

WIE ENTSTEHEN FUNKTIONELLER  
NEUROLOGISCHER SYMPTOME:  
HYPOTHESEN ZUR PATHOPHYSIOLOGIE

Selma Aybek

INSELSPITAL  
PSYCHIATRISCHES KRANKENHAUS  
KÖLN

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Research in FND



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**HOW?**



**Depend on attention**  
**Weakness:** discordances  
**Tremor:** distractibility

Van Poppel et al., *Mov Disorder* 2011  
Pares et al., *Mov Disorder* 2013

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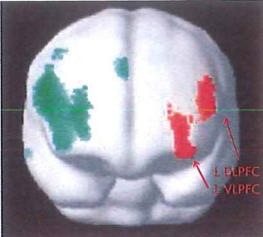
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### Simulation



Statistical parametric maps on a smoothed magnetic resonance image of the anterior surface of the brain (the right prefrontal cortex is on the left of the image). Red: regions where patients with hysterical ankle symptoms exhibit hypoactivation relative to controls; green: fingers exhibit hypoactivation relative to controls.

Spence, Lancet 2000

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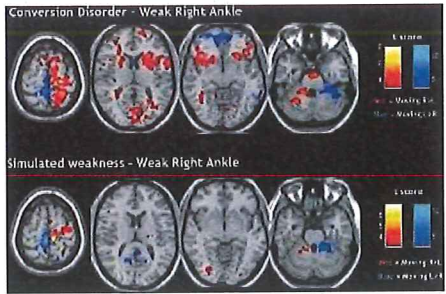
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### Simulation



Conversion Disorder - Weak Right Ankle

Simulated weakness - Weak Right Ankle

Stone Psychosomatic Med 2007

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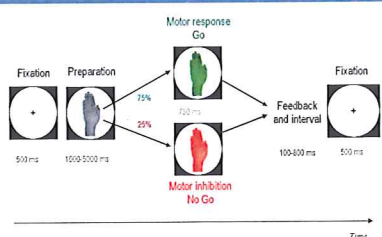
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### Go-NoGo



Fixation 500 ms

Preparation 1000-5000 ms

Motor response 700 ms

Go

Motor inhibition No Go

Feedback and interval 100-800 ms

Fixation 500 ms

Time

Cojan et al. Neuron 2009  
Cojan et al. NeuroImage 2009  
Vuilleumier P. Clin Neurophysiol 2014

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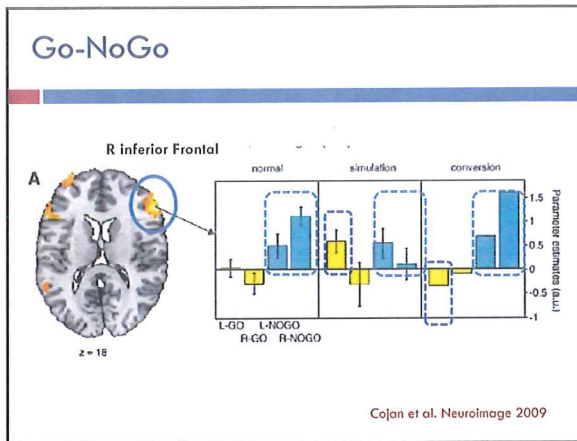
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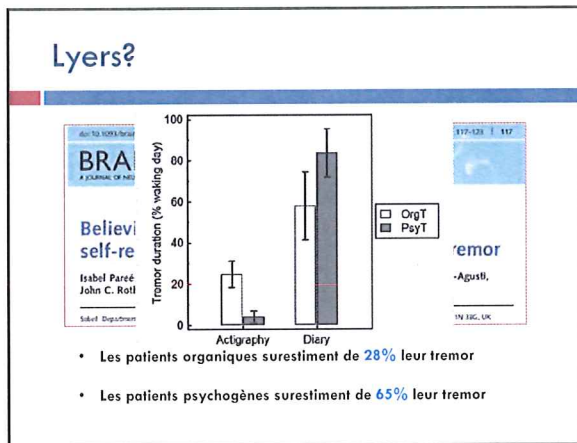
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### « Involuntary Simulation »

THE LANCET, OCTOBER 11, 1873.

**Clinical Lectures**

ON THE  
**NERVOUS MIMICRY OF ORGANIC DISEASES,**

Delivered at St. Bartholomew's Hospital,  
By **SIR JAMES PAGET, BART., F.R.S.,**  
CONSULTING PHYSICIAN TO THE HOSPITAL.

“the patient says “I cannot“  
it looks like “I will not“  
but it is “I cannot will”

Spence, Lancet 2000

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Invited review

**Volitional control of movement: The physiology of free will** ☆

Mark Hallett\*

*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH,  
Building 10, Room 5N226, 10 Center Dr. MSC 1426, Bethesda, MD 20892-1426, USA*

Clin Neurophys 2007

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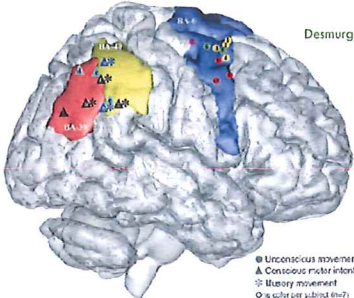
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**Illusion of Movement**



Desmurget et al. Science 2009

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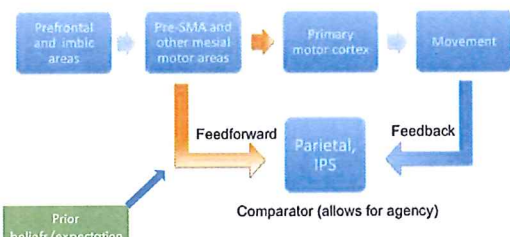
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**Sense of agency**



Clin Neurophys 2007

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### Prior Beliefs/Expectation

**BRAIN**  
A JOURNAL OF NEUROLOGY

OCCASIONAL PAPER  
**A Bayesian account of 'hysteria'**  
Mark J. Edwards,<sup>1,\*</sup> Rick A. Adams,<sup>2,\*</sup> Harriet Brown,<sup>2</sup> Isabel Pareés<sup>1</sup> and Karl J. Friston<sup>2</sup>

Normal sensation

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### Prior Beliefs/Expectation

SHORT REPORT  
**'Jumping to conclusions' bias in functional movement disorders**  
Isabel Pareés,<sup>1</sup> Panagiotis Kassavetis,<sup>1</sup> Tabish A Saifee,<sup>1</sup> Anna Sadnicka,<sup>1</sup> Kailash P Bhatia,<sup>1</sup> Aikaterini Fotopoulou,<sup>2</sup> Mark J Edwards<sup>1</sup>

Number of Draws to Decision	Patients	Controls
1	5	0
2	3	0
3	9	5
4	2	0
5	1	2
6	0	6
7	0	3
8	0	0
9	0	2

Figure 1 Number of draws to decision for patients and controls in condition 1. NNP 2012

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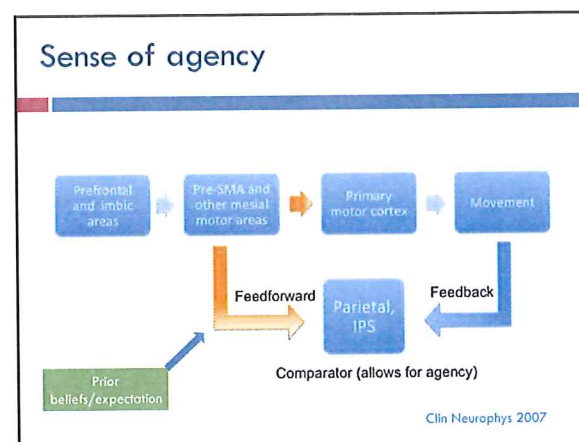
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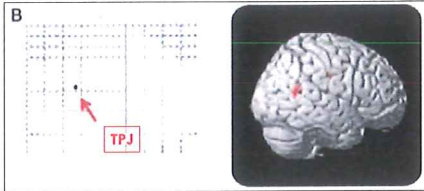
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## Sense of agency

**The involuntary nature of conversion disorder**  
V. Voon, C. Gallea, N. Hattori, M. Bruno, V. Ekanayake and M. Hallett  
*Neurology* 2010;74:223-228



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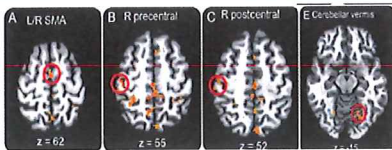
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## Self-agency

**ARTICLES**  
Carrie W. Meier, MD, PhD  
Kathrin LaFaver, MD  
Reyran Ansel, PhD  
Steven A. Egan, MD  
Mark Hallett, MD  
Sibona G. Horevitz, PhD

**Impaired self-agency in functional movement disorders**  
A resting-state fMRI study



Neurology 2016

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## HOW?



**Brain dysfunction**  
Sense of agency  
Right TPJ



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Research in FND



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Research in FND

Psychogenic



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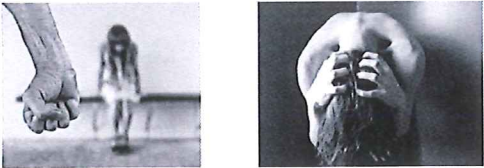
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Psychogenic



Early life experiences      Adverse life events

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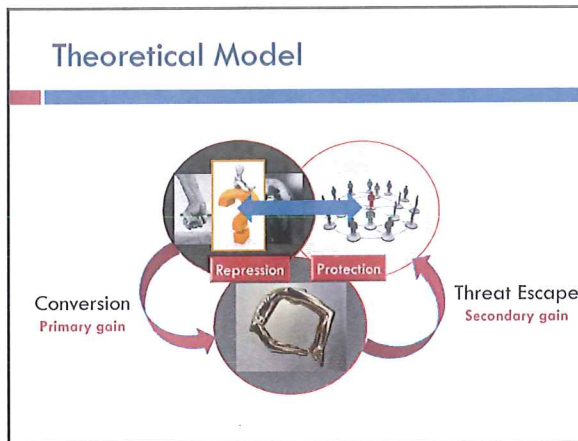
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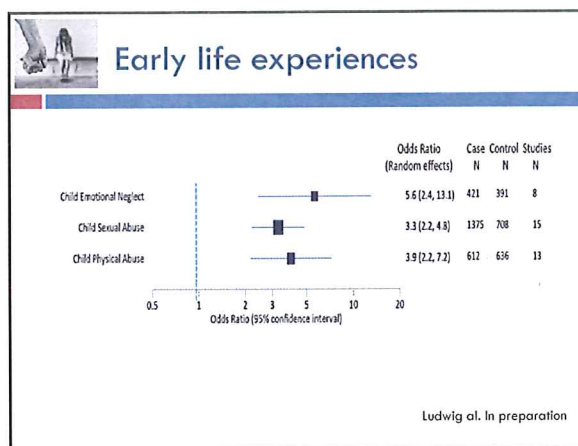
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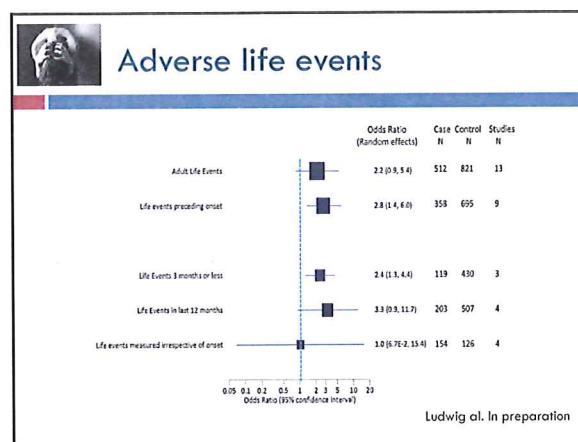
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**HOW?**



**Brain dysfunction**  
Sense of agency  
Right TPJ



**Psychological trauma**  
Risk factors



**WHY?**

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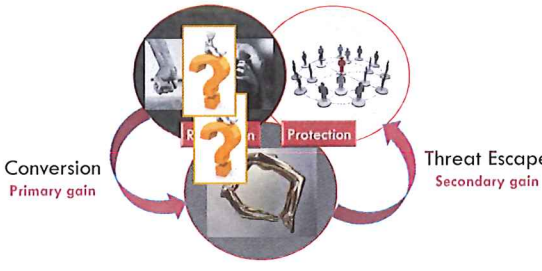
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**Theoretical Model**



**Conversion**  
Primary gain

**Protection**

**Threat Escape**  
Secondary gain

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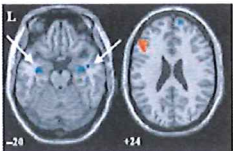
**Repression unwanted memories**

**nature**  
2001

**Suppressing unwanted memories by executive control**  
Michael C. Anderson & Collin Eick

**Science**  
AAAS

Neural Systems Underlying the Suppression of Unwanted Memories  
Michael C. Anderson, *et al.*  
Science 303, 232 (2004).  
DOI: 10.1126/science.1089504



DLPFC and hippocampus

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## Repression unwanted memories

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Original InvestigationJAMA Psychiatry 2014

### Neural Correlates of Recall of Life Events in Conversion Disorder

Selma Aybek, MD, Timothy R. Nicholson, MD, PhD, Fernando Zelaya, PhD, Owen G. GDaly, PhD, Tom J. Craig, MD, PhD, Anthony S. David, MD, Richard A. Kanaan, MD, PhD

*Life event and Difficulties Schedule (LEDS)*

- 'Psychological Stressor'
  - Severe + Secondary gain
- 'Control Stressor'
  - Severe + No secondary gain

ESCAPE  
event

SEVERE  
event

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## Repression unwanted memories

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Original InvestigationJAMA Psychiatry 2014

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**DLPFC**

**Hippocampus**

■ Patients   ■ Controls

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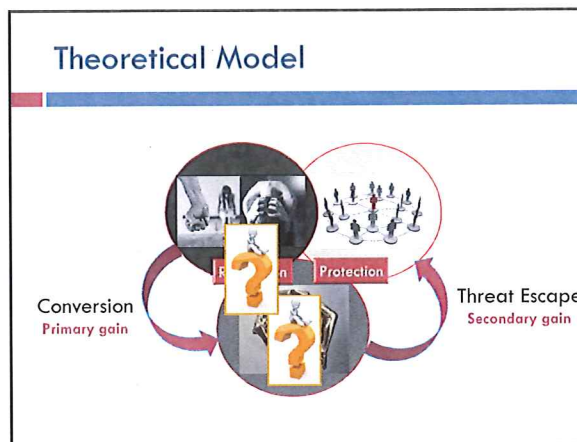
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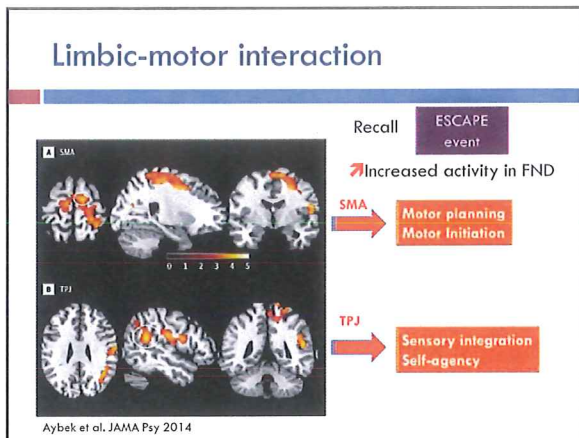
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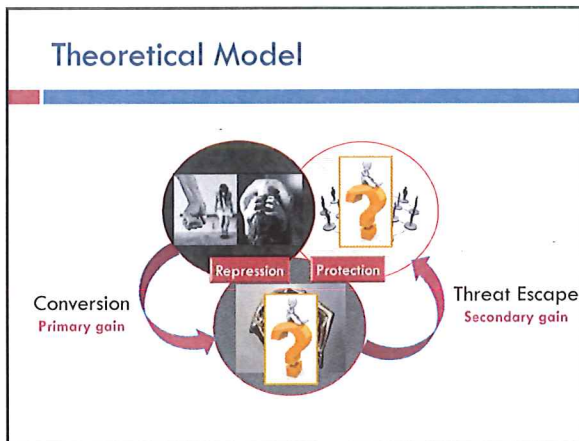
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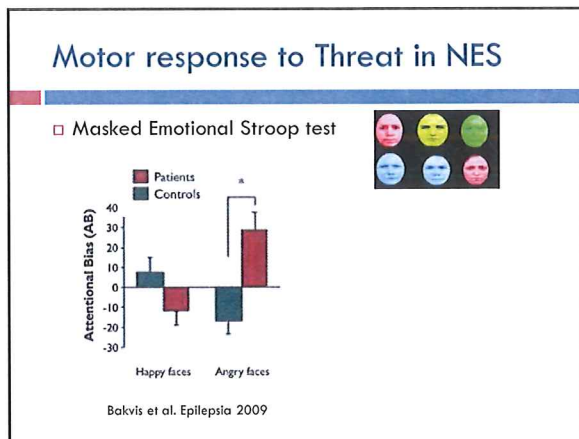
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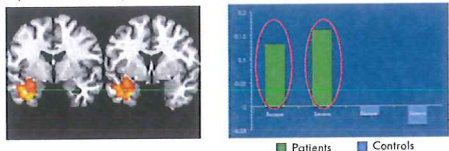
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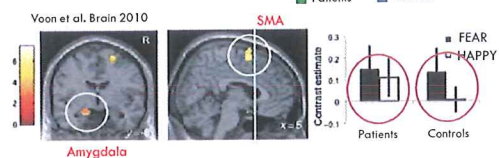


### Threat processing/Defense Behaviour

Aybek et al. JAMA Psy 2014



Voon et al. Brain 2010




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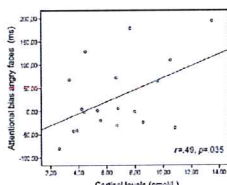
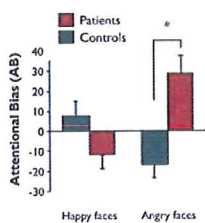
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### Biological Stress in NES

Masked Emotional Stroop test



Bakvis et al. Epilepsia 2009

Bakvis et al. Epi & Behav 2009

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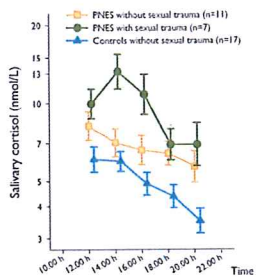
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### Biological Stress in NES



Early life experiences

Bakvis. Epilepsia 2010

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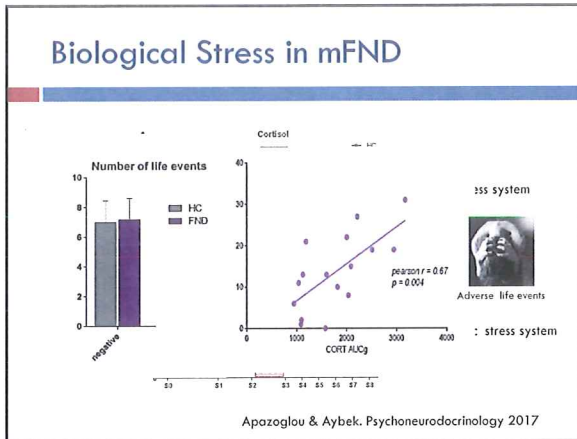
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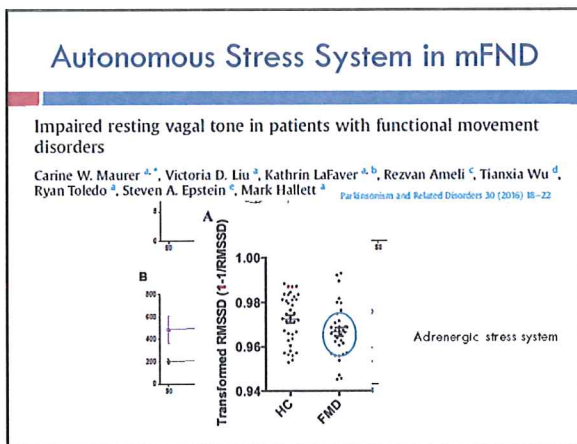
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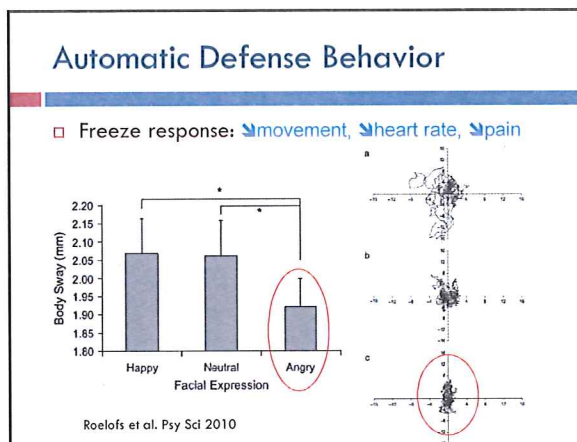
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### Automatic Defense Behavior

- Freeze response: ↓movement, ↓heart rate, ↓pain

Peri-aqueductal grey area (PAG)

Hermans et al. NeuroImage 2013

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### Freeze and FND

Contrast estimates and 95% CI plot

Group	SAD	FEAR
Patients	~1.0	~1.0
Controls	~0.2	~0.2

Aybek et al. PlosOne 2015

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### Theoretical Model

**PSYCHO-**

- ❖ Not unique cause
- ❖ Risk factors

**SOCIAL**

- ❖ Triggering
- ❖ Maintaining

**BIO-**

- Epigenetic/Genetic

Conversion Primary gain

Threat Escape Secondary gain

Repression P ?

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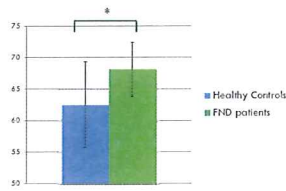
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## Epigenetic Factors

□ Methylation of Oxytocin receptor (%)



Apazoglou & Aybek. JNNP 2017

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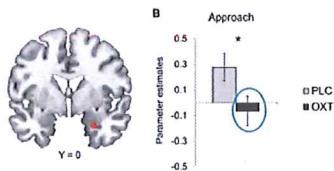
## Potential Future Treatments

Oxytocin reduces amygdala responses during threat approach

Sina Radke<sup>1,2,3\*</sup>, Inge Volman<sup>1,2,3\*</sup>, Idil Kokal<sup>1</sup>, Karin Roelofs<sup>1,2,3\*</sup>, Ellen R.A. de Bruijn<sup>1,2</sup>, Ivan Toni<sup>1,2</sup>

Psychoneuroendocrinology 79 (2017) 160–166

- Oxytocin nasal spray / Placebo
- Double-blind
- fMRI, Happy-Angry faces , approach-avoid task




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## Conclusion

Brain dysfunction  
Sense of agency  
Prior expectation  
Defense Behaviour?



Early life experiences  
Life events  
Stress dysregulation  
Amygdalar hyperarousal  
Epigenetic? Genetic?

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## Thank you!



Claudio Bossetti  
Mathias Sturzenegger  
Niklaus Egloff  
Anita Barbey



François Vingerhoets  
Alexandre Berney  
Corinna Daum  
Monica Hubschmid



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Viridiana Mazzola  
Rebekah Blakemore  
Kallia Apozoglu  
Jennifer Wegzyrk  
Valeria Kebets  
Giuseppe Zito  
Alexandre Dayer  
Dimitri Van de Ville



Pierre Pollak  
Silvio Galli  
Ninon Horie



Anthony David  
Richard Kanaan  
Tim Nicholson  
Fernando Zelaya  
Owen O'Daly  
Tirril Harris  
Tom Craig



Kamiar Aminian  
Anisoara Ionescu

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