Pain, Executive Functions, and Structural Brain Correlates in Children With and Without Chronic Abdminal Pain

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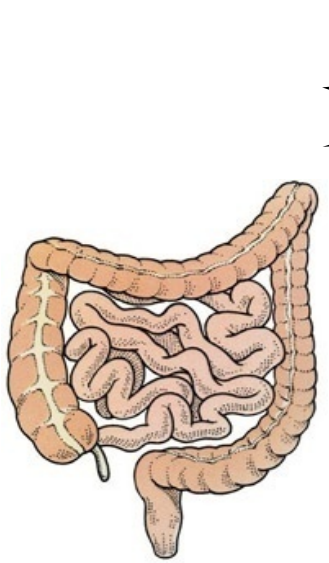
Why study pain and the brain in children?

- Chronic/recurrent abdominal pain (AP) is a hallmark symptom of several pediatric GI disorders **(Nurko et al 2009)**
  - IBD: chronic intestinal inflammation and pain
  - IBS: pain usually without inflammation
  - RAP: pain without inflammation
- Most common complaint in school-age children
  - 38% report weekly AP, 45% report GI symptoms **(Saps 2009)**
- Abdominal pain in IBD can become functional
  - 37% disabling abdominal pain in inactive/mild IBD **(Zimmerman 2010)**
- Mood problems frequently associated with AP **(Scharff 1997, Campo 2002)**
  - 61% of IBD patients with functional pain are depressed **(Szigethy 2010)**
- *Cognitive impairment* in IBD and IBS needs further definition.
  - Executive functions implicated **(Schreiber & Mrakotsky, 2011)**

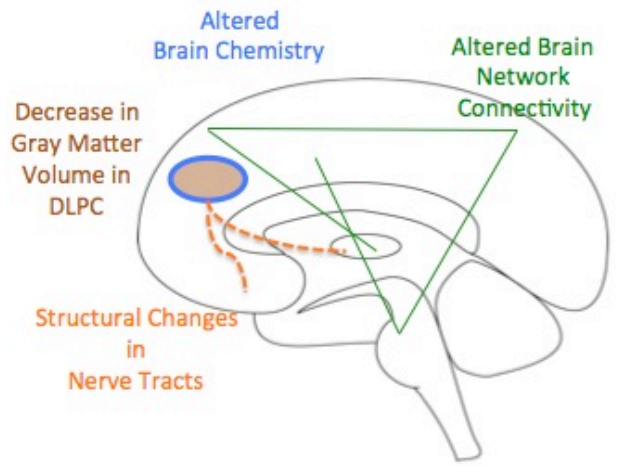
Why study pain and the brain in children?



Pain

Normal Brain

Chronic Pain Brain



Structure

Altered Behaviors

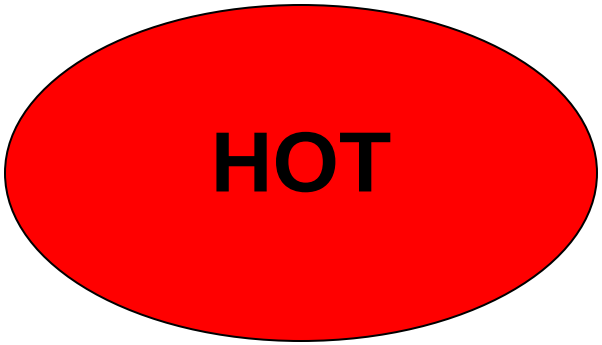
Sensory (e.g., spontaneous pain at rest)
Affective (e.g., anxiety, depression, suicide, addiction)
Cognitive (e.g., decreased attention)
Emotional (e.g., reward deficit state)

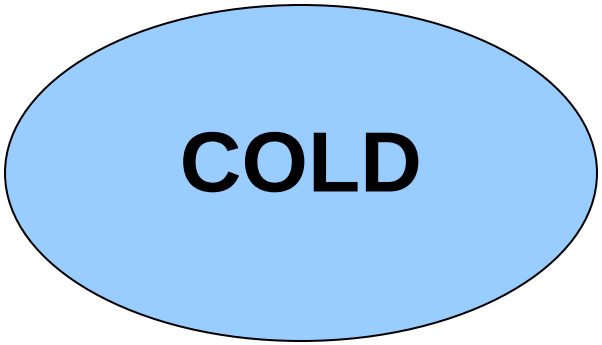
Executive Functions

Function

Borsook. Cerebrum. 2012 May-Jun;2012:7

What are executive functions (EF)?





Protracted Development

Behavior regulation

- Inhibitory control
- Emotional control
- Self-awareness

Cognitive functions

- Attention
- Planning/Strategizing
- Problem-solving
- Follow-through/Executing
- Monitoring

Pain Self-Management

HYPOTHESES

STUDY 1:

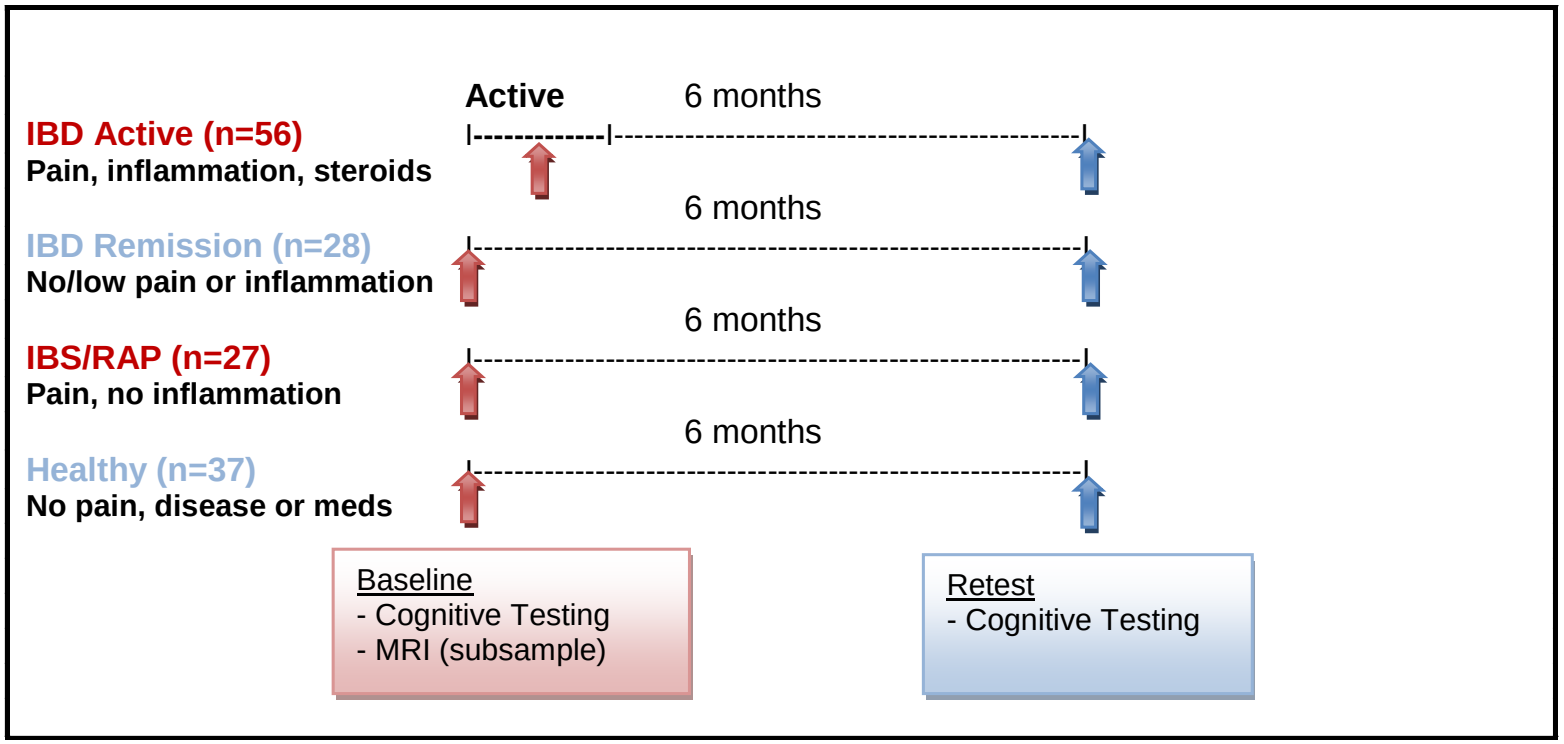
Does PAIN affect executive functions?

STUDY 2:

Does PAIN disrupt brain structures, particularly limbic?

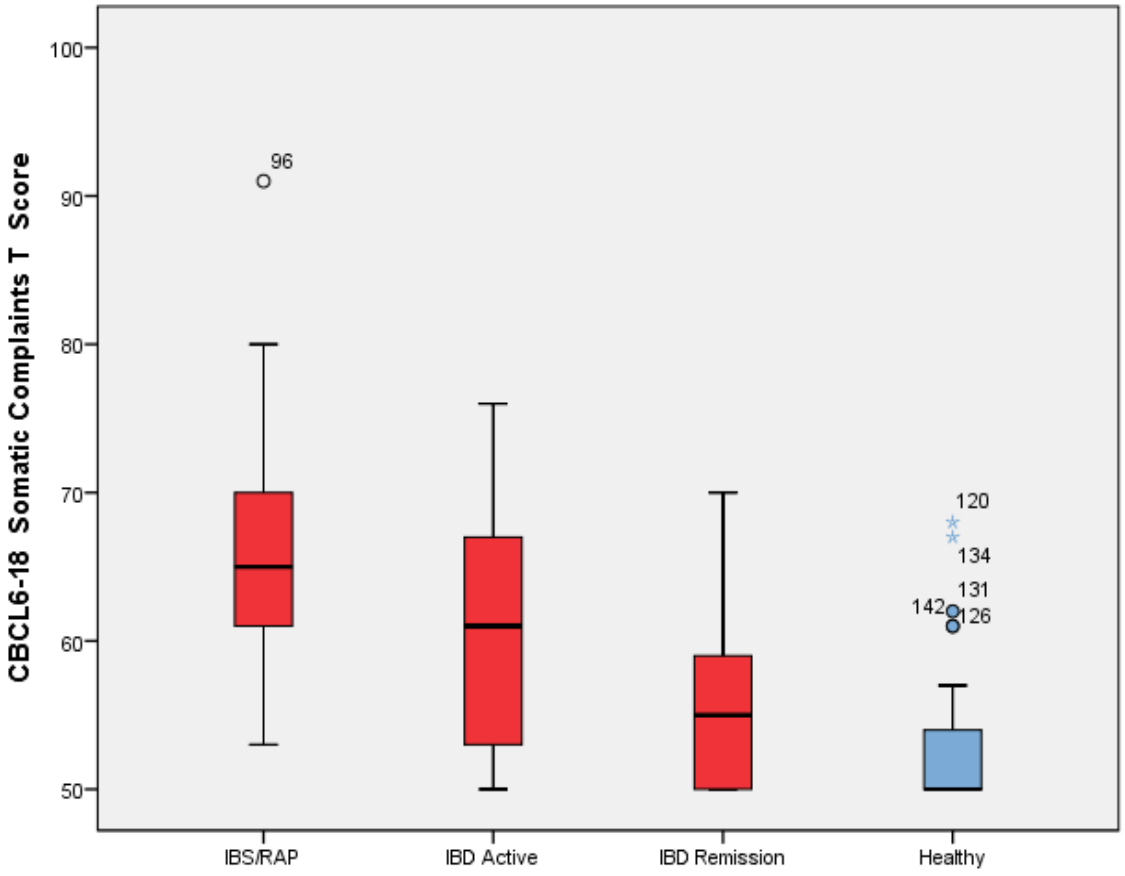
STUDY 1: Pain and Executive Function

- N=148 children age 8-16 years



  - Cognitive/Behavioral Assessment:
    - Standardized laboratory tests and parent/self ratings of cognitive, executive, and emotional functions

Study 1. Results – Group Comparison
Pain severity and somatic complaints higher in IBS and IBD Active groups



Study 1. Results – Whole Sample
Pain severity and somatic complaints are associated with poorer executive functions

Behavior/Cognitive Scales	Pain (VASP)	p	Somatic (CBCL)	p	Somatic (YSR)	p
BRIEF-Parent Behavior Regulation	.217	.008	.459	.000	.216	.036
BRIEF-Self Report Behavior Regulation	.290	.004	.337	.001	.430	.000
BRIEF-Parent Report Metacognitive	.304	.000	.402	.000	.239	.020
BRIEF-Self Report Metacognitive	.386	.000	.257	011	.394	.000
Cognitive Failures Rating Parent	.227	.005	.324	.000	.228	.026
Cognitive Failures Rating Self Report	.205	.013	.163	.047	.341	.001
CBCL Attention Problems	.183	.026	.400	.000	.250	.014
Rey Complex Figure Copy Errors	.203	.033	.202	.034	ns	ns
YSR Academic Performance	ns	ns	-.228	.025	-.220	.032

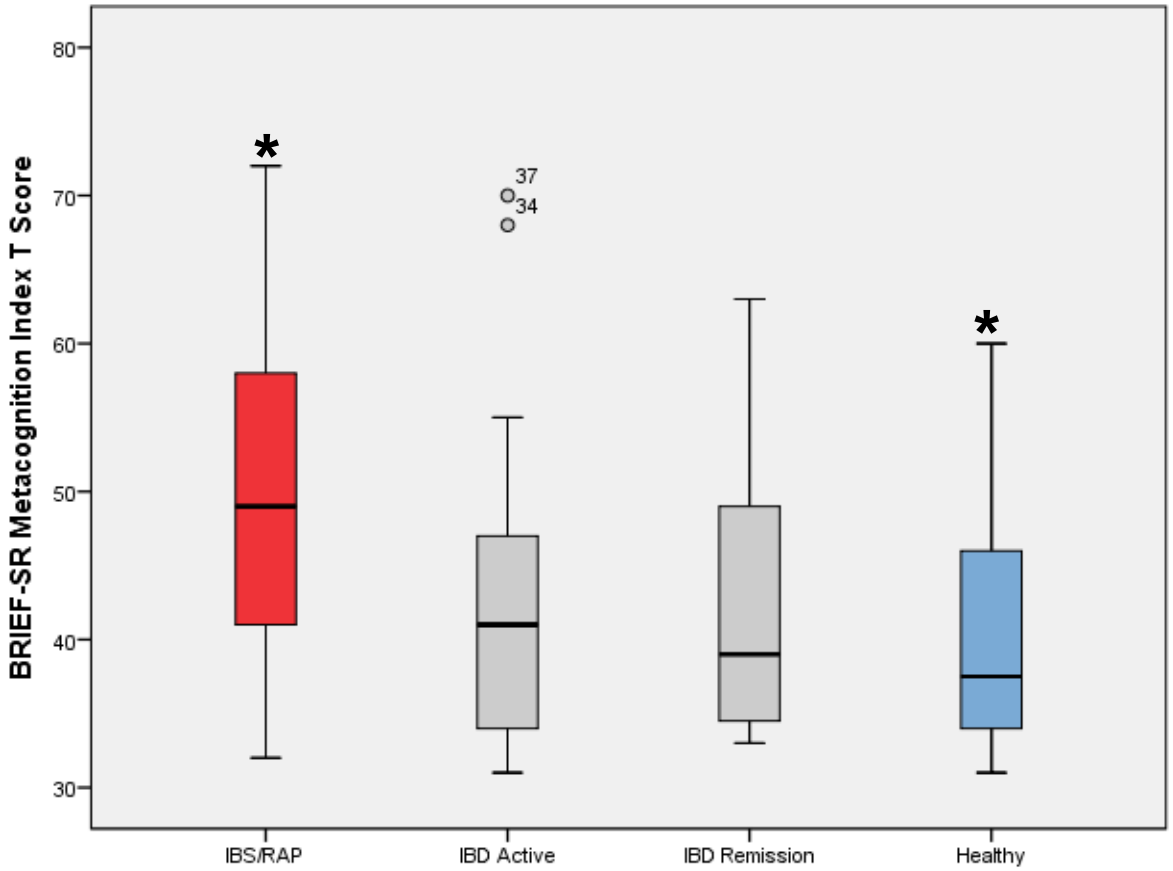
- ↑ pain - ↑ *executive function problems/ cognitive errors*

Study 1. Results
Pain severity and somatic complaints are associated with more emotional problems

Behavior/Cognitive Scales	Pain (VASP)	p	Somatic (CBCL)	p	Somatic (YSR)	p
CBCL Internalizing (anxiety, depression)	.308	.000	.808	.000	.514	.000
CBCL Externalizing (aggression)	.251	.002	.431	.000	.349	.001
YSR Internalizing (anxiety, depression)	.317	.002	.431	.000	710	.000
YSR Externalizing (aggression)	.247	.016	.229	.026	.416	.000
Children's Depression Inventory- Parent	.352	.000	.528	.000	.371	.000
Children's Depression inventory- Child	.357	.000	.241	.003	.296	.004

- ↑ pain - ↑ ***emotional problems*** in daily life
- Irrespective of condition → pain has debilitating effects on daily function

Study 1. Results
Executive functions most disrupted in IBS/RAP



***) p <.05** Bonferroni corrected

Study 1. Results
Executive functions at baseline predict pain severity and somatic symptoms 6 months later

Pain Symptom Scales at 6-months	Baseline Executive Composite (BRIEFparent)	p	Baseline Executive Composite (BRIEFself)	p
VASP Pain Severity Retest	.174	.040	.255	.015
CBCL Somatic Complaints Retest	.255	.003	.500	.000
YSR Somatic Complaints Retest			.457	.000
PedsQL Parent- Physical Function	-.385	.000	-.460	.000
PedsQL Child- Physical Function			-.436	.000
Perceived Stress Retest	.167	.057	.369	.000

- ↑ executive function problems at baseline → ↑ reported pain at retest

STUDY 2: Pain and Brain Correlates

- Pain can disrupt the brain, both gray and white matter (Geha 2008; Yu 2013)
- Reduced gray and white matter found in adults with IBS as compared to healthy controls (Seminowicz 2010; Ellingson 2013)
- No data available for pediatric IBD, IBS/RAP.
- Loss of white matter integrity has been associated with functional impairment
  - emotion regulation, memory, processing speed

    → **EXECUTIVE FUNCTIONS**

Study 2 Methods

- N= 35 children age 9-14 years (matched for age and gender)

IBD-Active n=12	Healthy controls n=23
Acute flare, pain, steroids	No illness, pain, medication

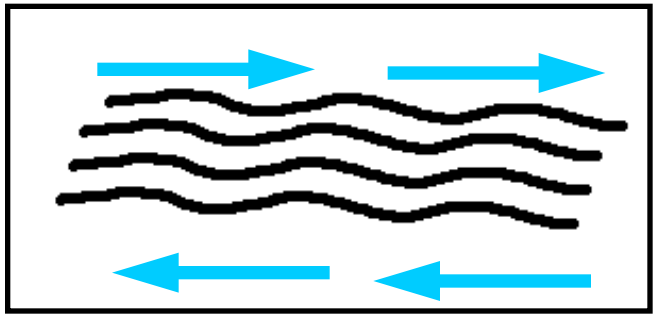
Groups comparable in demographics, SES, and IQ

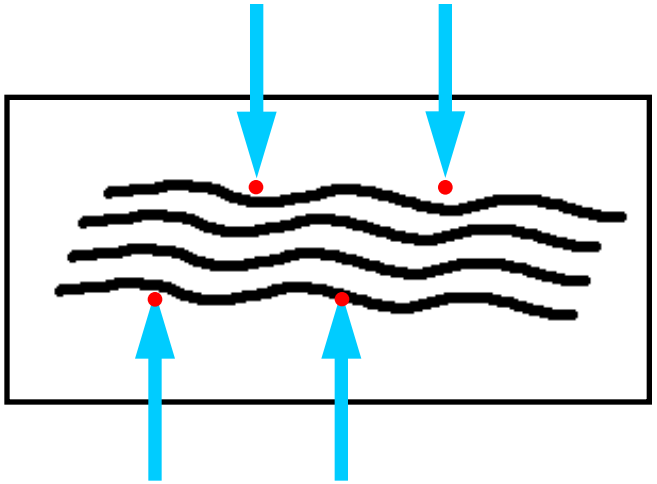
- **Structural and diffusion magnetic resonance imaging (MRI, DTI)**
  - 3 Tesla Siemens Trio MRI scanner
  - Single shot spin-echo echo planar imaging
  - 30 diffusion sensitization directions
  - Voxel sizes 1.7 x 1.7 x 1.7 mm
  - DTI: FSL TBSS
  - Volumetric: Freesurfer

Diffusion Tensor Imaging (DTI)

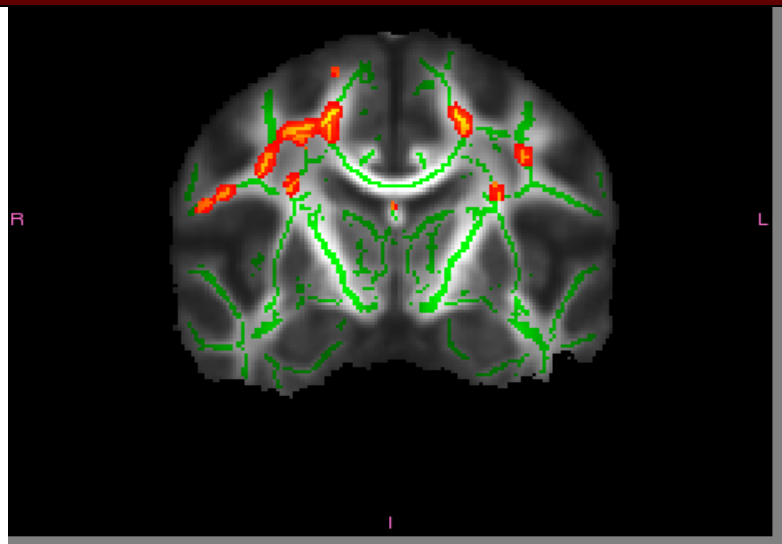
Diffusions Tensor Imaging (DTI)

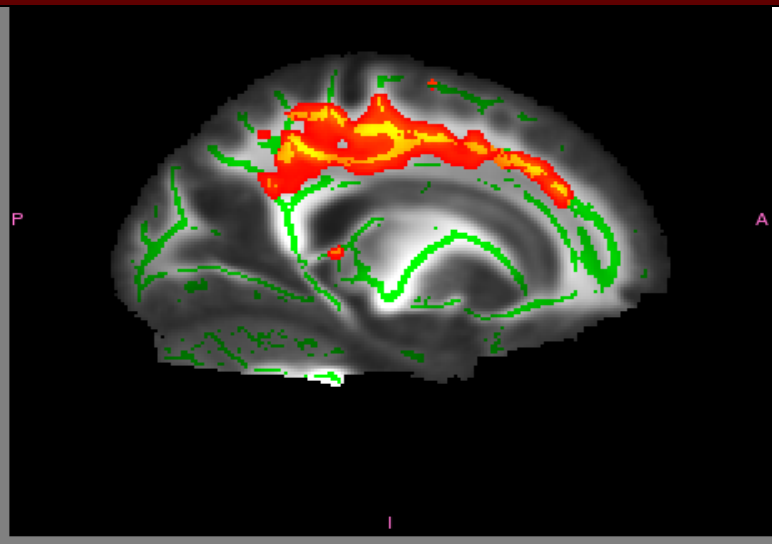
- Diffusion of water molecules in brain tissue
  - maps white matter fiber tracts & brain connectivity
- Fractional Anisotropy (FA)

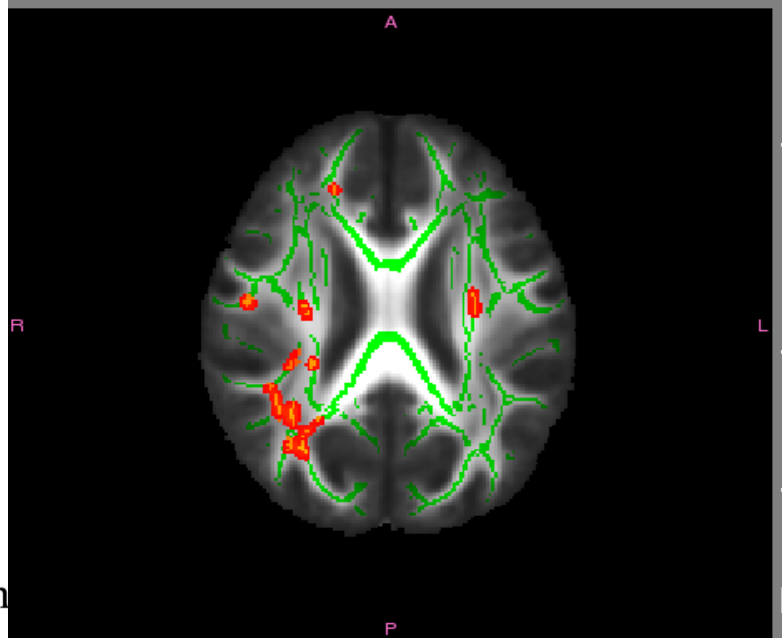




IBD patients during flare and acute pain show reduced white matter integrity compared to healthy controls







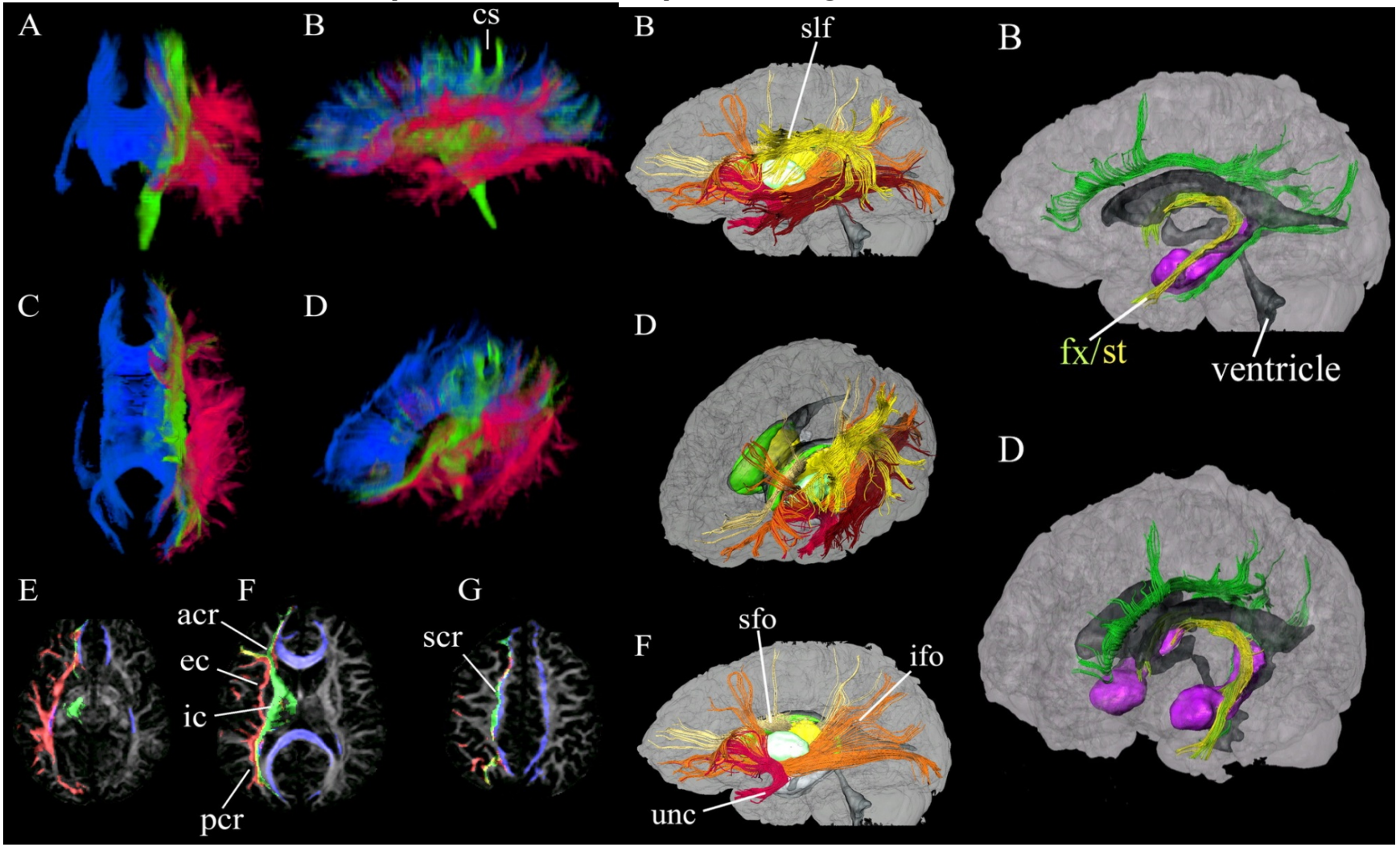
$FA_{\text{IBD-Active}} < FA_{\text{Healthy Control}}$

- R & L posterior and superior corona radiata/CST/R SLF (p= .010, .019)
- L superior longitudinal fasciculus (temporal) (p=.039)
- R & L fornix (p=.041, .044)

FSL TBSS- corrected analyses

3D presentation of white matter fiber tracts

Corona radiata-corticospinal tract **superior long. fasciculus** **fornix**



Wakana S et al. Radiology 2004;230:77-87

Higher report of pain/physical symptoms correlates with lower white matter integrity

	White Matter Tract (Mean FA)	Pain/Somatic Complaints (CBCL-parent) $r_{Spearman}$	p	Physical Problems (PedsQL-child) $r_{Spearman}$	p
Limbic connections	R fornix	-.38	.025		
	L fornix			.38	.026
	R uncinate	-.34	.045		
	L uncinate			.29	.090
Projection Fibers	R internal capsule- anterior limb	-.38	.024		
	R internal capsule- posterior limb	-.34	.045		
	R anterior corona rad/ thalamic rad			.40	.016
	L anterior corona rad/thalamic rad			.40	.017
	R posterior corona radiata	-.43	.009	.28	.099
	L posterior corona radiata			.37	.031
	R superior longitudinal fasciculus	-.37	.028		

↑ report of somatic symptoms, aches & pain- ↓ white matter integrity (FA)

Study 2 Results
Pain and executive problems are associated with lower brain volume

- Subcortical volumes

↑ Pain –

↓ R amygdala ***r* = -.447, *p* =.007**

↓ R & L thalamus **R: *r* = .432, *p* =.010**

L: *r* = .384, *p* =.023

↓ EF - ↓ nucleus accumbens

- Behavior Regulation (L)

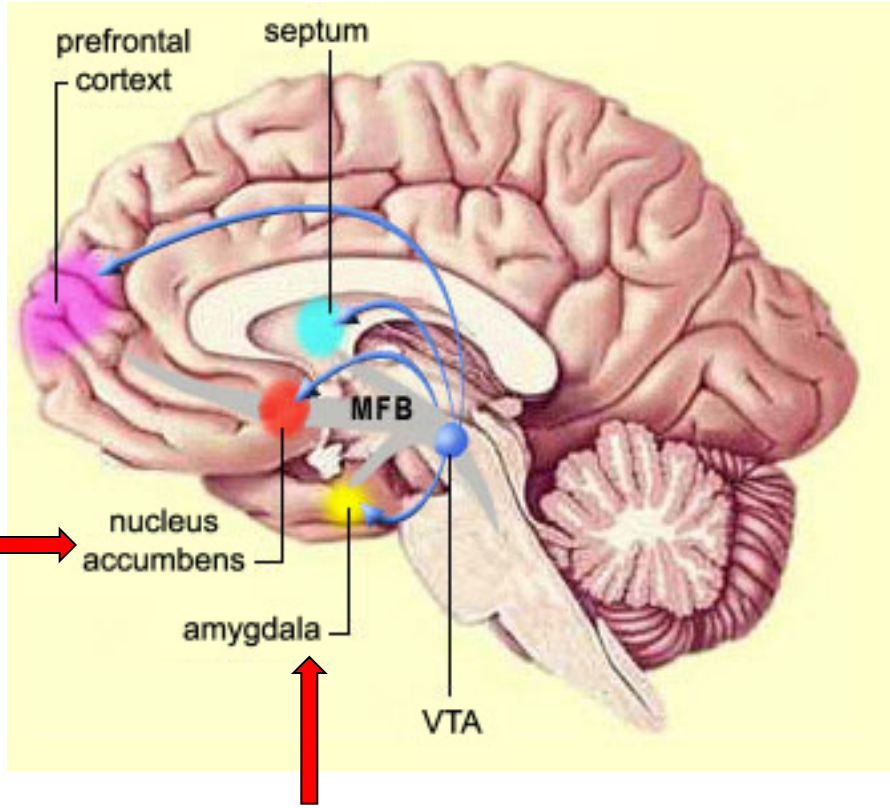
***r* = -.312 , *p*=.068**

- Metacognitive

***r* = -.398 , *p*=.018**

- Cognitive Failures

***r* = -.397 , *p*=.018**



Conclusion

STUDY 1

- Higher **pain** associated with more problems in **executive functions**, both on laboratory tests and in daily life
  - behavior regulation
  - metacognition
  - cognitive errors
- Presumed to be mediated by prefrontal cortex, limbic system, and interconnecting white matter
- Executive functions predict experience of pain at later time
  - Poorer EF → maladaptive coping strategies
- The direction of this relationship remains to be determined
- Clinical implications → *executive functions as target for intervention*

Conclusion

STUDY 2

- Current data suggests negative relationship between reported **pain** and **brain** regions, particularly limbic/subcortical
  - white matter: limbic (fornix, uncinate), projection (SCR, CST), association (SLF)
  - gray matter: amygdala, thalamus (nucleus accumbens for EF)
- Association between pain and reduced white and gray matter *clinically* relevant
  - limbic system is intricately interconnected with prefrontal cortex
  - Both have been linked to *hot* and *cold executive functions*

Determine those patients at greatest risk for difficulties in EF

- Cognitive/EF screen

Develop strategies to improve EF necessary for pain self-management

- integrate in behavioral interventions (CBT), classroom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