Approach

1. Goal – understand how anomalous primary sensory input due to atypical optic tract leads to disproportionate rate of VSP
2. Outcome – clinical programs to design novel cognitive strategies to enhance VSP in NF1
3. Objective – Combine VSP testing with ocular and optic pathy imaging to decipher structure-function relationships that contribute to VSP deficits in NF1
4. Central Hypothesis – VSP deficits arise from abnormalities in the optic pathway white matter tract
5. Approach
   1. Multi-disciplinary collaboration
      1. Cognitive neuroscience – behavioral testing
      2. Neuro-opthalmology- ocular imaging
      3. Imaging engineering – brain imaging
   2. Link VSP to clinical and subclinical abnormalities
6. Method (see aims page)
7. Background
   1. VSP
      1. Statement of the problem
         1. VSP Definition
         2. Clinical impact of VSP deficits
      2. Framework for understanding VSP deficits
         1. Perception – altered by higher level cognition
         2. Perception – altered by sensory input \*\*\* Overarching Goal
   2. NF1
      1. Common genetic disorder with unique phenotype
      2. Neurological - Abnormalities of the whole optic tract
         1. Local white matter abnormalities – OPG & UBOs
         2. Global white matter abnormalities suggested by UBOs
      3. Cognitive profile includes VSP deficits12
         1. VSP deficits are hallmark cognitive 3456feature - prevalence
            1. Clinical impact – may impact learning of reading and math
            2. Classic tools to measure VSP in NF1 research

Mental manipulation (JLO) - Not explained by working memory load

Perspective taking (vWM)

Translational from mouse models

May be important for effective pharmacological translational research

* + - 1. Proposed mechanism to explain prevalence
         1. Not fully explained by higher level cognition (not ADHD or working memory)
         2. Primary sensory mechanism

Localized structural abnormalities

Not fully explained by relatively rare OPG

Not explained by local UBO effects

Hypothesize that global subclinical white matter abnormalities affect the specific white matter bundle of the optic pathway to alter primary sensory input to VSP

* 1. Objective of the current study – decipher structure-function relationships of VSP deficits in NF1
     1. Expected vision and RNFL findings in NF1
        1. With OPG
        2. Without OPG
     2. Expected VSP in NF1
        1. Behavioral
           1. JLO
           2. vWM
           3. other measures
           4. any differences with or without OPG
        2. Imaging VSP in NF1
           1. fMRI
           2. other
           3. any differences with or without OPG
     3. Expected optic path structural findings in NF1
        1. OPG
        2. UBOs
        3. Optic nerve
        4. Optic tract
        5. Optic radiations
  2. Method
     1. Method – recruitment and study population
     2. Method - sources of data
        1. Multi-disciplinary collaboration – unique confluence of expertise at Vanderbilt
           1. Neuro-ophthalmology – Dr. Mawn and Dr. Donahue

Expected vision findings – cite literature

Expected optic projection finding – cite literature

* + - * 1. Cognitive neuroscience – Dr. Cutting and Dr. Rimrodt
        2. Imaging Engineering – Dr. Landmann and Dr. Smith advanced, robust techniques
        3. Prior collaboartions have formed strong interdisciplinary teams
      1. Multi-dimensional , multi-modal assessment of structure and function
         1. Neuro-ophthalmology clinic – to assess vision and optic projection
         2. Cognitive Neuroscience – EBRL to assess VSP function

VSP behavior

VSP fMRI- may identify activation differences

* + - * 1. Imaging engineering – Vanderbilt Vision Research Center (VVRC) and Vanderbilt University Institute of Imaging Sciences (VUIIS) to assess optic pathway with advanced imaging sequences and robust processing methods

3-D visualization of pre-chiasm(optic radius, tortuous)

DTI – assess for white matter disruption (FA average of right and left optic tract, radiations)

Structural to identify gross abnormalities

* + 1. Method - acquisition and analyses
       1. Data acquisition protocols
          1. Neuro-ophthalmology

Physician exam

Visual fields

OCT

* + - * 1. Cognitive Neuroscience

Behavioral assessment by trained research assistants

Functional MRI and DTI analysis

* + - * 1. Imaging engineering

MRI acquisition

non-fMRI imaging analyses

* + - 1. Data consolidation
         1. Neuro-ophthalmology

Vision composite (acuity, contrast sensitivity, visual fields)

RNFL thickness

* + - * 1. Cognitive Neuroscience

JLO correct, JLO reaction time and vWM index = VSP behavioral composite

VSP fMRI – comparative activation maps

* + - * 1. Imaging Engineering

ON radius

Tractography of optic nerve, tract and radiations to get FA at slices along the fascicles

ON tortuosity (y/n)

* + - * 1. Other measures not part of primary analyses but may be used as modifiers

IQ - WASI

ADHD status – Conners

Structural MRI for gross abnormalities and UBOs

* + - 1. Data analyses
         1. Aim 1: Do diagnosis, vision and/or structure predict VSP?

ANOVAs to test assumed findings of poorer vision and VSP for NF1 than no NF1

Multivariate regression

Dependent variable = VSP composite

Factor NF1 (y/n)

Independent variables

(a) Structural = optic nerve radius, optic nerve tortuosity (rating), optic tract FA (right and left), optic radiations FA (right and left)

(b) Functional = vision composite, RNFL thickness

(c) Include significant structural and functional independent variables and add Factor = OPG(y/n)

* + - * 1. Aim 2: Do VSP behavior, vision, and structure correlate to VSP activation?

Activation contrasts

(a) NF1 ≠ no NF1

JLO activation (especially in BA 17/18)

(b) NF1 ≠ no NF1

vWM activation (especially in hippocampus)

(c) VSP behavior correlate to activation map

Random select half sample to generate MVPA

Test on unselected half sample

(c) NF1 (y/n) correlate to activation map

Random select half sample to generate MVPA

Test on unselected half sample

* + - 1. Power Calculation
         1. Aim 1 – need to estimate how much difference expected in VSP by diagnosis.
         2. Aim 2 – need to estimate amount of expected difference between NF1 and no NF1 JLO activation in BA 17/18

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