

The Gut-Brain Axis and Development of Functional GI Disorders

Peter L. Lu, MD, MS

Division of Gastroenterology, Hepatology, and Nutrition

Nationwide Children's Hospital/The Ohio State University College of Medicine

Columbus, Ohio, USA

Twitter: **@PLLU**

Disclosures

Mahana Therapeutics

Overview

- Functional GI disorders (FGIDs)
- The gut-brain axis
- Early life events
- Future directions

What are functional GI disorders (FGIDs)?

Functional GI Disorders

- Disorders of gut-brain interaction
- Often involves changes in:
 - GI motility
 - Sensation
 - Mucosal and immune function
 - Gut microbiota
 - Central nervous system processing

Drossman D, et al. *Gastroenterology*. 2016

Infant	Toddler	Child
Infant regurgitation		
	Cyclic vomiting syndrome	
		Functional nausea
Infant colic		Functional dyspepsia
Dyschezia		Irritable bowel syndrome
		Functional abdominal pain
	Functional diarrhea	
Functional constipation		

Adapted from Benninga MA, Nurko S, et al. *Gastroenterology*. 2016

Infant	Toddler	Child
Infant regurgitation		
	Cyclic vomiting syndrome	
		Functional nausea
Infant colic		Functional dyspepsia
Dyschezia		Irritable bowel syndrome
		Functional abdominal pain
	Functional diarrhea	
Functional constipation		

Adapted from Benninga MA, Nurko S, et al. *Gastroenterology*. 2016

Infant	Toddler	Child
Infant regurgitation	Cyclic vomiting syndrome	
Infant colic		
Dyschezia	Functional dyspepsia	
	Irritable bowel syndrome	
	Functional abdominal pain	
	Functional diarrhea	
Functional constipation		

Adapted from Benninga MA, Nurko S, et al. *Gastroenterology*. 2016

Infant	Toddler	Child
Infant regurgitation		
	Cyclic vomiting syndrome	
		Functional nausea
Infant colic		Functional dyspepsia
Dyschezia		Irritable bowel syndrome
		Functional abdominal pain
	Functional diarrhea	
Functional constipation		

Adapted from Benninga MA, Nurko S, et al. *Gastroenterology*. 2016

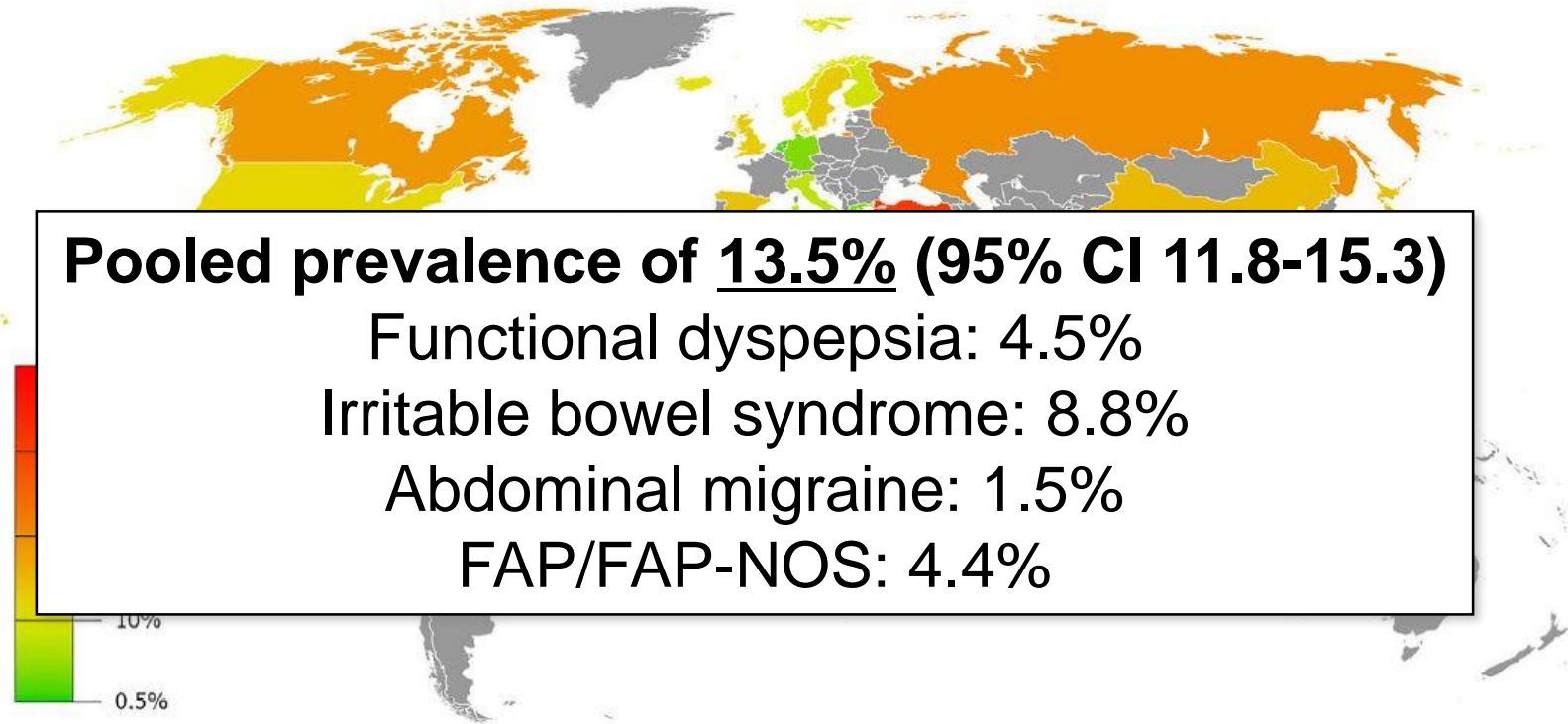


Fig 2. Geographic distribution of functional abdominal pain in children, presented in pooled-prevalence rates.

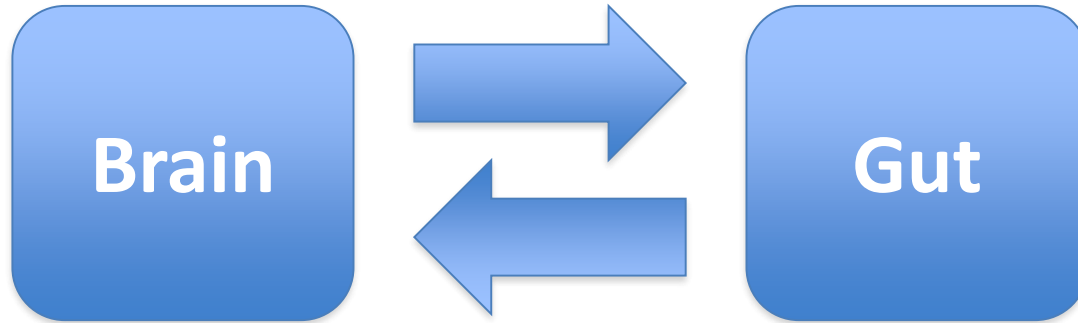
Korterink JJ, et al. *PLoS One*. 2015
Park R, et al. *Neurogastroenterol Motil*. 2015
Lu PL, et al. *Neurogastroenterol Motil*. 2016

What is the Gut-Brain Axis?

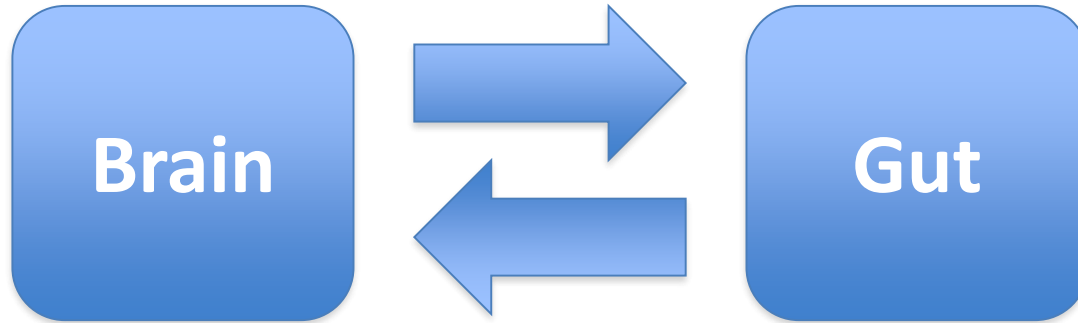


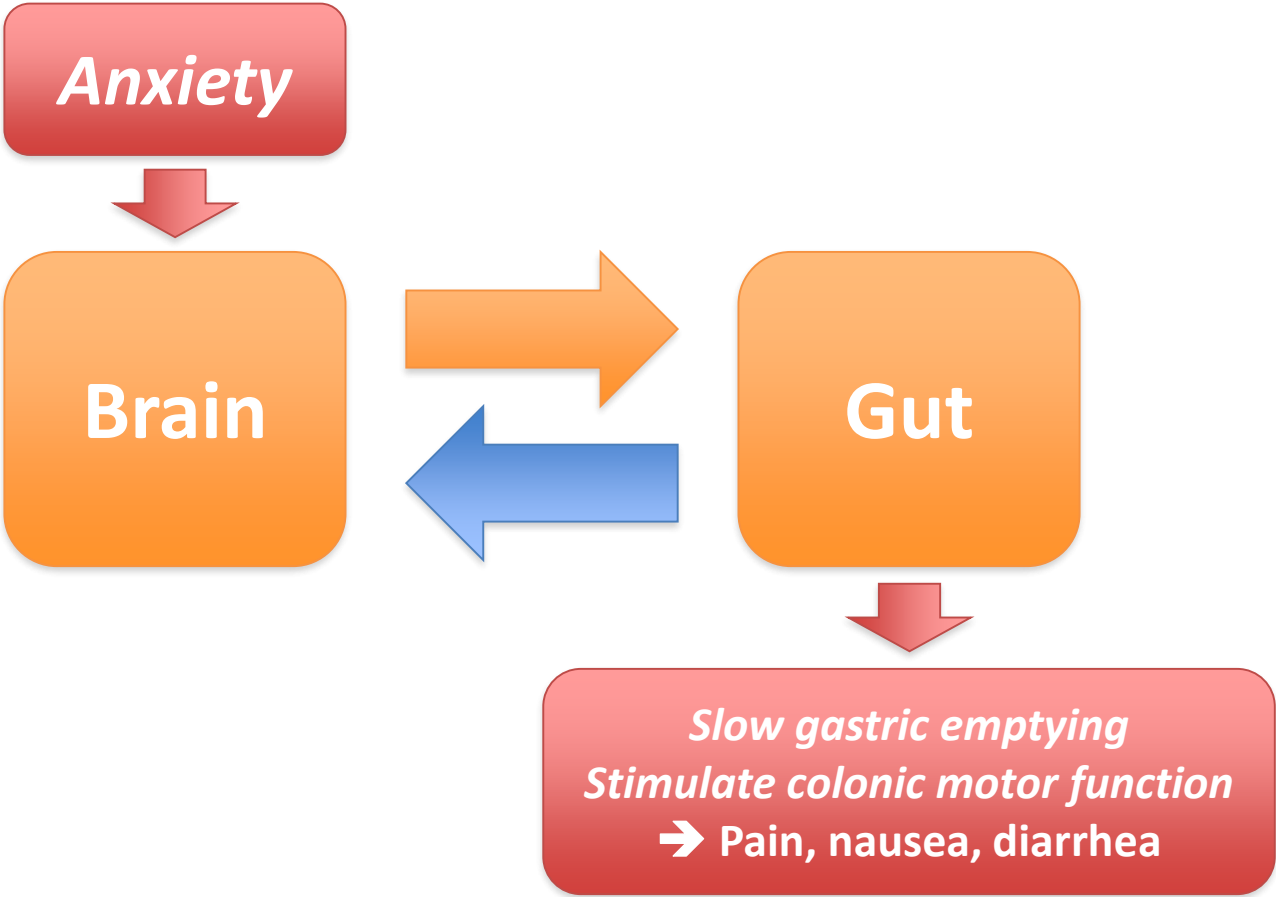


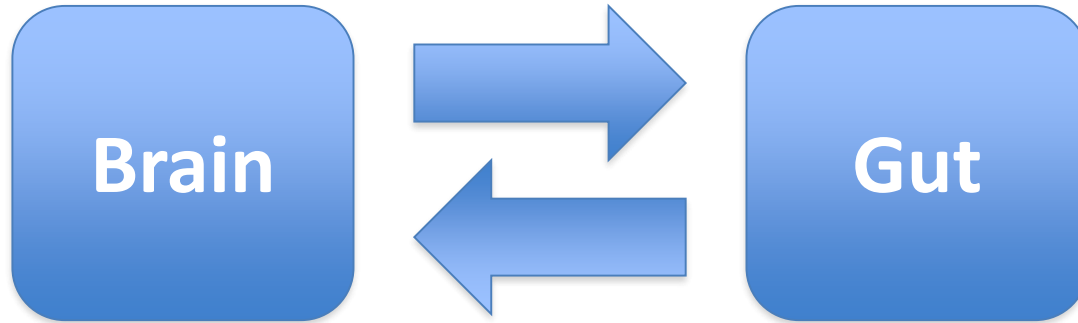
Gut-Brain Axis

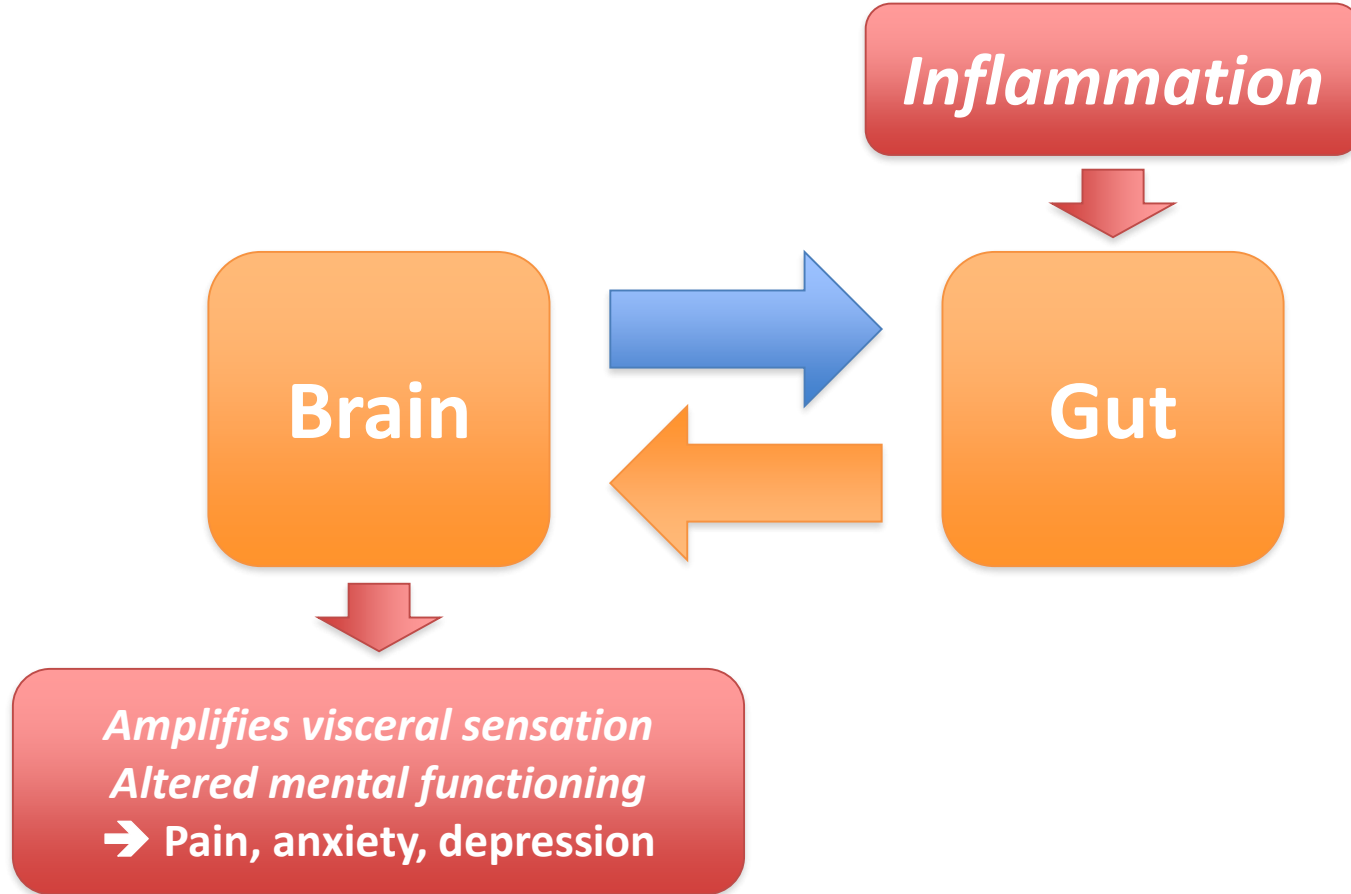


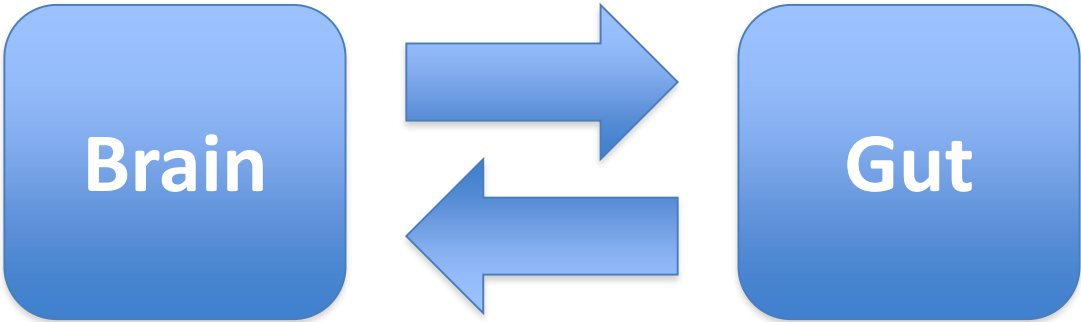
Drossman D, et al. *Gastroenterology*. 2016
Mayer EA, et al. *Nat Rev Gastroenterol Hepatol*. 2015

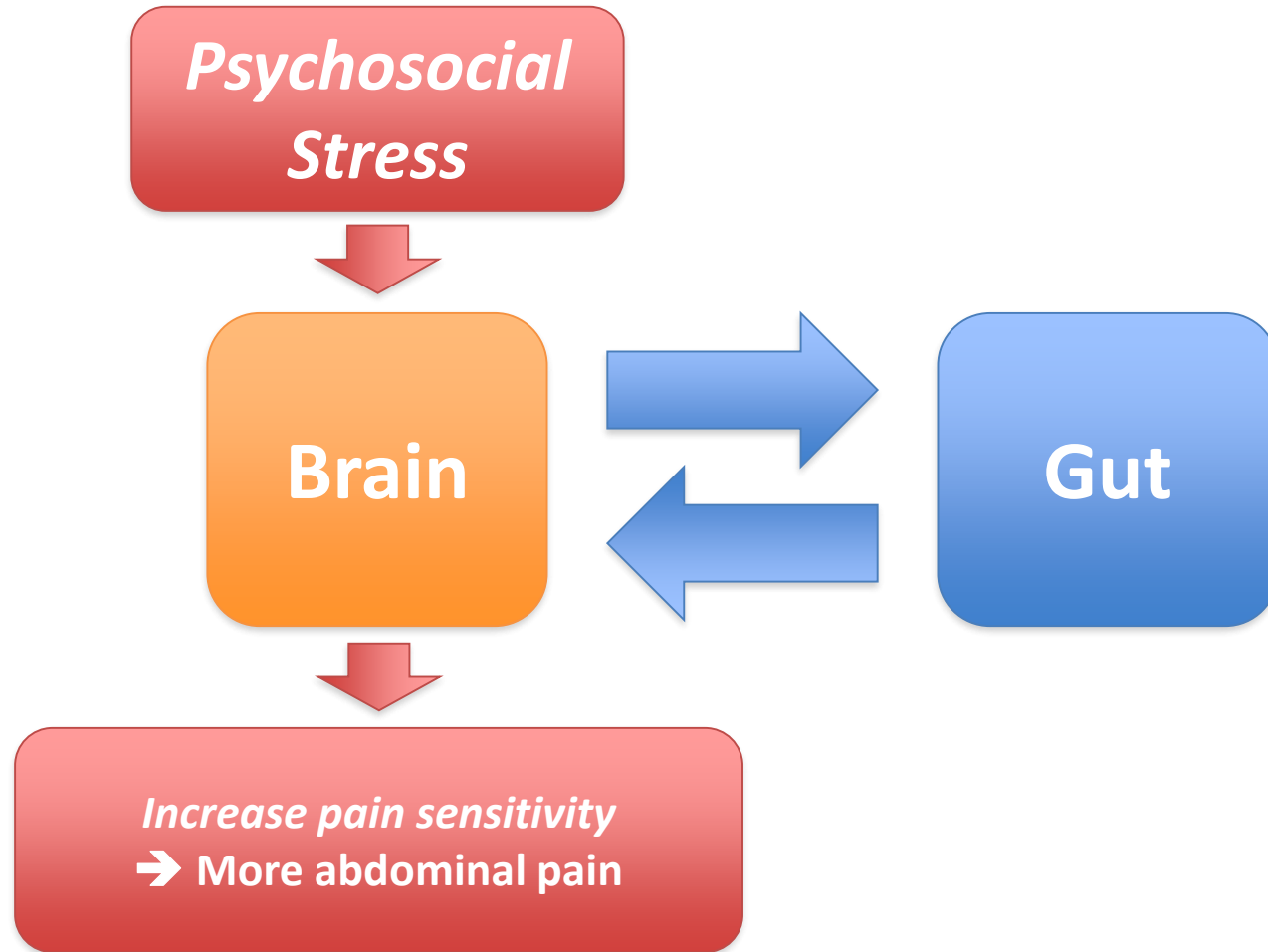


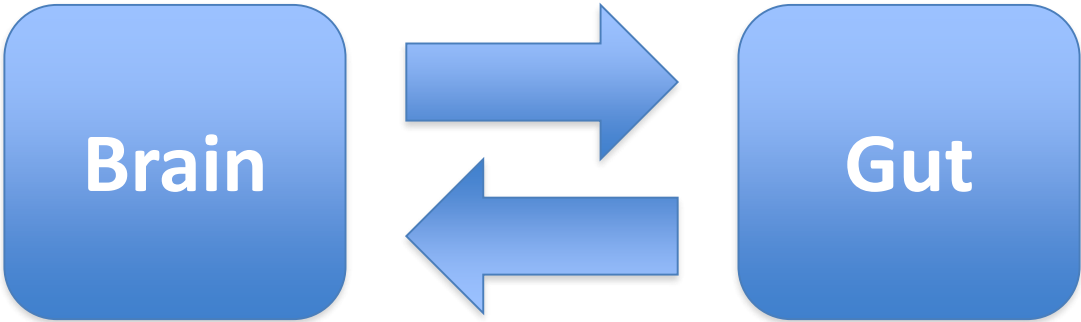


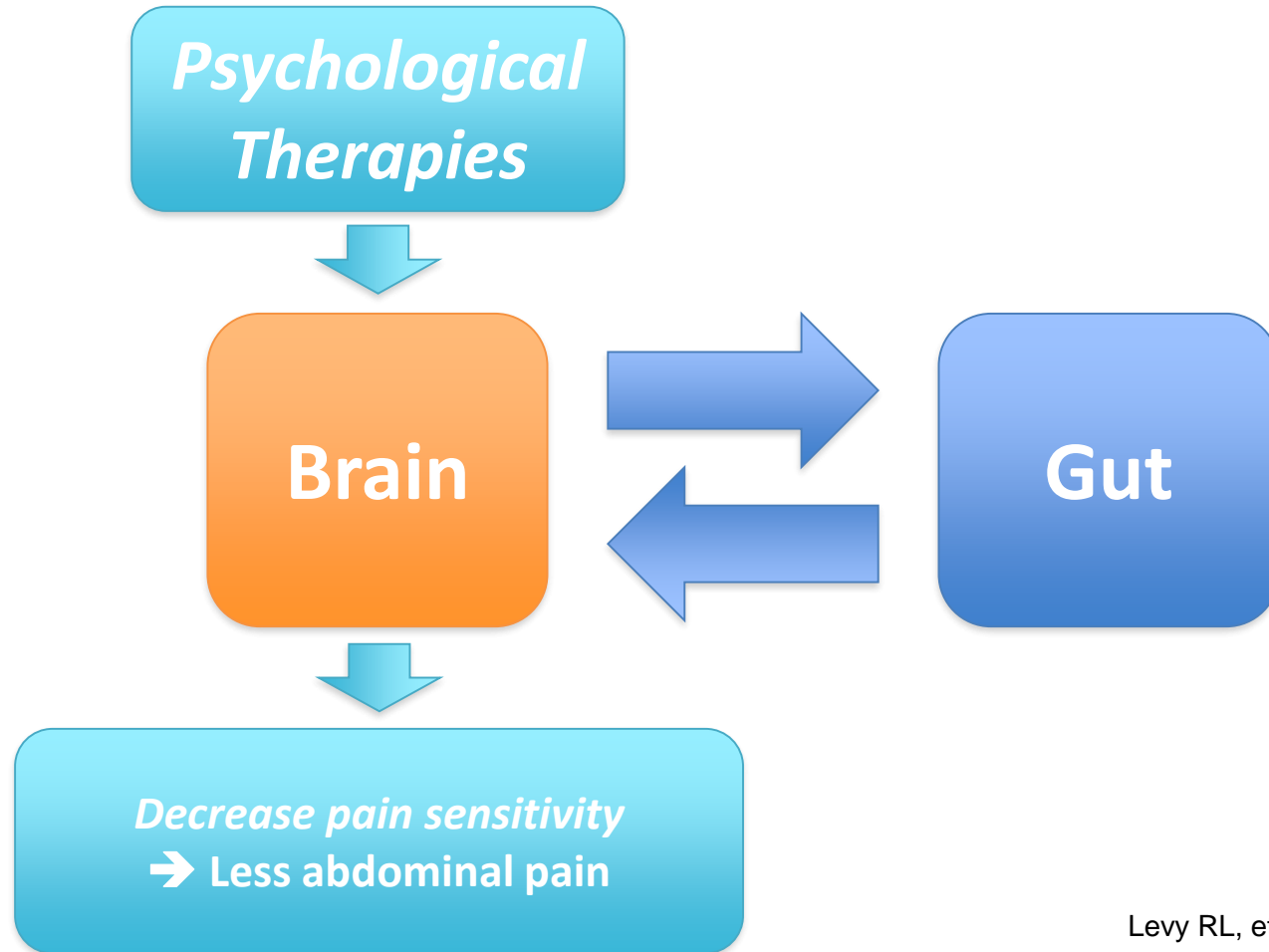












How do early life events affect development of FGIDs?

Early life factors

Genetic factors

Early life events: Physical and psychological stressors

Medical events: Infections and allergic conditions

Psychosocial factors

Psychological stressors

Response to stress

Comorbid psychological conditions

Physiological factors

Visceral hypersensitivity

Gastrointestinal dysmotility

Altered gut microbiome



Disordered gut-brain interaction

FGID presentation

Early life factors

Genetic factors

Early life events: Physical and psychological stressors

Medical events: Infections and allergic conditions

Psychosocial factors

Psychological stressors

Response to stress

Comorbid psychological conditions

Physiological factors

Visceral hypersensitivity

Gastrointestinal dysmotility

Altered gut microbiome



Disordered gut-brain interaction

FGID presentation

Early life events

- In animals, neonatal irritation of the GI tract can lead to dysfunction in adulthood
- In humans, physical stressors in infancy and childhood are associated with FAPDs later in childhood and adulthood

Liu LS, et al. *Gastroenterology*. 2008

Smith C et al. *Neurogastroenterol Motil*. 2007

Traub RJ, et al. *Gastroenterology*. 2008

Early life events

- Events in early infancy can cause lasting changes to nociceptive neuronal pathways
- Events later in childhood can also have lasting effects, potentially through epigenetic changes

Mayer EA, et al. *Nat Rev Gastroenterol Hepatol*. 2015

Miranda A. *JPGN*. 2008

Liu S, et al. *Neurogastroenterol Motil*. 2017

Perinatal Factors	Associated with FGID	Not associated with FGID
Cesarean delivery	<ol style="list-style-type: none"> 1. Waehrens R, et al. <i>Scand J Gastroenterol.</i> 2018 2. Olen O, et al. <i>Neurogastroenterol Motil.</i> 2018 	<ol style="list-style-type: none"> 1. Velasco-Benitez CA, et al. <i>JPGN.</i> 2020 2. Raslau D, et al. <i>Neurogastroenterol Motil.</i> 2016 3. Koloski NA, et al. <i>Neurogastroenterol Motil.</i> 2015
Prematurity	<ol style="list-style-type: none"> 1. Velasco-Benitez CA, et al. <i>JPGN.</i> 2020 	<ol style="list-style-type: none"> 1. Olen O, et al. <i>Neurogastroenterol Motil.</i> 2018 2. Koloski NA, et al. <i>Neurogastroenterol Motil.</i> 2015
Low birth weight	<ol style="list-style-type: none"> 1. Waehrens R, et al. <i>Scand J Gastroenterol.</i> 2018 2. Raslau D, et al. <i>Neurogastroenterol Motil.</i> 2016 	<ol style="list-style-type: none"> 1. Olen O, et al. <i>Neurogastroenterol Motil.</i> 2018
Gastric suctioning	<ol style="list-style-type: none"> 1. Anand KJ, et al. <i>J Pediatr.</i> 2004 	

Infancy

- Allergic proctocolitis
- Pyloric stenosis
- Urinary tract infection
- Antibiotic treatment

Saps M, Lu PL, et al. *JPGN*. 2011

Di Nardo G, et al. *J Pediatr*. 2018

Saps M, et al. *J Pediatr*. 2011

Rosen JM, et al. *JPGN*. 2015

Tan TK, et al. *J Investig Med*. 2018

Uusijarvi A, et al. *Neurogastroenterol Motil*. 2014

Childhood

- Gastrointestinal infections
- Allergic disorders
- Henoch-Scholein purpura
- Umbilical hernia repair

Saps M, et al. *J Pediatr.* 2008

Cremon C, et al. *Gastroenterology.* 2014

Tan TK, et al. *JPGN.* 2017

Saps M, et al. *Dig Dis Sci.* 2011

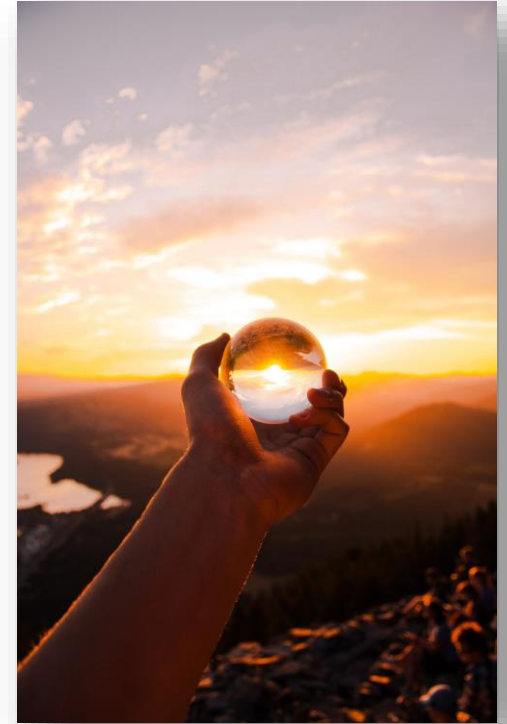
Rosen JM, et al. *J Pediatr.* 2013

Psychosocial Factors

	van Tilburg 2010 <i>Odds ratio</i>	Devanarayana 2014 <i>FAPD prevalence</i>
Physical Abuse	1.7	20%
Psychological Abuse	1.5	25%
Sexual Abuse	1.8	34%
<i>Control Group</i>		<i>13%</i>

van Tilburg MA, et al. *Ann Fam Med.* 2010
Devanarayana NM, et al. *J Trop Pediatr.* 2014
Talley NJ, et al. *Gut.* 1998

What does the future hold for children with FGIDs?



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™

Prevention

- FGIDs are common, costly, and challenging to treat
- We have identified many early life risk factors for FGID development
- It's time to work on ***prevention***

Lu PL, Saps M. *Clin Gastroenterol Hepatol*. 2018

Primary Prevention

- Limit unnecessary antibiotic use
- Try to prevent GI infections
- Teach coping skills to healthy children
- Be someone a child can confide in

Lu PL, Saps M. *Clin Gastroenterol Hepatol*. 2018

Lu PL, et al. *JPGN*. 2019

Secondary Prevention

- Involve a psychologist early
- Treat comorbid anxiety and depression
- Teach families to avoid reinforcement

Lu PL, Saps M. *Clin Gastroenterol Hepatol*. 2018

Conclusion

- FGIDs are disorders of gut-brain interaction
- Early life events can influence the gut-brain axis and FGID development
- Understanding gut-brain interactions will improve our care for children with FGIDs

Thank you to Dr. Miguel Saps and Dr. Carlo Di Lorenzo