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Dysautonomia and Erratic Breathing in Rett Syndrome and the underlying mechanisms

#### The clinical symptoms of Rett Syndrome are complex

## Speechless for Rett

5

Silence in recognition of one of most challenging symptoms the loss of speech.

rett syndrome

The Story of Rett Syndrome: From Clinic to Neurobiology Maria Chahrour<sup>1</sup> and Huda Y. Zoghbi

Neuron



These abnormalities become visible after the children turn two years

# Longitudinal course of epilepsy in Rett syndrome and related disorders

Daniel C. Tarquinio,<sup>1</sup> Wei Hou,<sup>2</sup> Anne Berg,<sup>3</sup> Walter E. Kaufmann,<sup>4</sup> Jane B. Lane,<sup>5</sup> Steven A. Skinner,<sup>4</sup> Kathleen J. Motil,<sup>6</sup> Jeffrey L. Neul,<sup>7</sup> Alan K. Percy<sup>5</sup> and Daniel G. Glaze<sup>6</sup>



Brain Dev. 2018 August ; 40(7): 515–529.

#### The course of awake breathing disturbances across the lifespan in Rett syndrome

Daniel C. Tarquinio, DO MS-Cl<sup>1,2</sup>, Wei Hou, PhD<sup>3</sup>, Jeffrey L. Neul, MD, PhD<sup>4</sup>, Gamze Kilic Berkmen, PhD<sup>1,2</sup>, Jana Drummond, PhD<sup>1,2</sup>, Elizabeth Aronoff, MS<sup>1,2</sup>, Jennifer Harris, MSN, APRN, PNP-AC<sup>2</sup>, Jane B. Lane, BSN, RN<sup>5</sup>, Walter E. Kaufmann, MD PhD<sup>6</sup>, Kathleen J. Motil, MD, PhD<sup>7</sup>, Daniel G. Glaze, MD<sup>7</sup>, Steven A. Skinner, MD<sup>6</sup>, and Alan K. Percy, MD<sup>5</sup>



#### The course of awake breathing disturbances across the lifespan in Rett syndrome

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Breathing disturbances show daily variations Example for one individual patient

Rohdin et al. 2007 Pediatr Neurol 37:338-344.



## e occurrence of apneas

**Table 6** Frequency of medically prescribed treatments for irregular breathing (n = 31)

Treatment type	Perceived effect of treatment		Total
	Not improved	Improved	
Medications	8	13	21
Antiepilepsy drugs <sup>a</sup>	-	5	5
Serotonin agonist <sup>b</sup>	3	3	6
Benzodiazepine <sup>c</sup>	1	-	1
SSRIs <sup>d</sup>	5	1	6
Other <sup>e</sup>	3	4	7
Use of equipment <sup>f</sup>	4	11	15
Oxygen	2	4	6
Rebreathing apparatus	1	2	3
CPAP/BIPAP	-	5	5
Compression vest	1	-	1

<u>From:</u> Mackay et al. 2017 Journal of Neurodevelopmental Disorders 9:15

## There is also large individual variability in the response to treatments

#### nature medicine

Great success – but still lots of individual variability

Article

https://doi.org/10.1038/s41591-023-023

# Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study



#### We need to understand: How the brain copes with mutations and disturbances "How the brain works"





#### Brain rhythms are highly interactive and coordinated

Medial prefrontal Cortex-breathing



inspl

Heart



**Cortex-hippocampus** 



Substantia nigra - cortex

EEG area 4



Amygdala - hippocampu<mark>s</mark>

تمريط بالمترجعات بالأرد المراجع

Most neuronal networks in the brain are *independently rhythmogenic* when isolated



# Neocortical & hippocampal networks

### Breathing is controlled by three microcircuits giving rise to three phases Postinspiratory complex **Pre-Bötzinger complex** Dbx1 **PiCo** Inspiration **Postinspiration Active Expiration** High metabolic demand/Sleep Each breathing center also controls other behaviors Parafacial respiratory group RPa VII

#### Laryngeal-swallowing coordination







Huff et al. 2023 eLife

#### Parasympathetic control



#### Sympathetic control



#### Dr. Marlusa Amarante Dr. Alyssa Huff Dr. Luiz Oliveira

## **CONCLUSION:**

# Respiratory networks control and coordinate somatic and autonomic motor outputs



#### Breathing also controls cortical activity

#### **Pre-Bötzinger complex**

#### Postinspiratory complex



**Inspiration**/postinspiration

#### **Interim Conclusions**

The brain consists of numerous *interacting rhythmogenic microcircuits* that control not only motor and autonomic behaviors but all concurrently ongoing neuronal processes.

Behavioral functions emerge from <u>the coordinated interactions</u> between numerous functionally specialized networks

For each network it is critical that the excitability, plasticity and stability is homeostatically regulated and modulated to serve the overall function of the behaving organism



# Microcircuits are differentially modulated by aminergic and peptidergic modulators



of Child Neurology

www.elsevier.com/locate/braindev

Original article

Reduced expression of neuropeptides can be related to respiratory disturbances in Rett syndrome

> Yoshiaki Saito<sup>a,b,\*</sup>, Masayuki Ito<sup>c</sup>, Yuri Ozawa<sup>b</sup>, Toyojiro Matsuishi<sup>d</sup>, Kenzo Hamano<sup>e</sup>, Sachio Takashima<sup>c</sup>

#### Substance P acting on NK1 receptors

**Rett Syndrome** 



Control

## The isolated network seems to cope with the <u>genetic removal of Substance P</u> (KO mouse) On average the rhythm is not significantly more irregular





Telgkamp et al. 2009, Journal of Neurophysiology

Atsushi Doi, and Jan-Marino Ramirez J. Neurosci. 2010;30:8251-8262

The Journal of Neuroscience

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But the <u>average</u> doesn't tell the whole story

#### Even though these are inbred genetically homogenous mice, individual networks cope very differently to the same mutation





# Networks have multiple synaptic and intrinsic mechanisms

#### at their disposal to cope with the situation



In response to an "incidence" it is necessary to find **Individual solutions to cope with this situation** 

# Activity balance is regulated by homeostatic plasticity: **Synaptic scaling**

Maintain firing rate within range

HOMEOSTATIC PLASTICITY IN THE DEVELOPING NERVOUS SYSTEM

#### Maintain network stability

Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same





## When activity is reduced synaptic amplitude increases

But this homeostatic mechanism is not perfect!

Activity Deprivation Leads to Seizures in Hippocampal Slice Cultures: Is Epilepsy the Consequence of Homeostatic Plasticity?

Trasande, Caitlin Aptowicz; Ramirez, Jan-Marino Journal of Clinical Neurophysiology24(2):154-164, April 2007.

doi: 10.1097/WNP.0b013e318033787f



氢 Wolters Kluwer

#### If activity is persistently reduced:

## Activity deprivation leads to paroxysmal depolarizations in 67% of the hippocampal networks



#### Paroxysmal depolarizations are a hallmark of epileptic seizures

#### This is relevant for Rett Syndrome





## Rett syndrome patients have heightened Delta power ("deep sleep")

#### But there are individual differences in sleep



Heightened Delta Power during Slow-Wave-Sleep in Patients with Rett Syndrome Associated with Poor Sleep Efficiency – PLOS ONE 2015 – 10/10

Simon Ammanuel, <sup>1,5</sup> Wesley C. Chan, <sup>1,5</sup> Daniel A. Adler, <sup>1,5</sup> Balaji M. Lakshamanan, <sup>2</sup> Siddharth S. Gupta, <sup>3,4</sup> Joshua B. Ewen, <sup>2,3</sup> Michael V. Johnston, <sup>3</sup> <sup>,4</sup> Carole L. Marcus, <sup>6</sup> Sakkubai Naidu, <sup>3</sup> <sup>,4</sup> and Shilpa D. Kadam<sup>1,3</sup>

#### Imbalance in cortical control also causes breathing dysfunctions





#### Activation of the Medial Prefrontal Cortex Reverses Cognitive and Respiratory Symptoms in a Mouse Model of Rett Syndrome

C. James Howell, Michael P. Sceniak, <sup>®</sup>Min Lang, Wenceslas Krakowiecki, Fatimah E. Abouelsoud, <sup>®</sup>Saloni U. Lad, Heping Yu, and David M. Katz



#### **Respiratory networks** themselves are also unbalanced

#### **Pre-Bötzinger complex**



#### The respiratory rhythm generated within the pre-Bötinger Complex is irregular at 14 days

Isolated network of Mecp2 -/y mice



VIEMARI ET AL. 2005; JNEUROSCI





#### Breathing is also irregular in Rett Syndrome patients



Weese-Mayer et al. 2006



#### Breathing is also irregular in Rett Syndrome patients

but there is considerable individual variability



Awake

Weese-Mayer et al. 2006

Irregularity Score

The increased breathing irregularity is also seen during all phases of sleep

## Cycle Period by Sleep Stage



Box plots are using Wilcoxon signed-rank test.



Mean and std plots are using ttest.

Jessica Parker & Jia Der Wang In preparation



Most apneas / breath-holds occur **during wakefulness** 

## Hypopneas are increased during sleep, but not as much when compared to OSA patients



Jessica Parker & Jia Der Wang In preparation

## <u>These</u> recurrent breath holds are problematic because they reveal disturbances in cardiorespiratory coupling





**Inspiration**/postinspiration



Breath-holds:

Concurrent inhibition of cardiovagal neurons and excitation of sympathetic neurons gives rise to respiratory sinus arrhythmia





Breathing and heart are also functionally linked during a breath-hold in healthy control



Heart rate (bpm)

Weese-Mayer et al. 2006

# Cardiorespiratory coupling is disturbed in Rett Syndrome: NOT "Diving response"



Weese-Mayer et al. 2000

Breath-holds cause Hypoxia & oxidative stress

Oxidative Stress

Hypoxic Stress



#### **Breath holds cause intermittent hypoxia**

Breath-holds cause Hypoxia & oxidative stress

Oxidative Stress

Hypoxic Stress



## Pre-Bötzinger complex Nucleus ambiguus

NA

preBötC

NA ) preBötC

Intermittent hypoxia interferes with cardiorespiratory coupling between cardiovagal and preBötC neurons

#### Hypoxia causes oxidative stress



#### **EXPERIMENTAL MODEL**

**Oxidative Stress Hypoxia-inducible Factor** (HIF-1α)



control Intermittent Hypoxia

## Hypoxia causes oxidative stress

#### **RETT SYNDROME**





#### **EXPERIMENTAL MODEL**



De Felice et al. Free Radical Biology & Medicine 47 (2009) 440–448

Ciaccio et al. (2017) Mol. Cell Biochem. 426:2-5=213

# H<sub>2</sub>O<sub>2</sub> decreases cardiac vagal activity & blunts respiratory modulation of cardiac tone.

#### **EXPERIMENTAL MODEL**





H<sub>2</sub>O<sub>2</sub> decreases cardiac vagal activity & blunts respiratory modulation of cardiac tone.

#### **EXPERIMENTAL MODEL**



#### **RETT SYNDROME**



Weese-Mayer et al. 2006



#### CIH increases sympathetic activity at all phases of in vivo breathing

|≩

|≩

13

500ms





Daniel G. Glaze, MD,\* Jeffrey L. Neul, MD, PhD,\* Walter E. Kaufmann, MD,\* Elizabeth Berry-Kravis, MD, PhD, Sean Condon, DPH, George Stoms, BS, Sean Oosterholt, MSc, Oscar Della Pasqua, MD, PhD, Larry Glass, BA, Nancy E. Jones, PhD, and Alan K. Percy, MD,\* on behalf of the Rett 002 Study Group Mecp2

#### **Rett Syndrome**

<u>Neurology</u>. 2019 Apr 16; 92(16): e1912–e1925.

#### **HOMEOSTATIC PLASTICITY**

normal

IGF1

Trofinetide

setpoint

Dr. Tatiana Anderson Dr. Henner Koch Dr. Steve Lieske Dr. JC. Viemari Dr. Tatiana Dashevskiy Dr. Fred Garcia Dr. Andrew Tryba



University of Washington



Drs. Debbie Weese-Mayer & Michael Carroll



Dr. Monica & Chelsea Coenraads

#### Universität Göttingen



Drs. Bernd Wilken & Diethelm Richter

