

Understanding the effects of Noonan Syndrome on the brain through imaging

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Agenda

Introduction to Noonan syndrome, neurocognitive traits and psychiatric disorders:

Current gaps in understanding

From the lab: Behavior and Brain in Noonan syndrome

From the lab: Comparing between Noonan and Turner syndrome – what is syndrome specific?

Take home messages

Currently recruiting – Join our research study @BRIDGE lab

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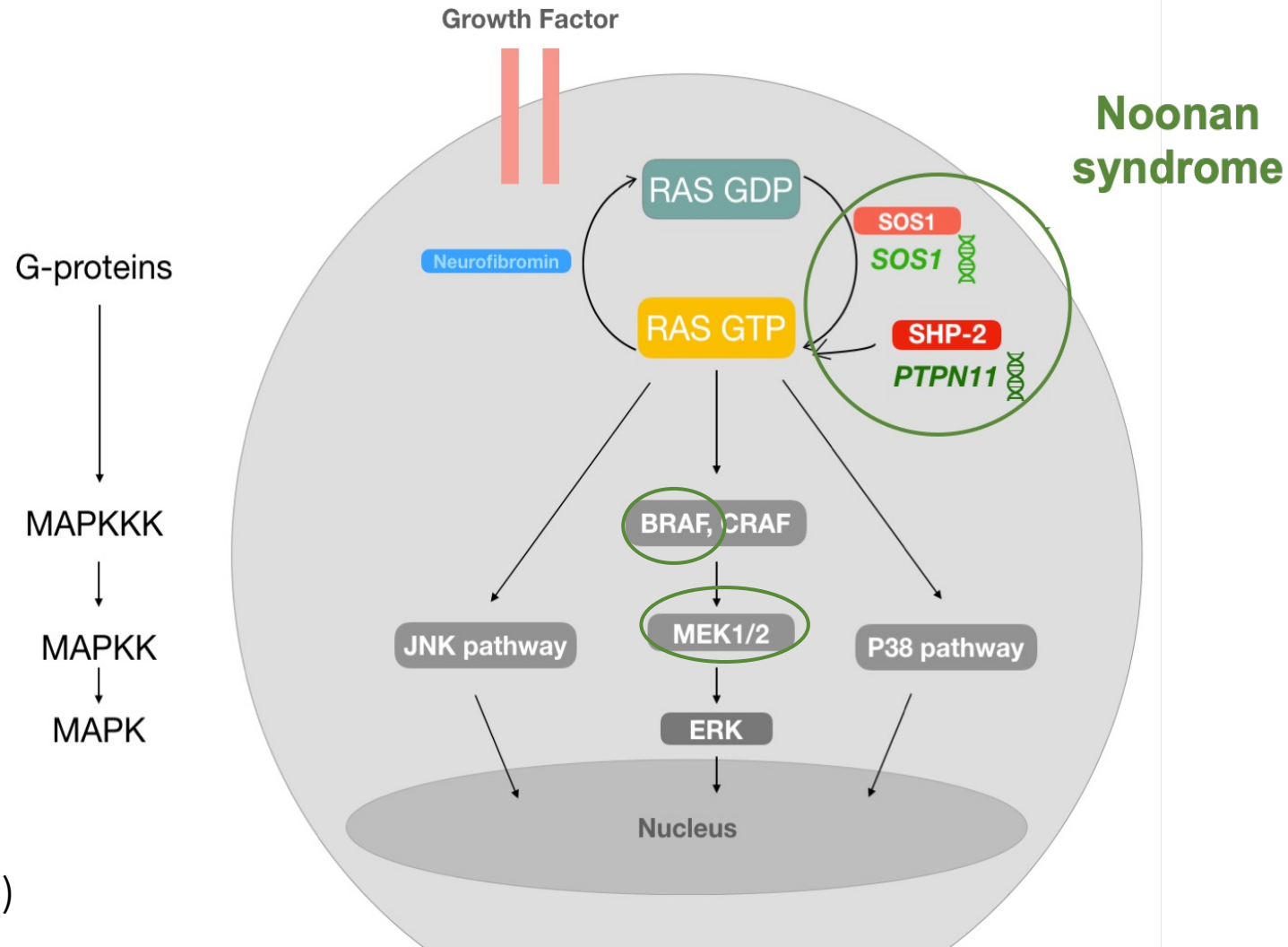
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Noonan Syndrome (NS) is caused by mutations encoding components of the Ras/mitogen-activated protein kinase (RMK) pathway

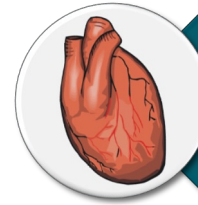


(Bruno et al. 2022)

NS affects several body systems resulting in:



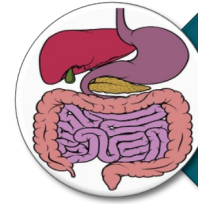
Short stature



Congenital heart anomalies



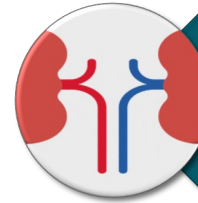
Craniofacial features (e.g. webbed neck)



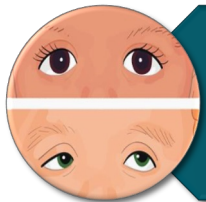
Gastrointestinal issues



Hearing loss



Kidney issues



Eyelid ptosis



Delayed/absent pubertal development

Common behavioral and cognitive traits in NS

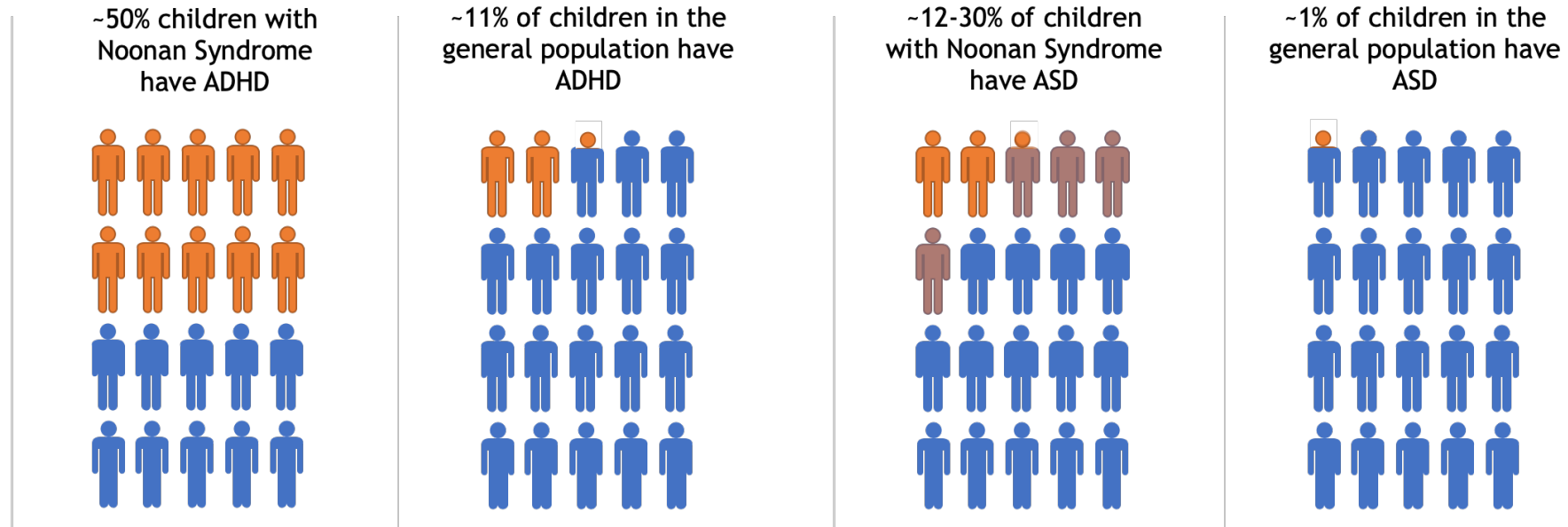
Mostly average IQ (70 -120 IQ)
(~6%-23% below average IQ)

Emotional difficulties

Executive function deficits



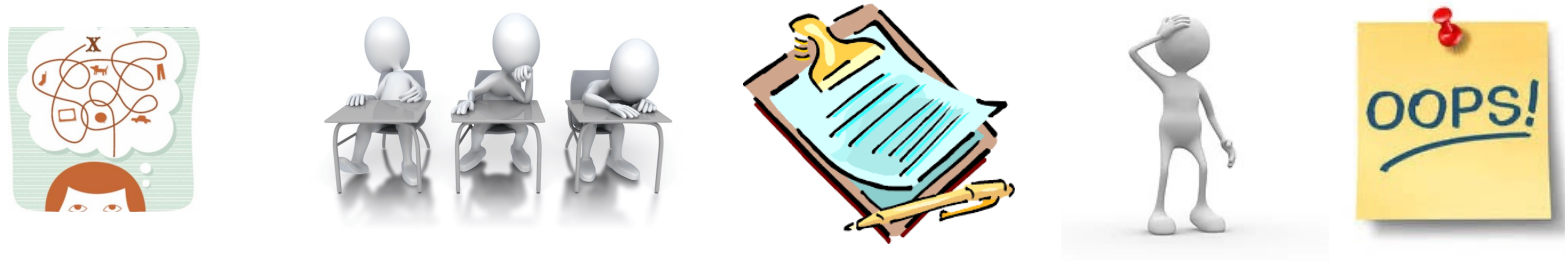
Psychiatric disorders and psychopathology in NS



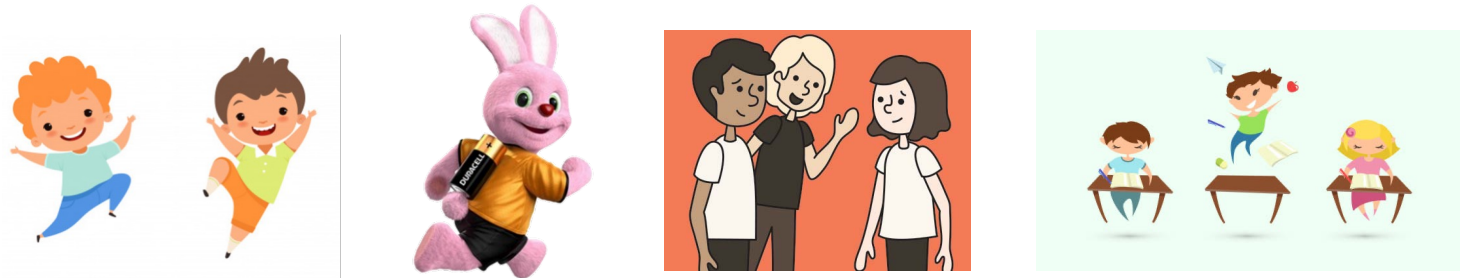
- Higher rates of attention-deficit/hyperactivity disorder (ADHD)
- Higher rates of autism spectrum disorders (ASD) and social difficulties
- Higher rates of anxiety and anxiety traits compared to the general population

Attention Deficit and Hyperactivity Disorder (ADHD)

Inattention

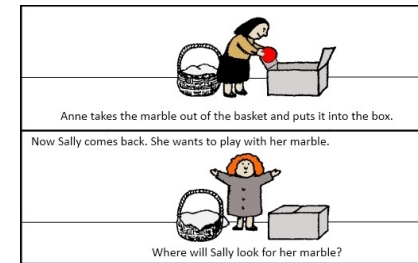
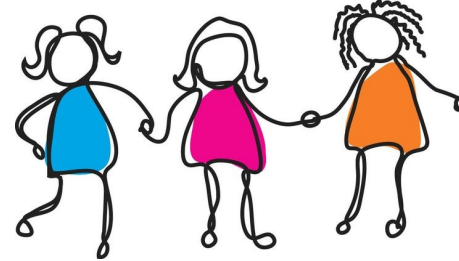


Hyperactivity and Impulsivity



Autism Spectrum Disorder (ASD)

Social communication and interaction deficits



Restrictive, repetitive behaviors and insistence on sameness



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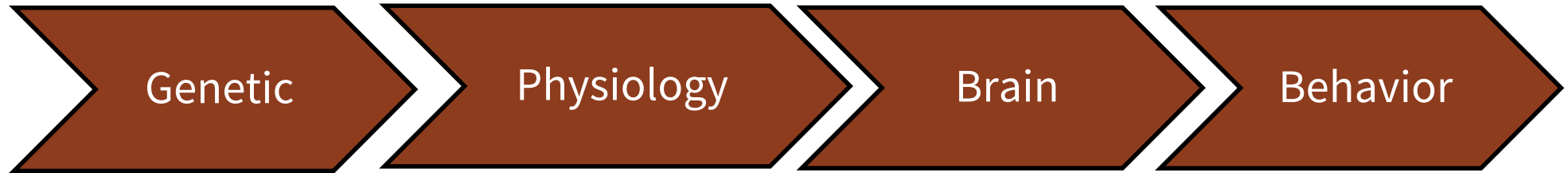
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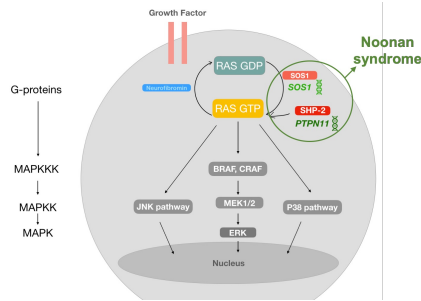
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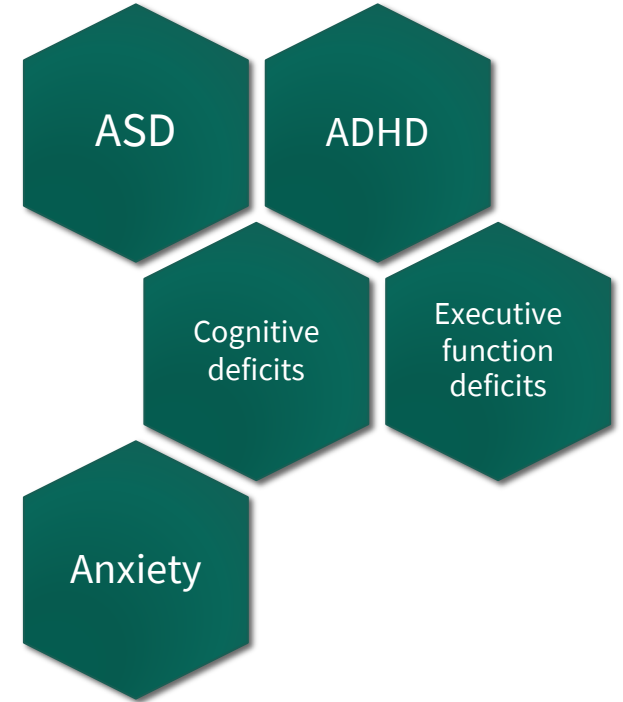
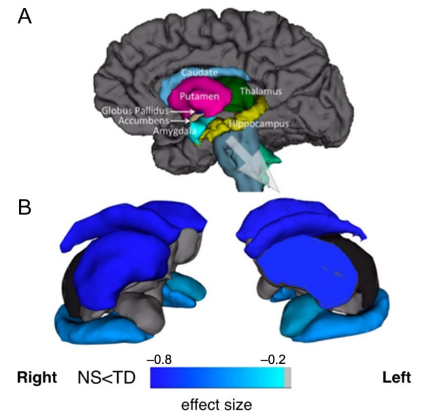
Current gaps in understanding



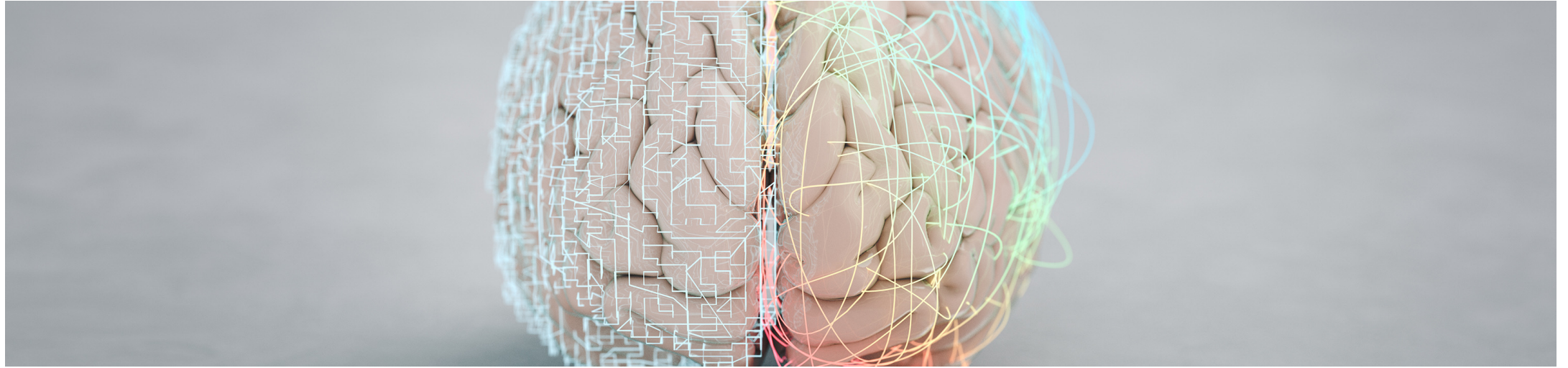
Noonan Syndrome



- Short stature
- Craniofacial features (e.g. webbed neck)
- Hearing loss
- Eyelid ptosis
- Congenital heart anomalies
- Gastrointestinal issues
Kidney malformations
- Delayed/absent pubertal development



Current gaps in understanding



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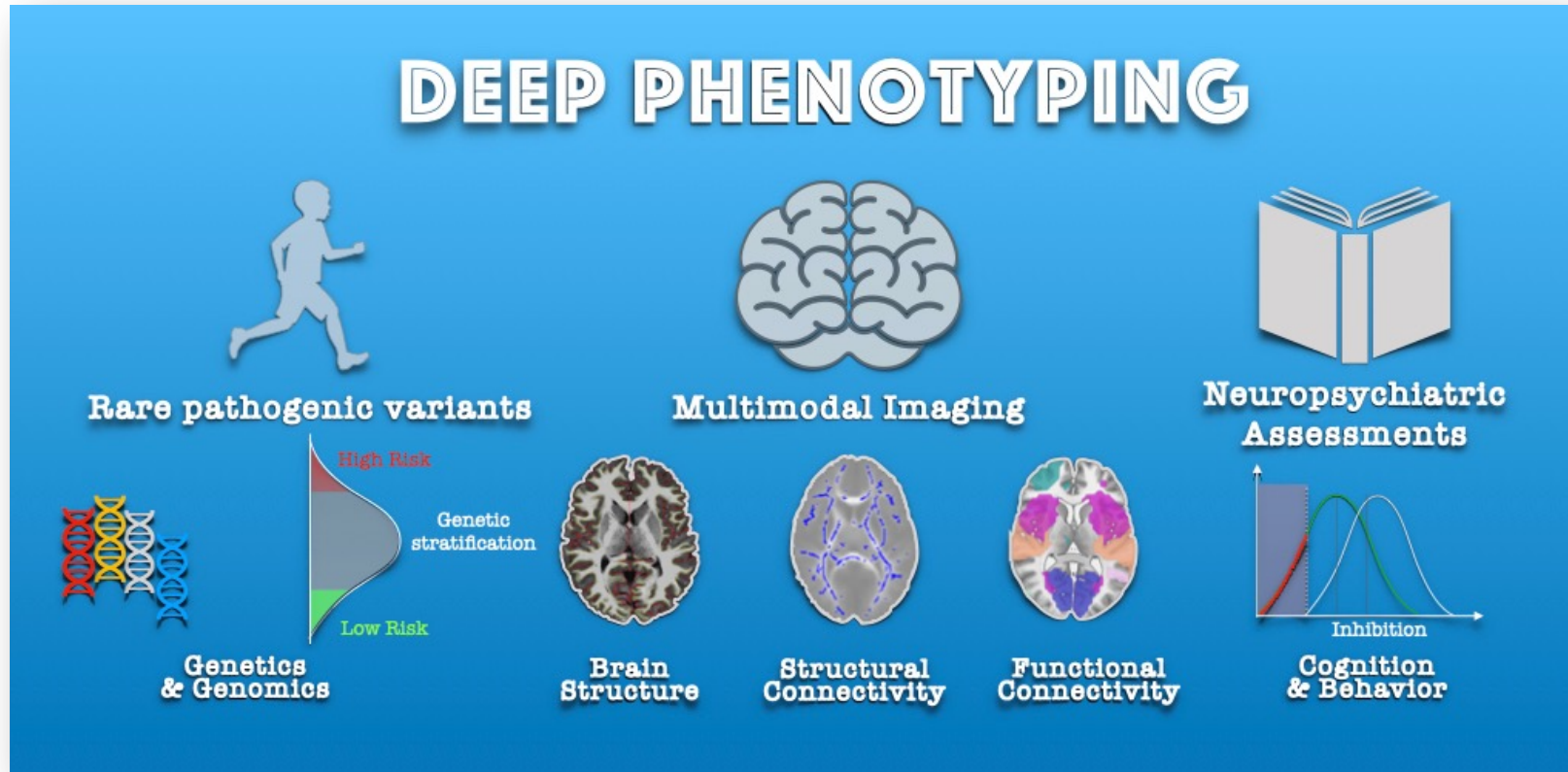
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The Noonan Syndrome Study @BRIDGE Lab



Led by
Dr. Tamar Green

<https://web.stanford.edu/group/bridgelab/>

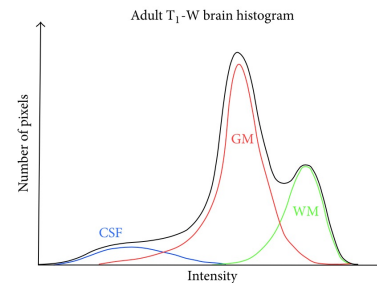
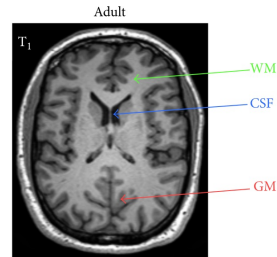


Neuropsychiatric phenotypes in children with NS

ADHD traits and Executive Function deficits in children with NS

ASD and ODD traits in children with NS

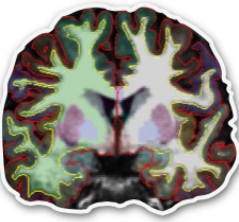
A very brief introduction to neuroimaging



Despotović et al. 2015



<https://med.stanford.edu/lucasmri/>



Structural neuroimaging (sMRI)



Looks at brain anatomy



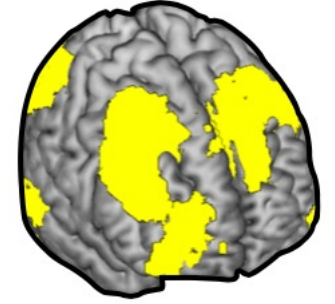
Gives us metrics of **different brain tissues** such as volume of gray matter and white matter



Why look at the brain?

Behavioral differences between people can be traced to subtle differences in brain anatomy

Functional neuroimaging (fMRI)



Looks at **brain activity** during a task or at rest

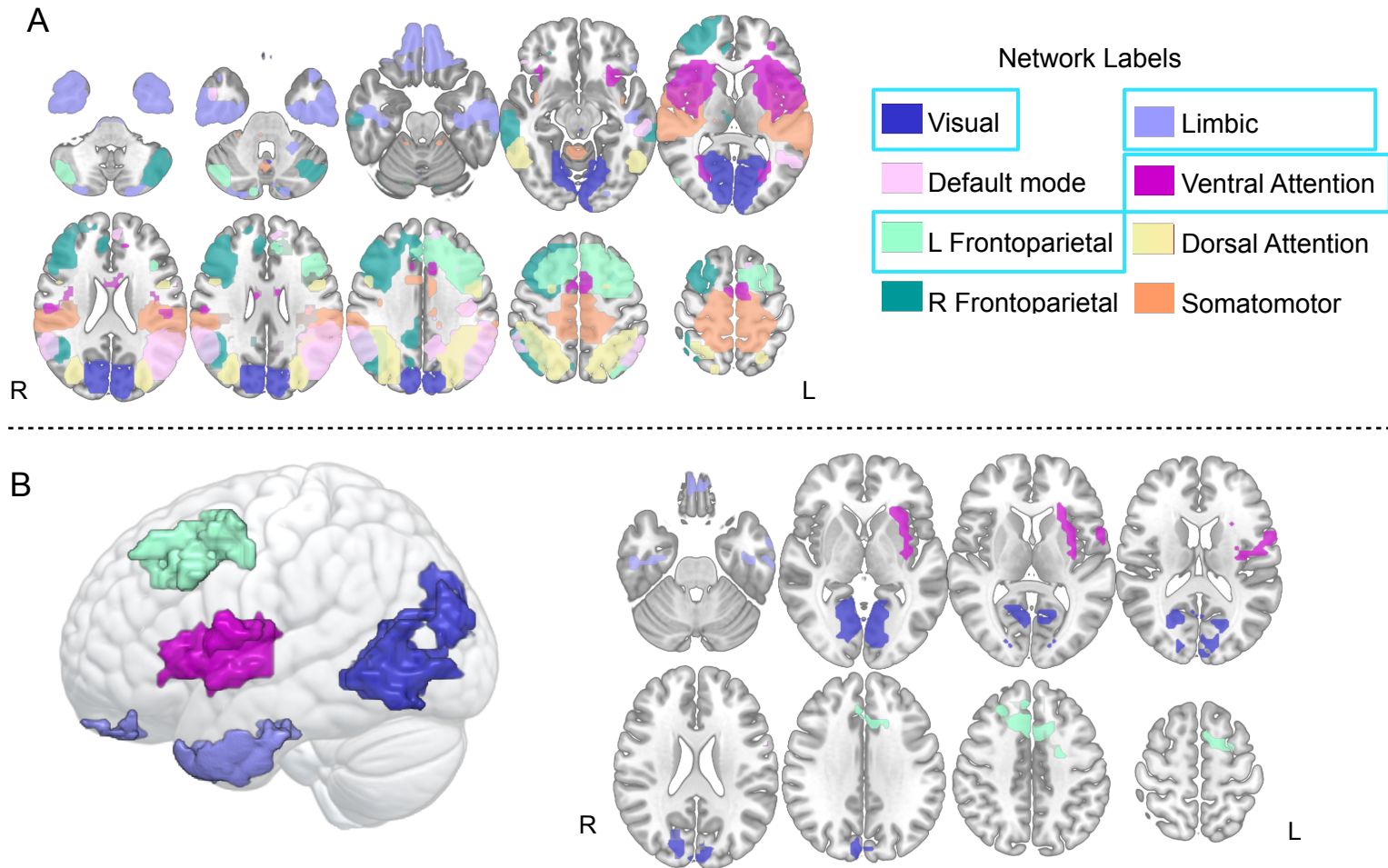


The signal that is picked up reflects correlates of neural activity like blood flow and oxygenation

“active areas = energy consumption”



Effects of NS on function of the human brain



(Bruno et al. 2022)

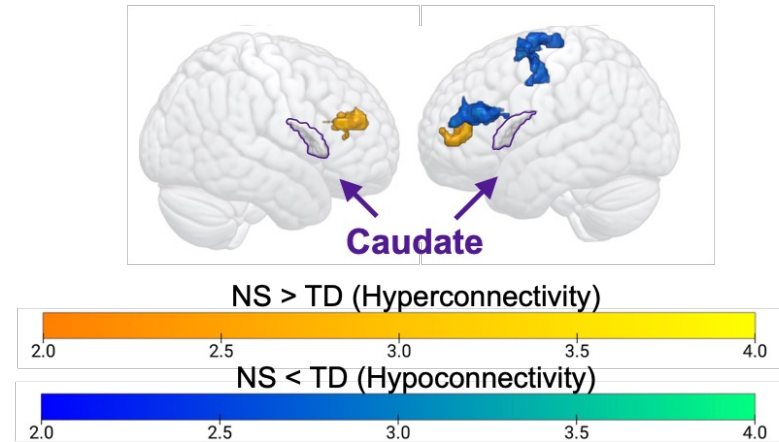


Hyper and hypoconnectivity with subcortical structures

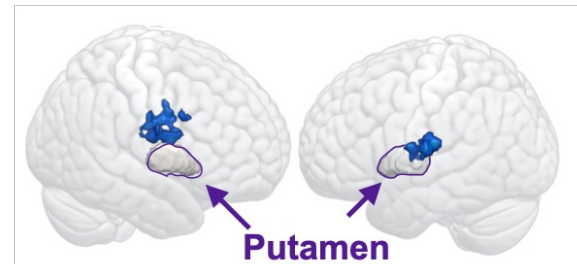
The corpus striatum is composed of the **caudate, putamen,** and nucleus accumbens

The striatum is implicated in attention and hyperactivity, core symptoms of ADHD

Noonan syndrome group demonstrates hyper- and hypo-connectivity with caudate

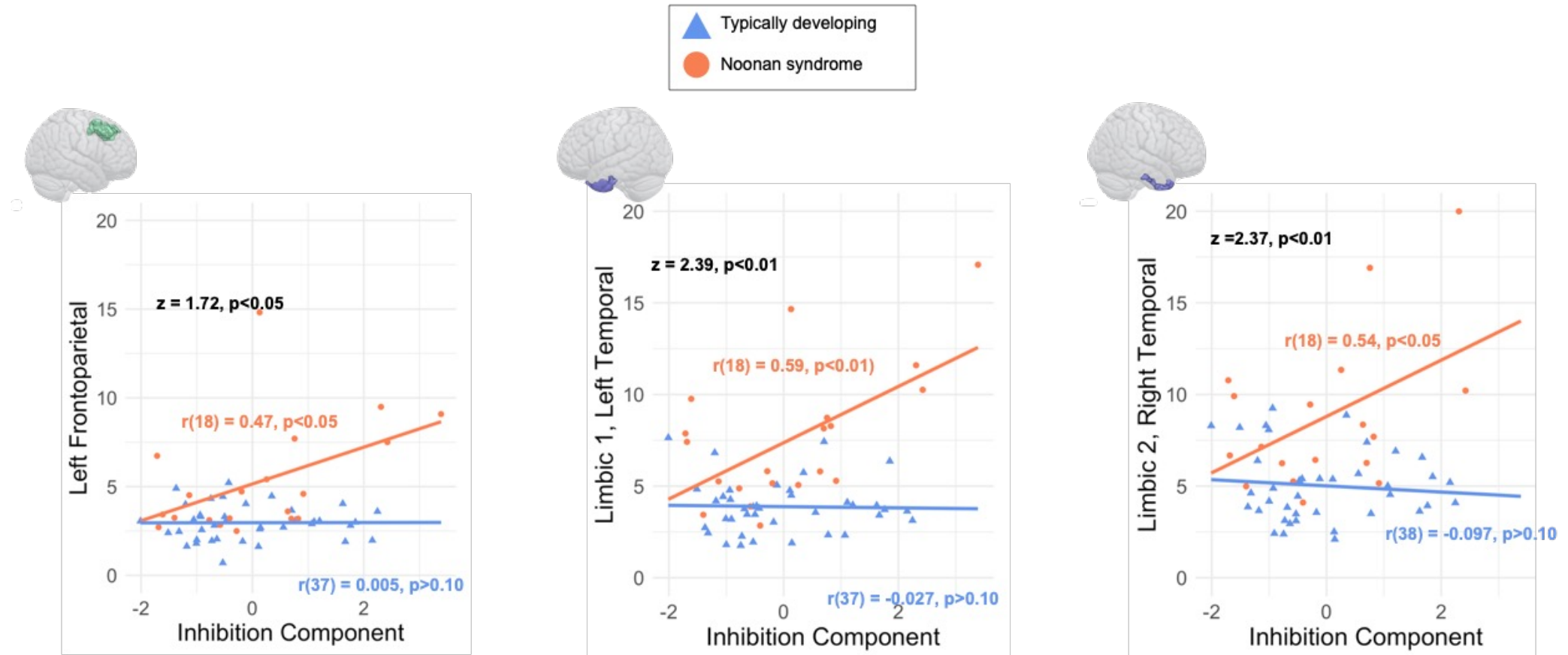


Noonan syndrome group demonstrates hypo-connectivity with putamen



(Bruno et al. 2022)

Connectivity is correlated with inhibition for Noonan syndrome group



(Bruno et al. 2022)

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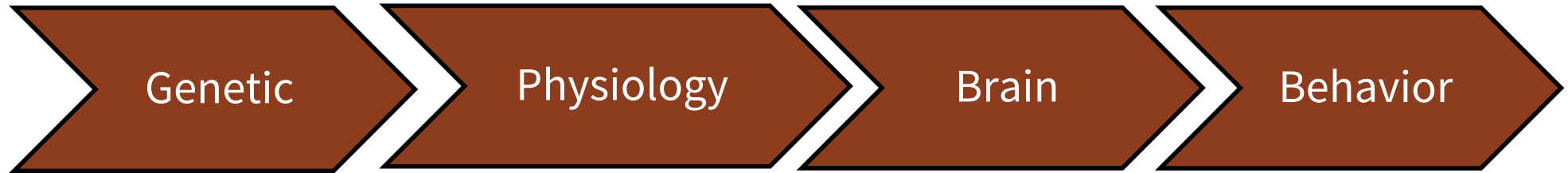
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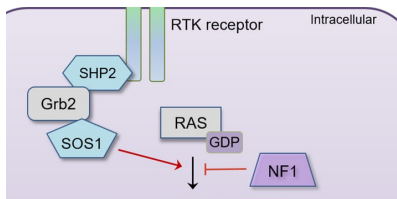
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NS and Turner Syndrome (TS) are highly similar on physiological/clinical and behavioral phenotypes

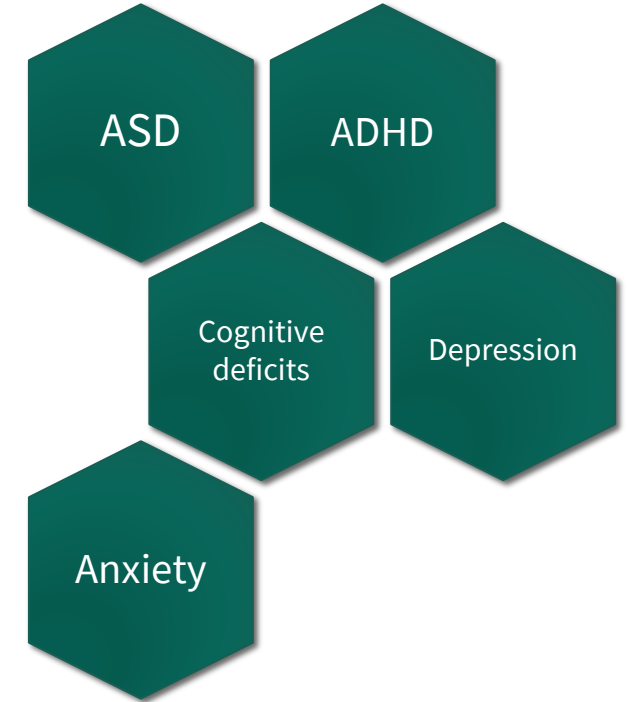
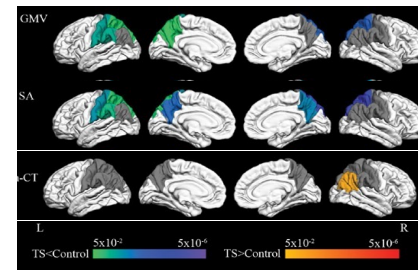
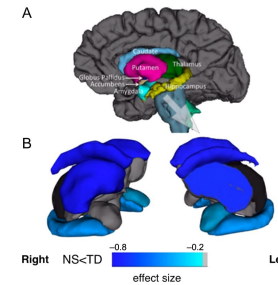
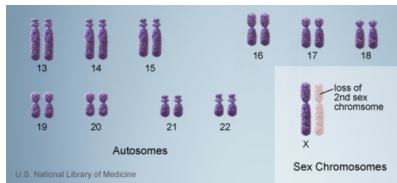


Noonan Syndrome



- Short stature
- Craniofacial dysmorphic features, webbed neck
- Hearing loss
- Eyelid ptosis
- Congenital heart anomalies
- Gastrointestinal issues
Kidney malformations
- Delayed/absent pubertal development

Turner Syndrome



Green, T., et al. (2014). Aberrant parietal cortex developmental trajectories in girls with turner syndrome and related visual-spatial cognitive development: A preliminary study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 165(6), 531-540.
 Rai, B., Naylor, P. E., Siqueiros Sanchez, M., Jo, B., Reiss, A. L., Green, T. Novel effects of Ras-MAPK pathogenic variants on the developing human brain and neuropsychiatry (under review)

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There are **higher rates of ADHD, ASD, Anxiety, Depression and ODD traits** in Noonan syndrome (but also diagnoses)

Traits (“subthreshold variation”) are also important as we can delineate an individual profile of strengths and areas of opportunity → develop tailored treatment plans

- *Early intervention!*
- *Psychotherapeutic interventions (behavioral, emotional)*
- *Pharmacological interventions to alleviate symptoms (ADHD, anxiety) – in some cases*
- *Individualized school plans (in collaboration with the school)*

Specific biomarkers in Noonan syndrome in the form of brain structure and function

Structure

- Reduced striatal and hippocampal volumes
- Larger SA in fronto-temporal regions
- Smaller CT in temporal, frontal and parietal regions

Function

- Hyperconnectivity in attentional and limbic networks
- Hypoconnectivity with striatal structure

Take home messages

Some of these biomarkers are associated to behaviors to ADHD behaviors like **inhibition**, executive functioning components (**memory**) and social cognition

Again, there is power in knowledge, for developing but also tailoring interventions!

We want to find connections between  &  & behavior → targeted and knowledge-based interventions

Brain biomarkers are closer biologically to the genetic cause and may be more sensitive to interventions targeting molecular causes

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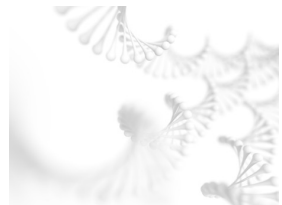
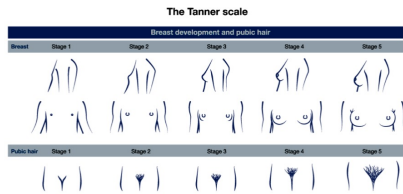
Join our Rasopathies research study!



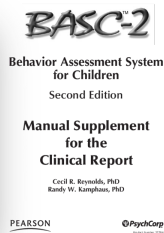
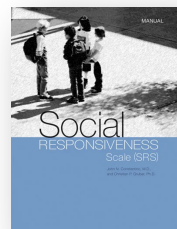
Currently recruiting participants for Rasopathies study!

What will you participate in?

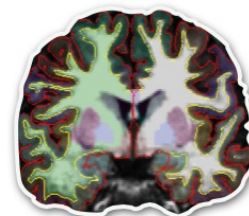
Clinical
Physical



Cognitive
Behavioral



Imaging prep
Imaging



New Brain Imaging Research
Opportunity for Children

Study includes:

- MRI scan of brain
- Comprehensive neuropsychological evaluation

You may qualify if your child is:

- 5-13 years of age
- Has Noonan syndrome or Neurofibromatosis type 1 or is typically developing

You will receive:

- A report summarizing results from neuropsychological evaluation
- \$100 honorarium for your participation

BRIDGE
Brain Imaging, Development, Genetics

STANFORD
SCHOOL OF MEDICINE

Travel costs for the study are covered by Stanford

Sign up online!



redcap.link/nf1_study

For more information, or to enroll in the study, please contact us at bridgelab@stanford.edu or (650) 440 1902.

For general information about participant rights, please contact the Stanford IRB at (866) 680-2906



Thank you!

Q & A