment of a causative region in CNS disease.

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Research paper

Cell-specific effects of *Dyt1* knock-out on sensory processing, network-level connectivity, and motor deficits

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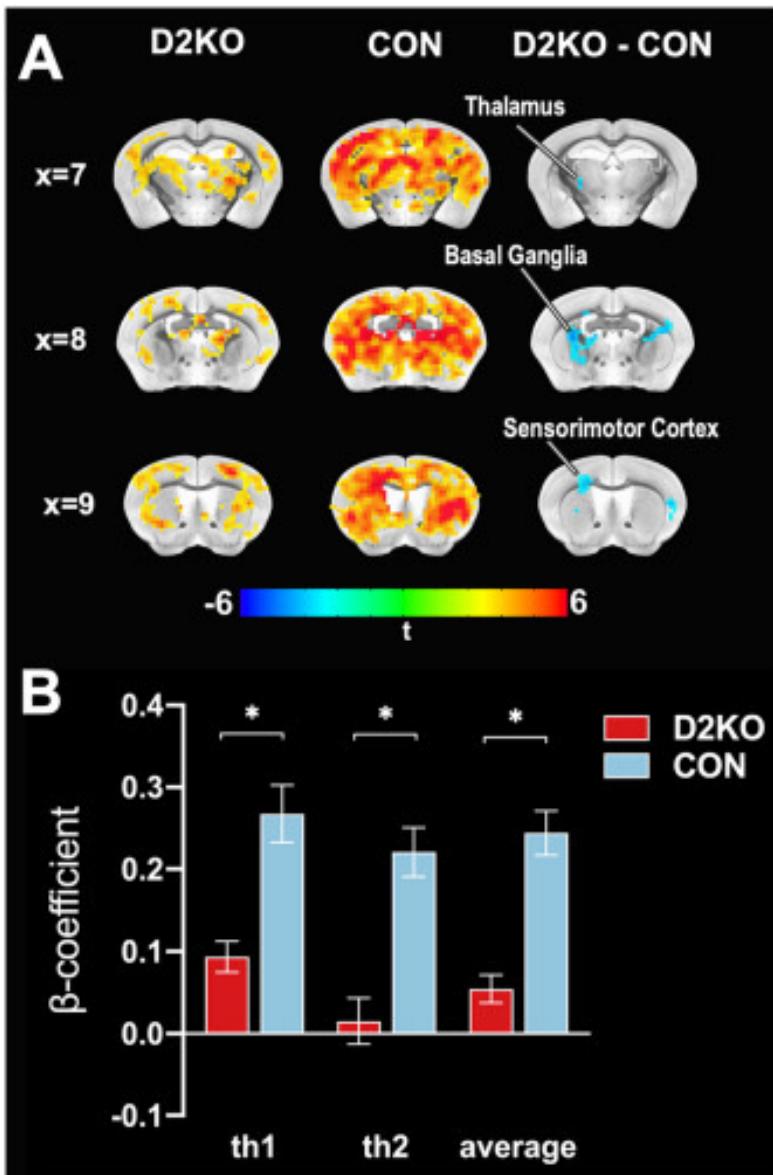
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^b Department of Neurology, University of Florida, Gainesville, FL, USA

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A B S T R A C T

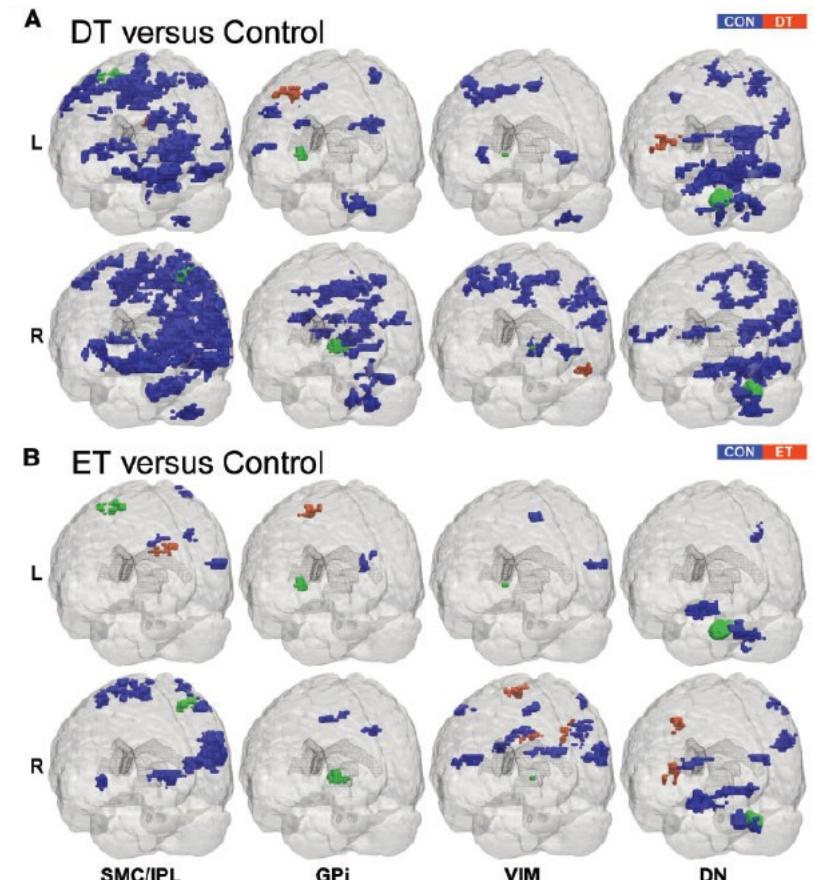
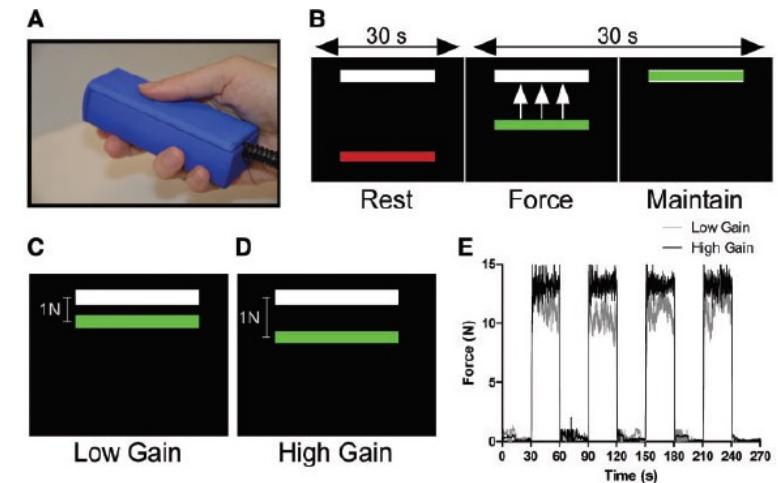
DYT1 dystonia is a debilitating movement disorder characterized by repetitive, unintentional movements and postures. The disorder has been linked to mutation of the *TOR1A/DYT1* gene encoding torsinA. Convergent evidence from studies in humans and animal models suggest that striatal medium spiny neurons and cholinergic neurons are important in DYT1 dystonia. What is not known is how torsinA dysfunction in these specific cell types contributes to the pathophysiology of DYT1 dystonia. In this study we sought to determine whether torsinA dysfunction in cholinergic neurons alone is sufficient to generate the sensorimotor dysfunction and brain changes associated with dystonia, or if torsinA dysfunction in a broader subset of cell types is needed. We generated two genetically modified mouse models, one with selective *Dyt1* knock-out from dopamine-2 receptor expressing neurons (D2KO) and one where only cholinergic neurons are impacted (Ch2KO). We assessed motor deficits and performed *in vivo* 11.1 T functional MRI to assess sensory-evoked brain activation and connectivity, along with diffusion MRI to assess brain microstructure. We found that 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. These findings suggest that (1) the added impact of torsinA dysfunction in medium spiny and dopaminergic neurons of the basal ganglia generate more profound deficits than the dysfunction of cholinergic neurons alone, and (2) that sensory network impairments are linked to motor deficits in DYT1 dystonia.



Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor

Jesse C. DeSimone,¹  Derek B. Archer,¹ David E. Vaillancourt^{1,2,3} and Aparna Wagle Shukla^{3,4}

Dystonia is a movement disorder characterized by involuntary muscle co-contractions that give rise to disabling movements and postures. A recent expert consensus labelled the incidence of tremor as a core feature of dystonia that can affect body regions both symptomatic and asymptomatic to dystonic features. We are only beginning to understand the neural network-level signatures that relate to clinical features of dystonic tremor. At the same time, clinical features of dystonic tremor can resemble that of essential tremor and present a diagnostic confound for clinicians. Here, we examined network-level functional activation and connectivity in patients with dystonic tremor and essential tremor. The dystonic tremor group included primarily cervical dystonia patients with dystonic head tremor and the majority had additional upper-limb tremor. The experimental paradigm included a precision grip-force task wherein online visual feedback related to force was manipulated across high and low spatial feedback levels. Prior work using this paradigm in essential tremor patients produced exacerbation of grip-force tremor and associated changes in functional activation. As such, we directly compared the effect of visual feedback on grip-force tremor and associated functional network-level activation and connectivity between dystonic tremor and essential tremor patient cohorts to better understand disease-specific mechanisms. Increased visual feedback similarly exacerbated force tremor during the grip-force task in dystonic tremor and essential tremor cohorts. Patients with dystonic tremor and essential tremor were characterized by distinct functional activation abnormalities in cortical regions but not in the cerebellum. We examined seed-based functional connectivity from the sensorimotor cortex, globus pallidus internus, ventral intermediate thalamic nucleus, and dentate nucleus, and observed abnormal functional connectivity networks in dystonic tremor and essential tremor groups relative to controls. However, the effects were far more widespread in the dystonic tremor group as changes in functional connectivity were revealed across cortical, subcortical, and cerebellar regions independent of the seed location. A unique pattern for dystonic tremor included widespread reductions in functional connectivity compared to essential tremor within higher-level cortical, basal ganglia, and cerebellar regions. Importantly, a receiver operating characteristic determined that functional connectivity z-scores were able to classify dystonic tremor and essential tremor with 89% area under the curve, whereas combining functional connectivity with force tremor yielded 94%. These findings point to network-level connectivity as an important feature that differs substantially between dystonic tremor and essential tremor and should be further explored in implementing appropriate diagnostic and therapeutic strategies.



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

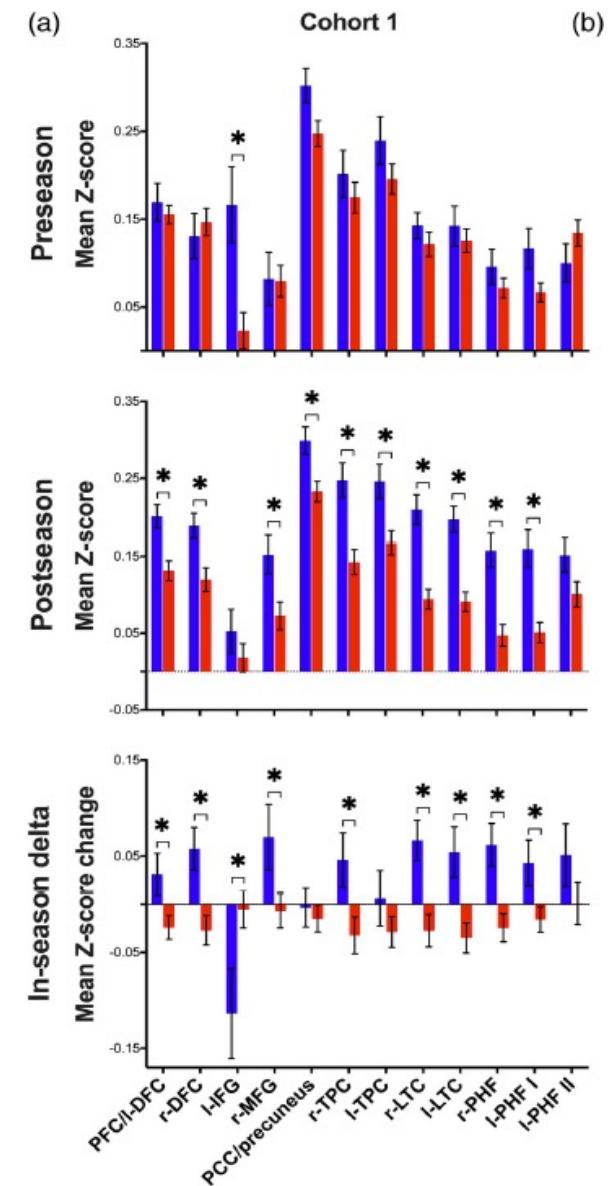
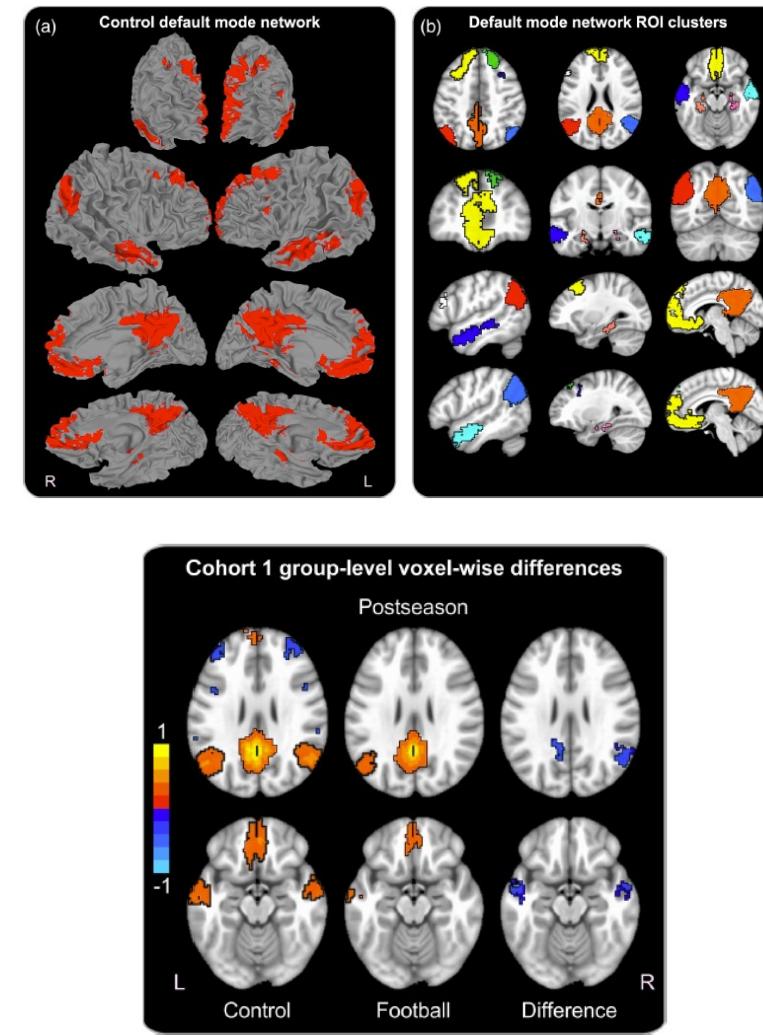
Repetitive head impact (RHI) exposure in collision sports may contribute to adverse long-term neurological outcomes, such as CTE. In contrast to a concussion, or mild traumatic brain injury, “subconcussive” RHIs represent a more frequent and asymptomatic form of exposure. It has been hypothesized that 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 default mode connectivity alterations following a single season of subconcussive impact exposure in youth football

Jesse C. DeSimone^{1,2} | Elizabeth M. Davenport^{1,2} | Jillian Urban^{3,4} | Yin Xi² | James M. Holcomb^{1,2} | Mireille E. Kelley^{3,4} | Christopher T. Whitlow^{4,5,6} | Alexander K. Powers⁷ | Joel D. Stitzel^{3,4,6,8} | Joseph A. Maldjian^{1,2}

Abstract

Repetitive head impact (RHI) exposure in collision sports may contribute to adverse neurological outcomes in former players. In contrast to a concussion, or mild traumatic brain injury, "subconcussive" RHIs represent a more frequent and asymptomatic form of exposure. The neural network-level signatures characterizing subconcussive RHIs in youth collision-sport cohorts such as American Football are not known. Here, we used resting-state functional MRI to examine default mode network (DMN) functional connectivity (FC) following a single football season in youth players ($n = 50$, ages 8–14) without concussion. Football players demonstrated reduced FC across widespread DMN regions compared with non-collision sport controls at postseason but not preseason. In a subsample from the original cohort ($n = 17$), players revealed a negative change in FC between preseason and postseason and a positive and compensatory change in FC during the offseason across the majority of DMN regions. Lastly, significant FC changes, including between preseason and postseason and between in- and off-season, were specific to players at the upper end of the head impact frequency distribution. These findings represent initial evidence of network-level FC abnormalities following repetitive, non-concussive RHIs in youth football. Furthermore, the number of subconcussive RHIs proved to be a key factor influencing DMN FC.



Complete List of Published Work

[PubMed](#)

[ORCID](#)

[Google Scholar](#)

Thesis & Dissertation

[Thesis, The Antisaccade Task: Visual Distractors Elicit a Location-Independent Planning ‘Cost’, University of Western Ontario, 2012](#)

[Dissertation, In Vivo Multi-modal Neuroimaging in Mouse Models of DYT1 Dystonia, University of Florida, 2019](#)

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
- Task-related BOLD 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