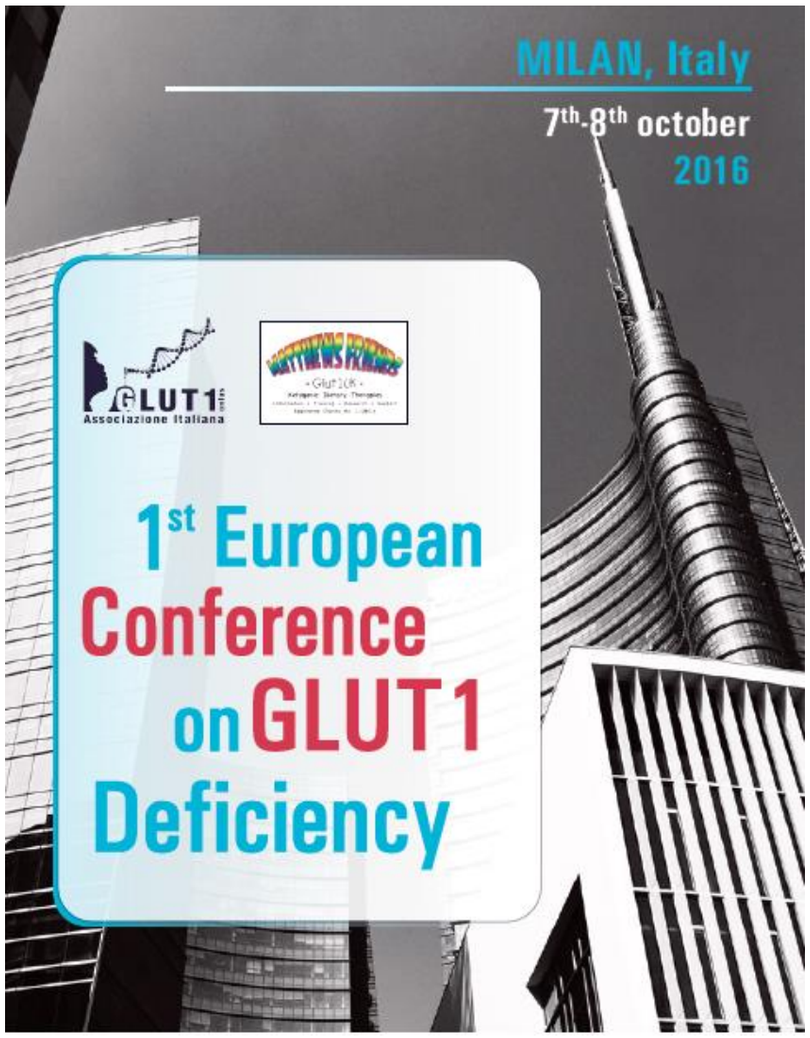


UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

FONDAZIONE ISTITUTO NEUROLOGICO NAZIONALE C. MONDINO
Istituto di Ricovero e Cura a Carattere Scientifico

Brain correlates of Spike And Waves Discharges in Glut1-DS

Anna Elisabetta Vaudano, Sara Olivotto, Giuliana Gessaroli, Valentina De Giorgis, Antonia Parmeggiani, Pierangelo Veggiotti, Stefano Meletti

7th October 2016

GLUT1 mutations are a rare cause of familial idiopathic generalized epilepsy

P. Striano, MD, PhD*
Y.G. Weber, MD*
M.R. Toliat, PhD
J. Schubert
C. Leu, PhD

ABSTRACT

Objective: The idiopathic g
mined epilepsies. However,

ONLINE FIRST

Glucose Transporter 1 Deficiency as a Treatable Cause of Myoclonic Astatic Epilepsy

Saul A. Mullen, MBBS; Carla Marini, MD, PhD; Arvid Suls, PhD; Davide Mei, BSc; Elvio Della Giustina, MD; Daniela Buti, MD; Todor Arsov, MD, PhD; John Damiano, BSc; Kate Lawrence, BSc; Peter De Jonghe, MD, PhD; Samuel F. Berkovic, MBBS, MD; Ingrid E. Scheffer, MBBS, PhD; Renzo Guerrini, MD

BRIEF COMMUNICATION

Refractory absence epilepsy associated with GLUT-1 deficiency syndrome

*Susan Byrne, *Jacin

Glucose Transporter 1 Deficiency in the Idiopathic Generalized Epilepsies

doi: 10.1111/epi.12007

BRIEF COMMUNICATION

ogers, PhD,[3]
Damiano, BSc,[1]
Kivity, MD,[4]
erkovic, FRS,[1]

Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency

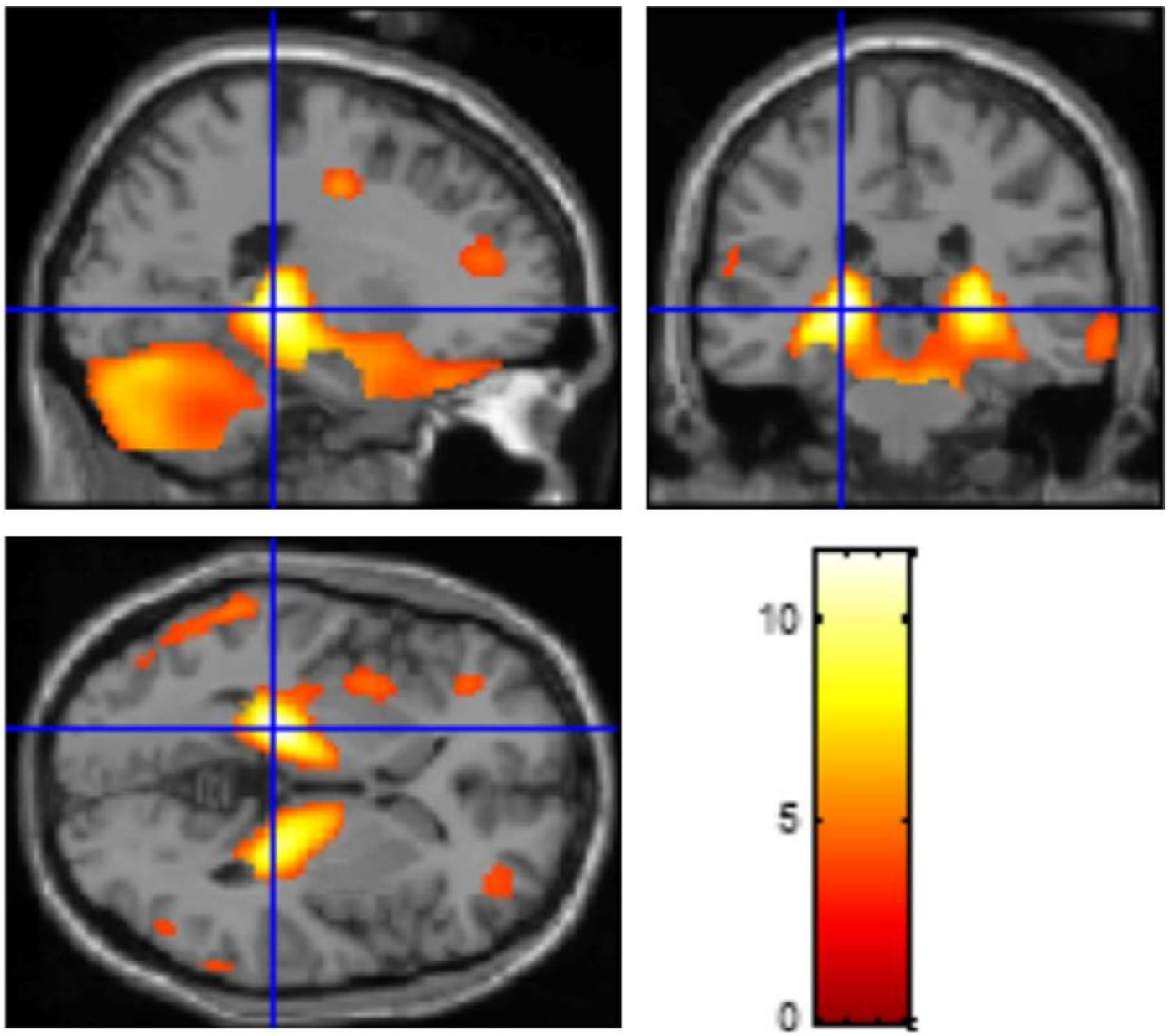
***Todor Arsov, *†Saul A. Mullen, *John A. Damiano, *Kate M. Lawrence, ‡Linda L. Huh, §Melinda Nolan, ¶Helen Young, #Anaïs Thouin, *Hans-Henrik M. Dahl, *Samuel F. Berkovic, **Douglas E. Crompton, ††Lynette G. Sadleir, and *†‡‡Ingrid E. Scheffer**

Structural MRI

is considered uninformative in GLUT1 deficiency syndrome. Minor, nonspecific abnormalities have been described in some patients:

- Slight degrees of brain hypotrophy
- Mild frontal lobe atrophy (1pt) (Akman, 2015)
- Atrophy of the cerebellar vermis (1pt) (Akman, 2015)
- Diffuse myelination delay (1pt) (Boles, 1999)
- Hypoplasia of the corpus callosum and the cerebellar vermis- not related to the disease (Klepper ,1999)

PET imaging in GLUT1 with epilepsy



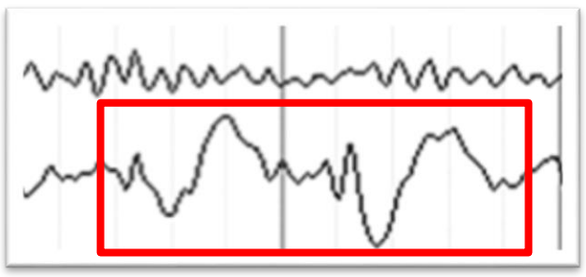
Akman et al., 2015

AIMS OF THE STUDY

Provide biomarkers of GLUT1-DS by means of non-invasive imaging techniques

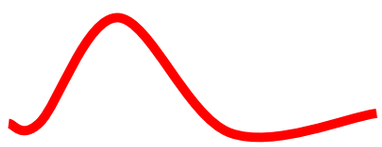
- **BOLD correlates of spike and waves discharges**
- **Functional connectivity networks (resting state networks)**

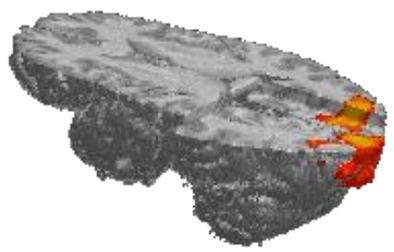
1. To define the brain networks involved in SWD generation in GLUT1



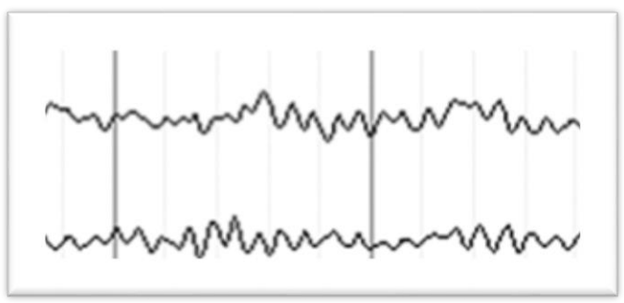
GSW event of interest

Segnale BOLD

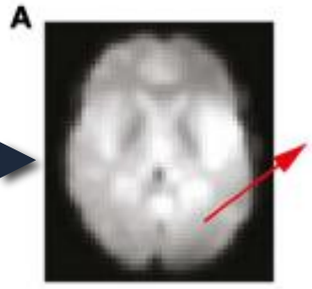


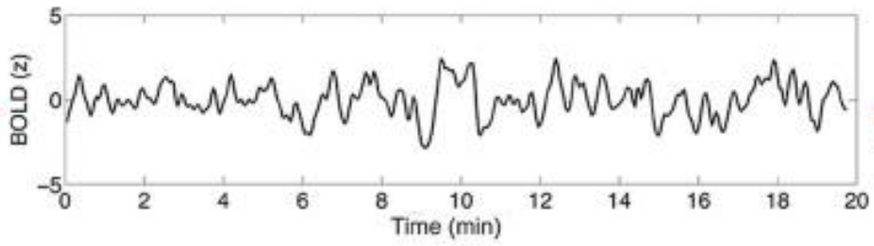


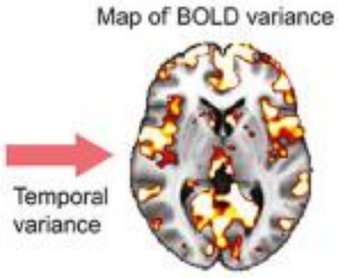
2. To define functional connectivity of **resting state network**



→ rest







GLUT-DS patients

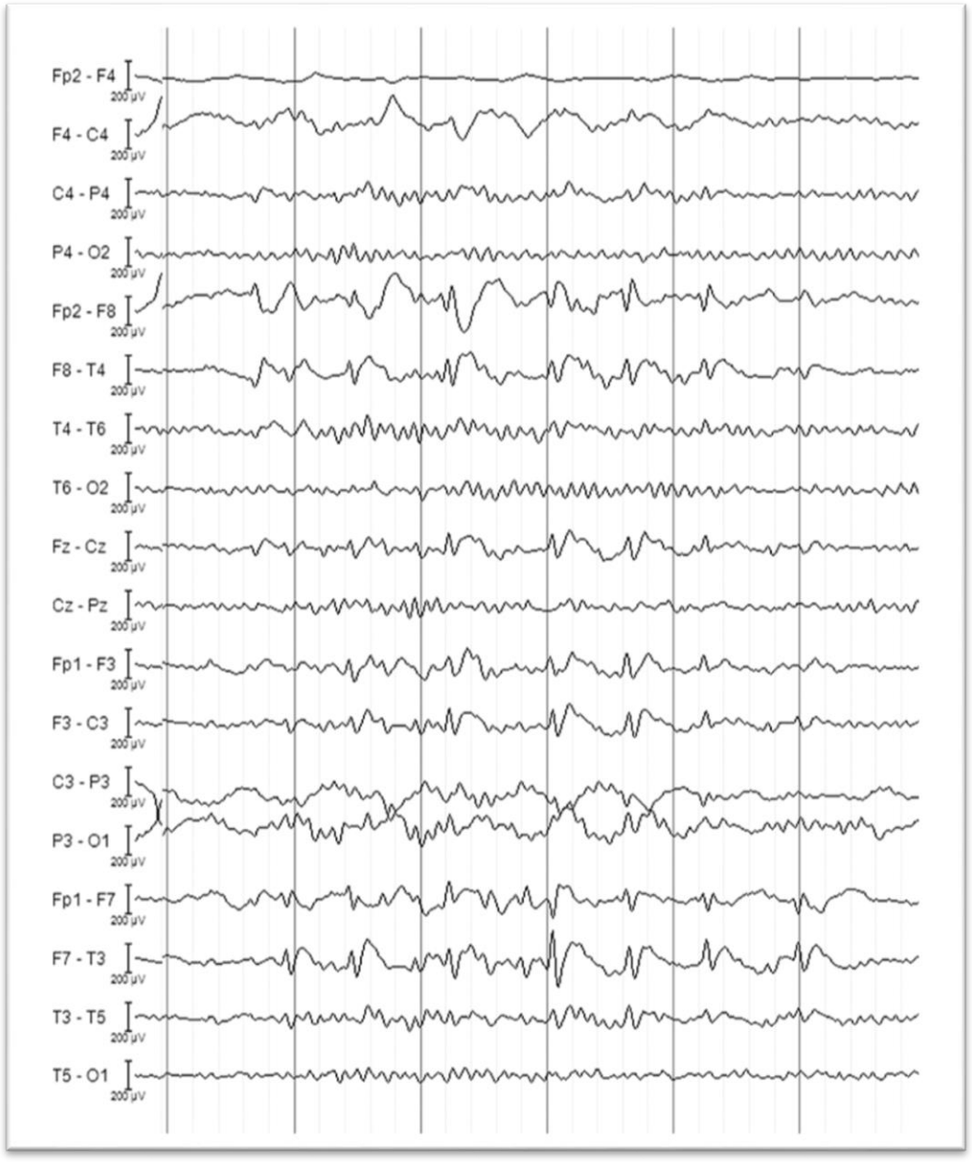
Clinical Features

N° of patients	18
Mean Age	19.2 yrs (range: 6-43)
Sex	6M/12F
Mean Age at dg	16,2 yrs
N° of children (<18 yrs)	10
Mean Age at seizures ’onset	33,81 months
Movement Disorder	13/18 (ataxia 3/11; dystonia 9/11; coreoatetosis 3/11)
Seizures	16/18 (10/18 A; 4/18 GTC; 3/18 MS)
SLC2A1 Mutations	17/18 (9 familiar e 8 sporadic)
Mean QI	70,94 (range 44 -112)
Mean Glycorrhachia	38, 06 mg/dl (range 31-46 mg/dl)
Ketogenic Diet	7/18 (3/17 solo KD; 4/7 KD+AED)

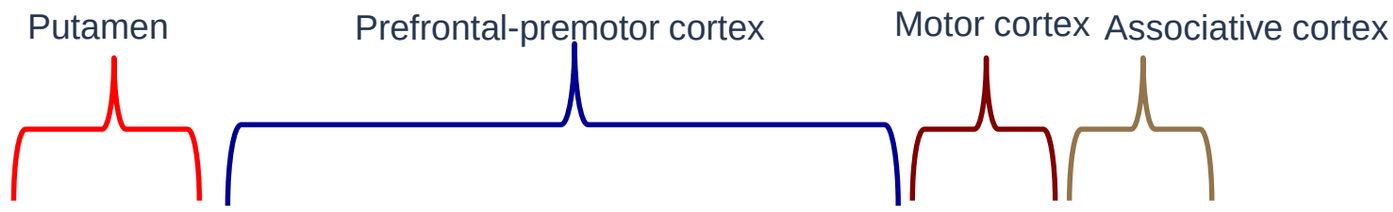
S.C. di Neuropsichiatria Infantile, Fondazione Istituto Neurologico "C. Mondino" – IRCCS, Pavia; S.C. di Neuropsichiatria Infantile , Policlinico S.Orsola Malpighi, Bologna

RESULTS

Network generating GSWD in GLUT1-DS
Single Subject



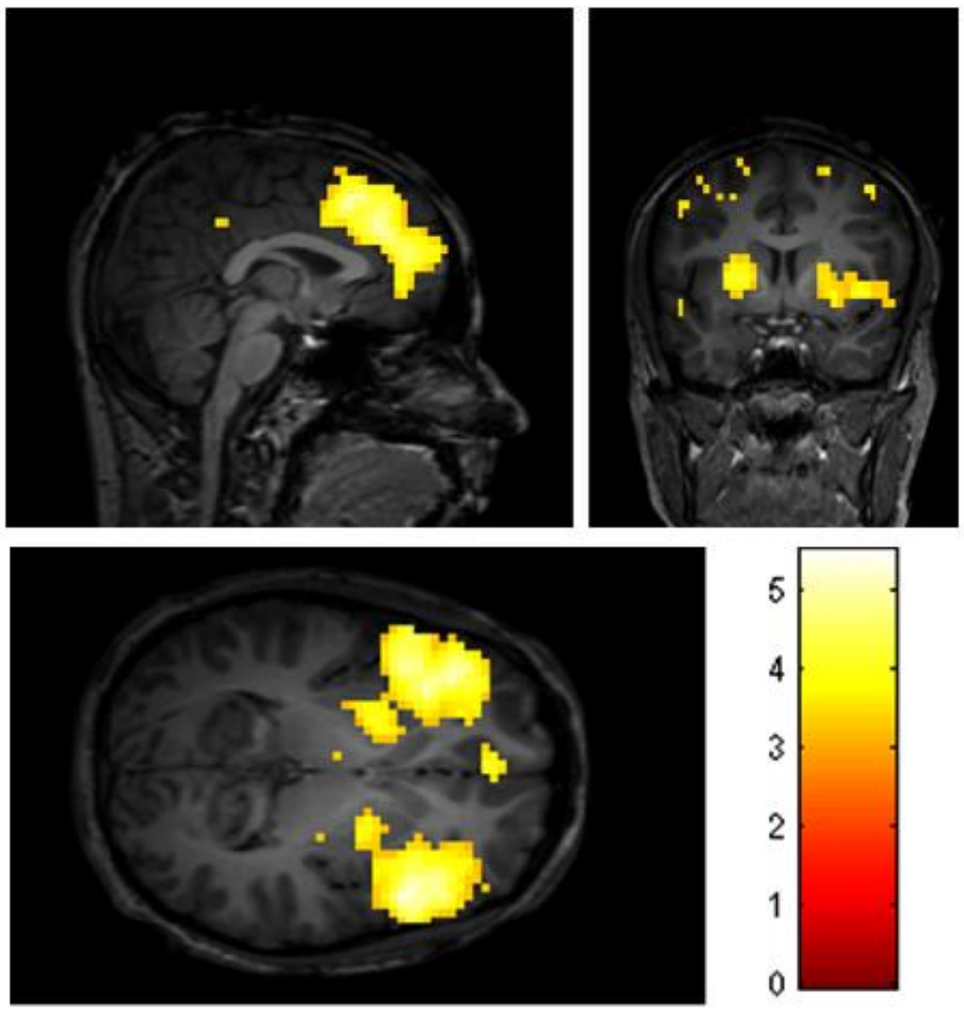
10 GLUT1 (152 SWD, 4.31 sec)



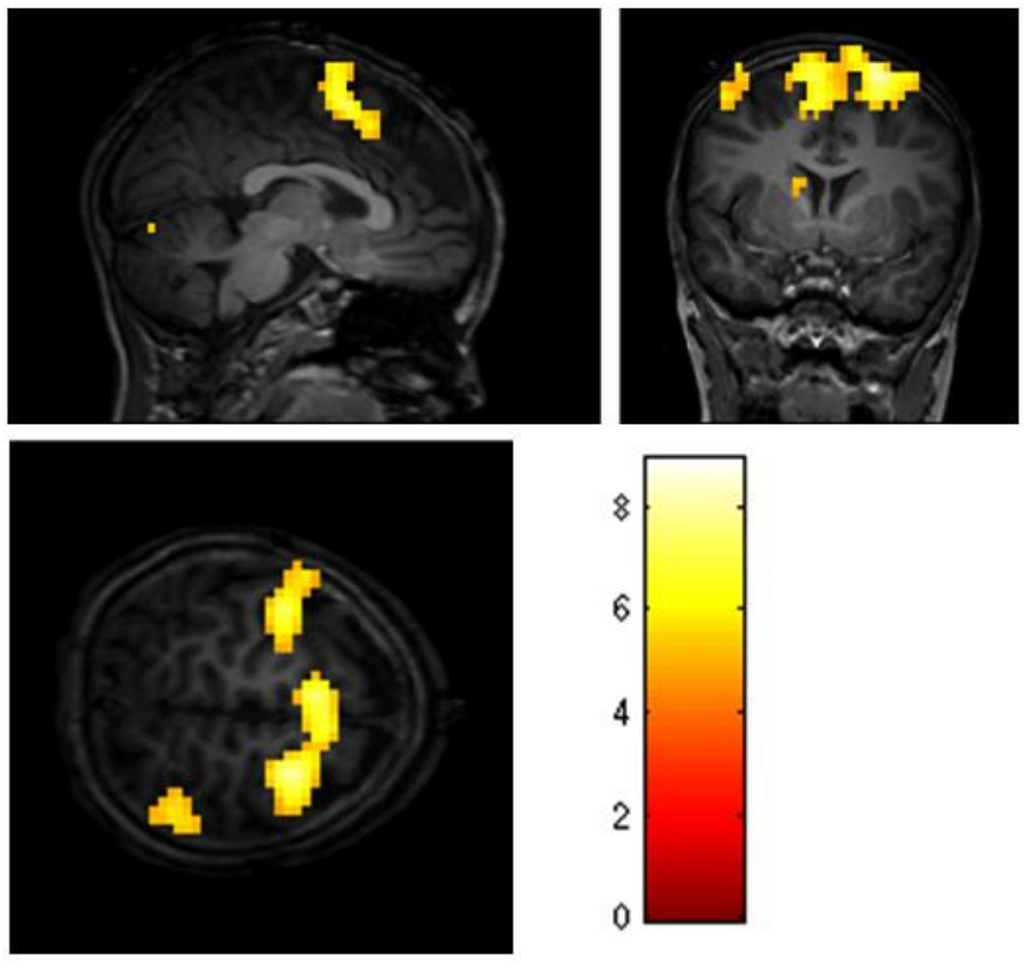
PT ID	BOLD CHANGES							
	Basal Ganglia	**Frontal Operculum**	**Premotor Cortex**	**SMA**	**Cingulate Cortex**	**Pericentral Cortex**	**DMN****	**Other**
Pt3	B (>R) (3.51) (i)	B (>L) (4.94) (i)	B (>R) (5.07) (i)	L (4.50) (i)	--	--	L (4.90) (i)	--
Pt5	--	B(>R) (4.82) (i)	R (4.88) (i)	--	--	--	--	--
Pt6	B (>L) (2.58) (i)	--		L (3.46) (d)*	B (>L) (2.89) (d)*	B (>L) (3.82) (d)*	--	B cerebellum (2.99) (d)*
Pt8	--	--		R (4,8) (d)*	--	--	--	--
Pt9	L (2.72) (i)*	—	R (4.35) (i)	L (3.02) (i)*	--	B (>R) (3.75) (i)*	B (>R)(4.30) (i)*	B cerebellum (4.32) (i)
Pt10	B (>L)(4.86) (i)	B(>L) (3.99) (i)	B (>R) (>7.59) (i)	B (>L) (>7.59) (i)	L (>7.59) (i)	B (>L) (6.35) (i)	L (5.07) (i)	--
Pt11	--	B (4.92) (i)	--	B (4.94) (i)	--	--	B (6.15) (i)	--
Pt13	L (3.82) (i)*	B (>R)(5.67) (d)		B (>R) (6.41) (d)		B (>R) (7.81) (d)	B (>L)(7.81) (d)	B thalamus (4.40) (i)* B cerebellum (4.12) (i)*
Pt17	--	--		--	--	B (>R) (3.32) (i)*	B (>R)(3.17) (i)*	L TP junction (i)
Pt18	--	--	B (5.39) (d)	--	--	--	R (3.77) (i)*	--

RESULTS

Network generating GSWD in GLUT1-DS
Single Subject



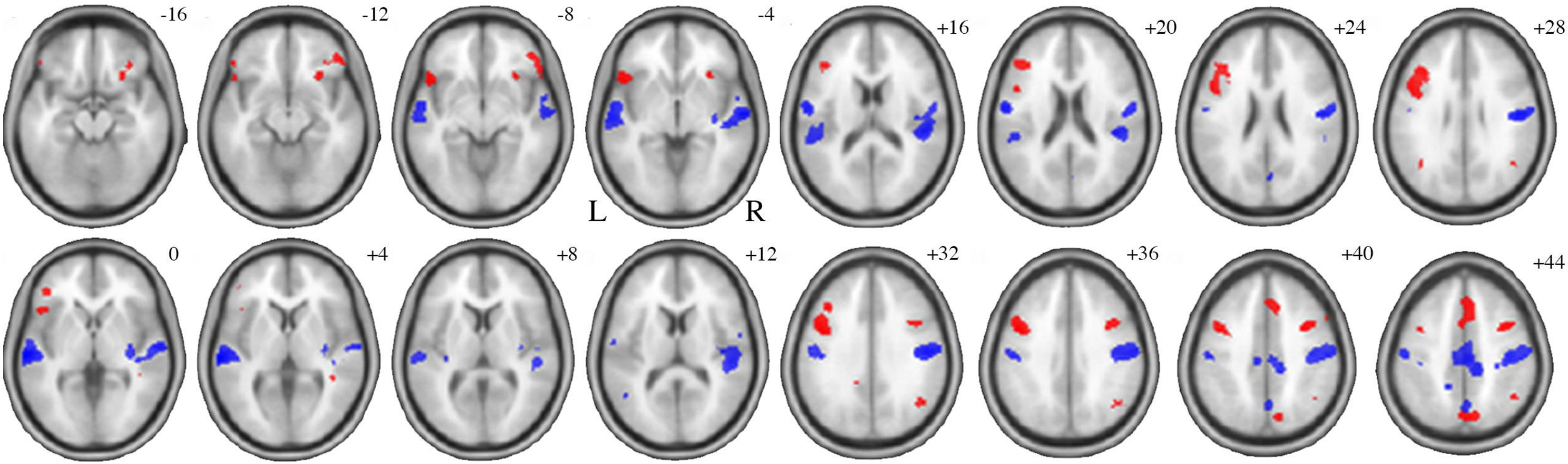
Pt 3: M, 14 yrs, no clinical seizures



Pt 9: F, 6 yrs, GTC & MS

RESULTS

Network generating GSWD in GLUT1-DS
Group Level-fixed effect



Positive BOLD changes

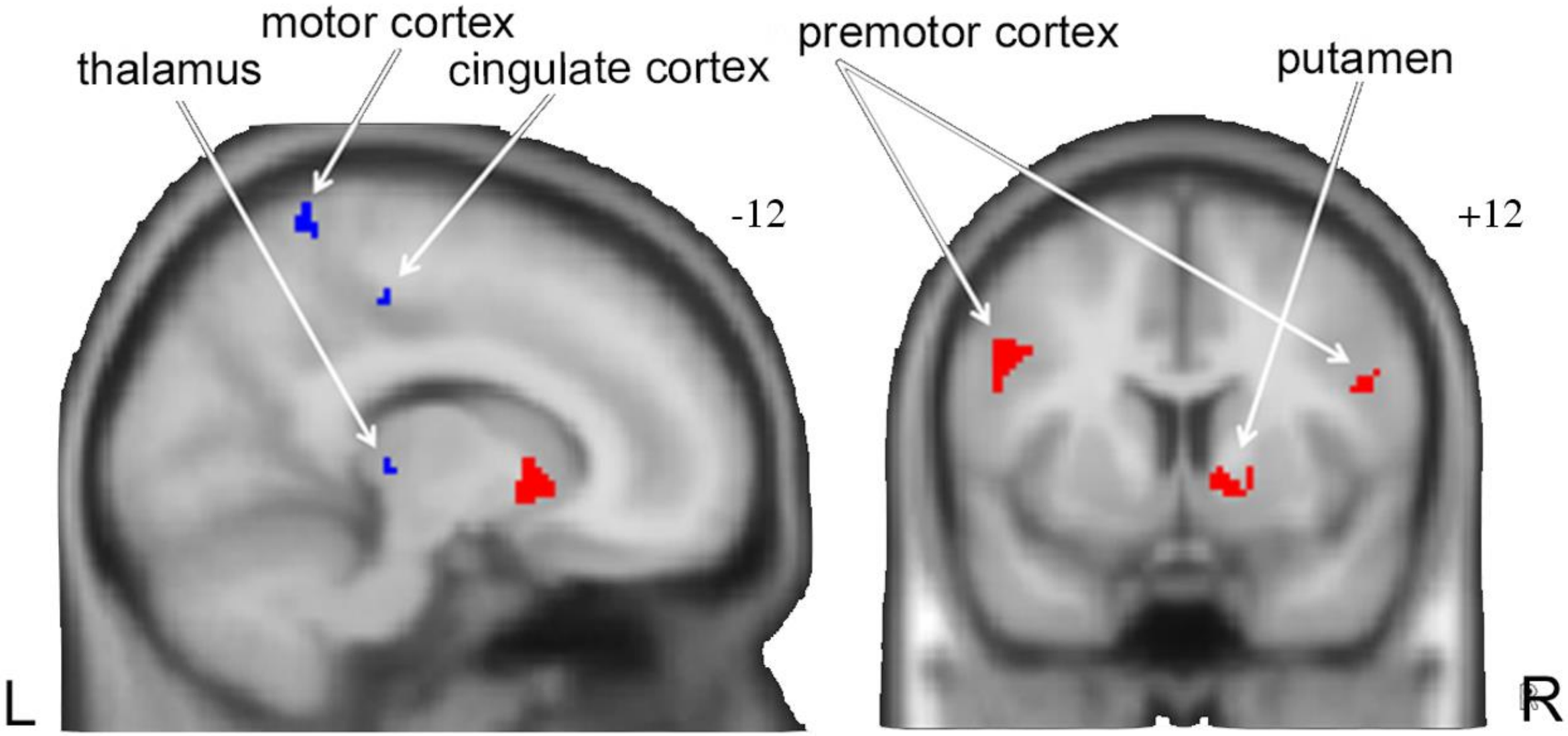
Negative BOLD changes

P<0.05 FWE

Vaudano et al., under revision

RESULTS

Network generating GSWD in GLUT1-DS
Group Level-Conjunction analysis



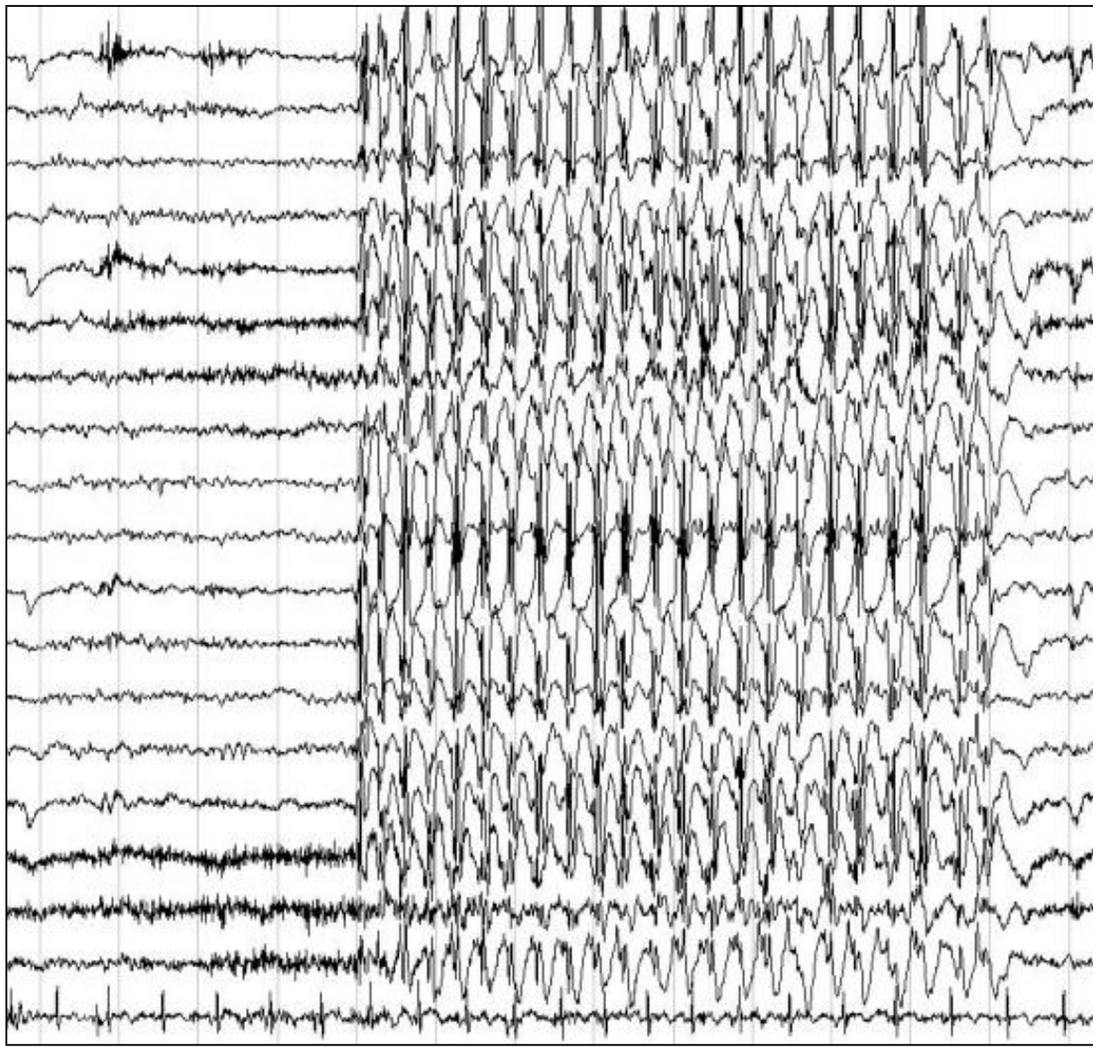
Positive BOLD changes

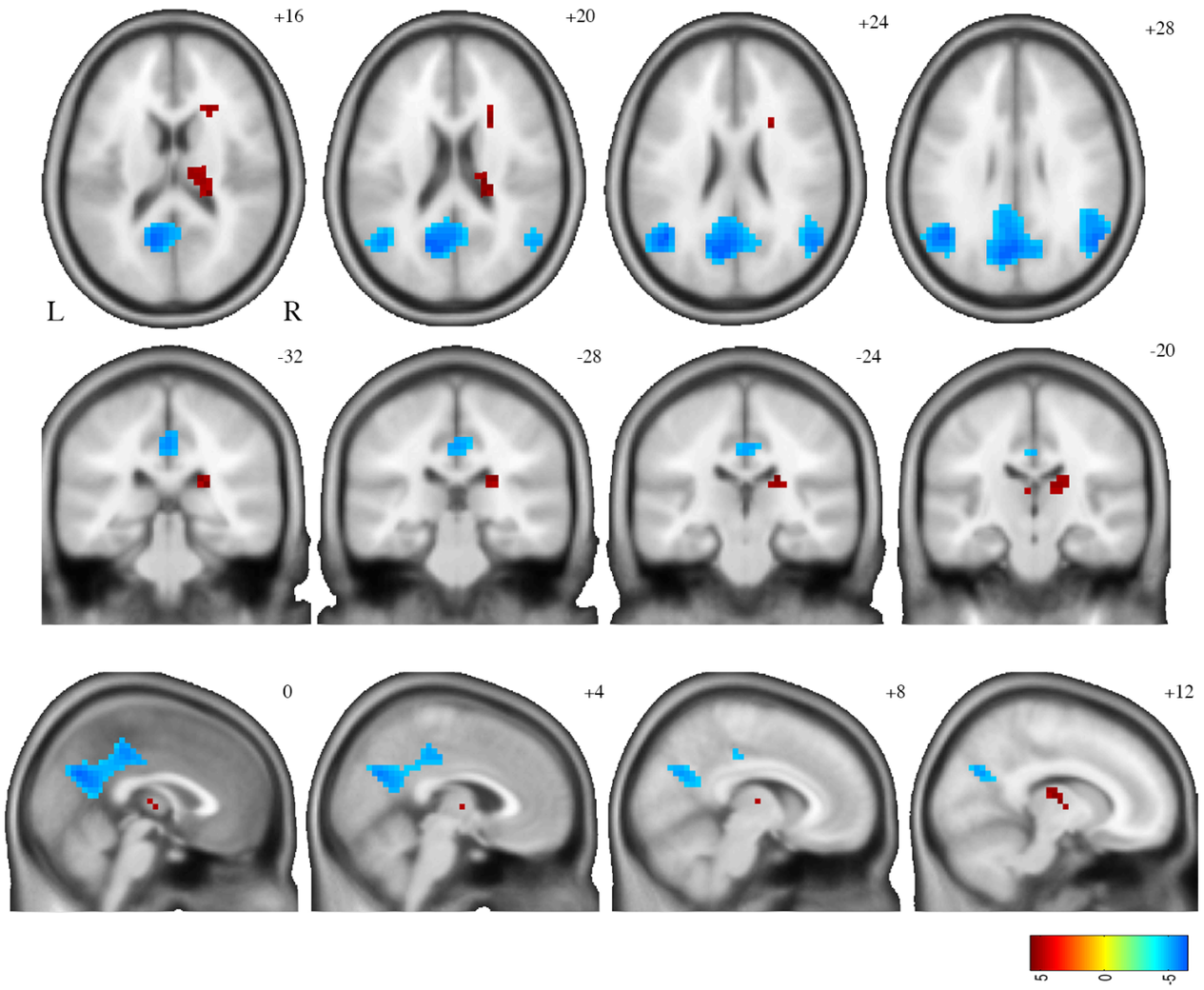
Negative BOLD changes

P<0.001 uncorrected, 5 voxels

Vaudano et al., under revision

Same or different BOLD pattern respect with IGE…

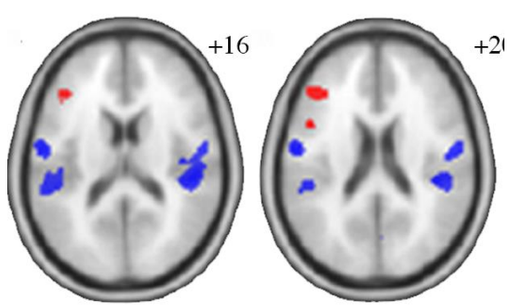




In IGE identical BOLD maps independently of sub-syndrome and GSWD length (Pugnaghi et al., 2014)

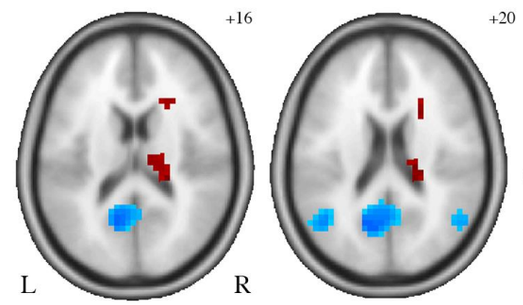
Hemodynamic patterns→ disease biomarkers?

10 GLUT1-DS

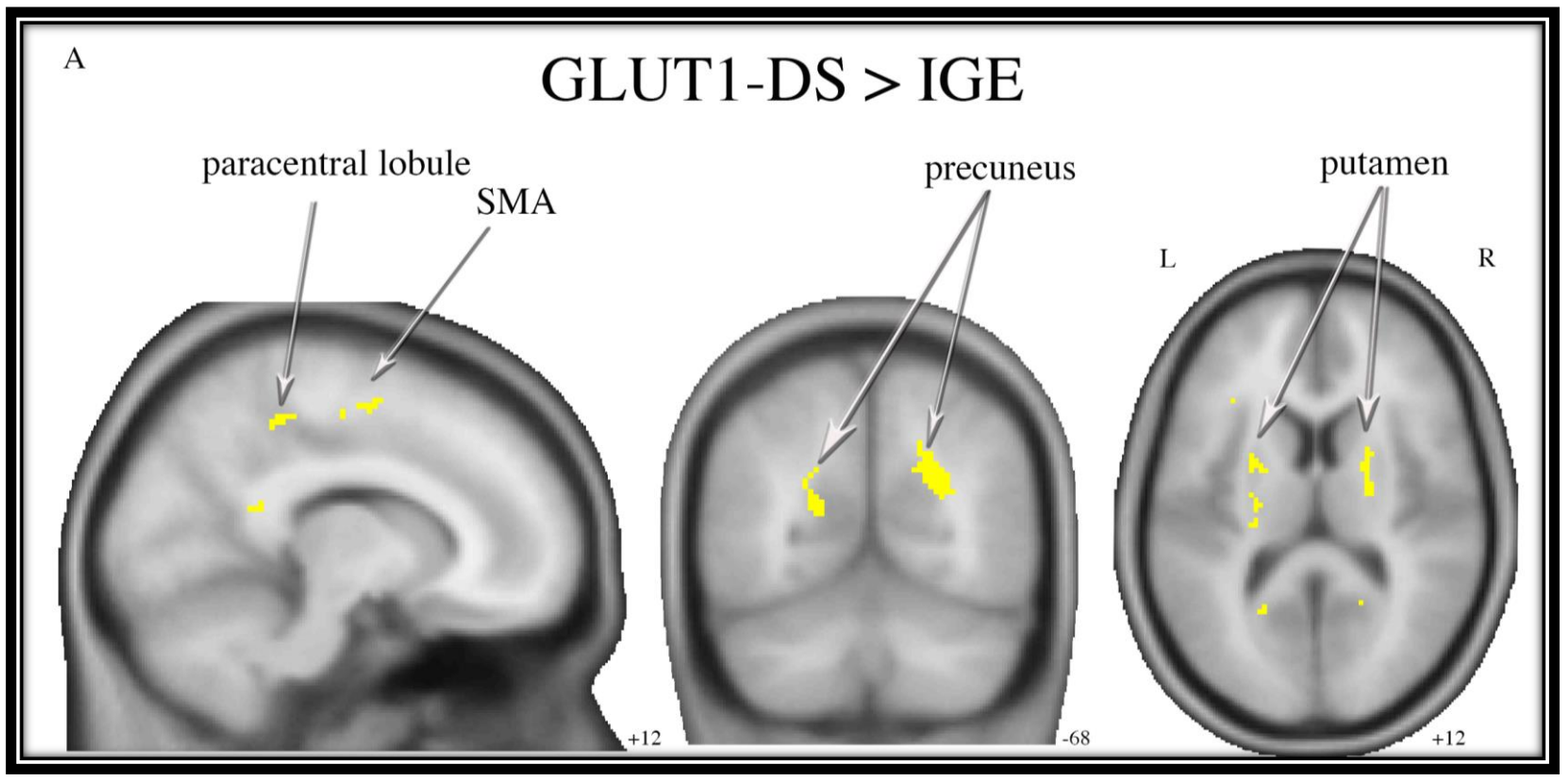


≠

10 IGE, sex and age matched
149 GSW (4.59 sec)



?



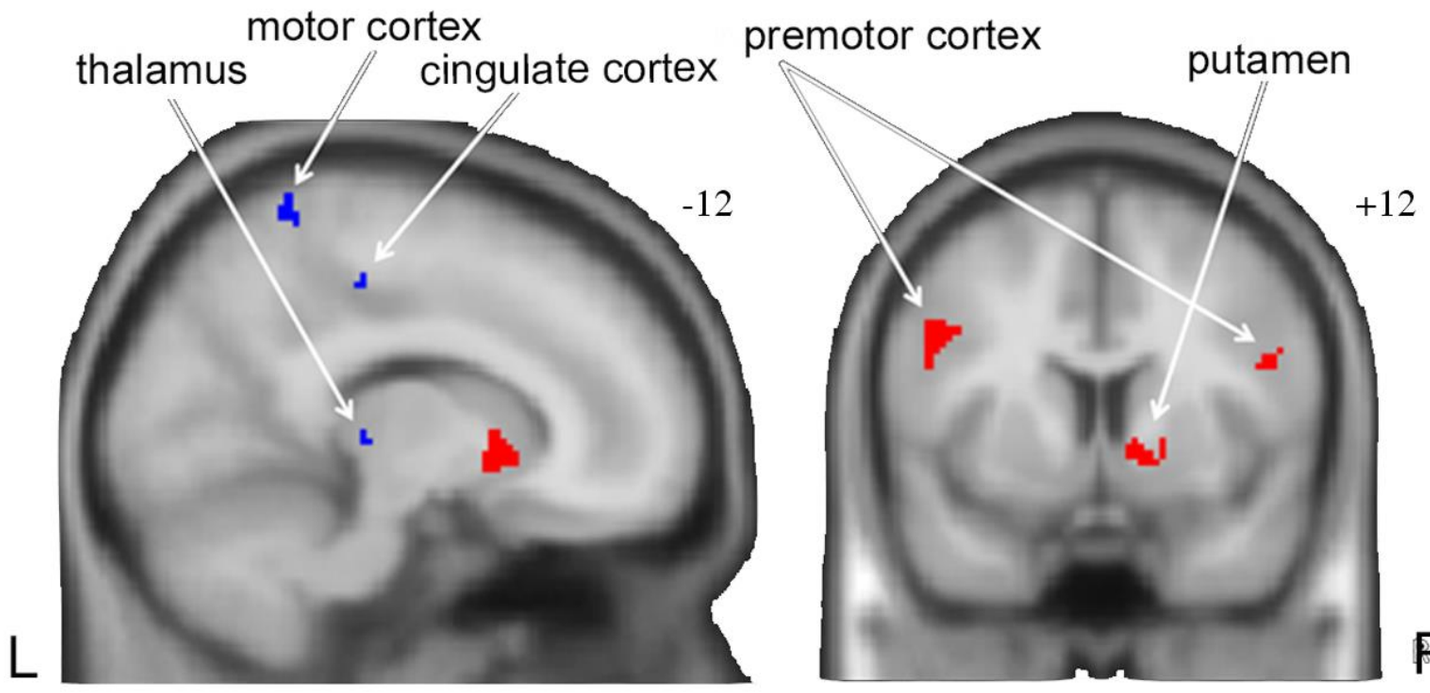
Discussion-I

1. GLUT1-DS

The observed BOLD findings-related to epileptic activity delineated a well-defined network of cortical-subcortical regions that are involved in the generation of GSWD in GLUT1-DS and are different from Idiopathic Generalized Epilepsy

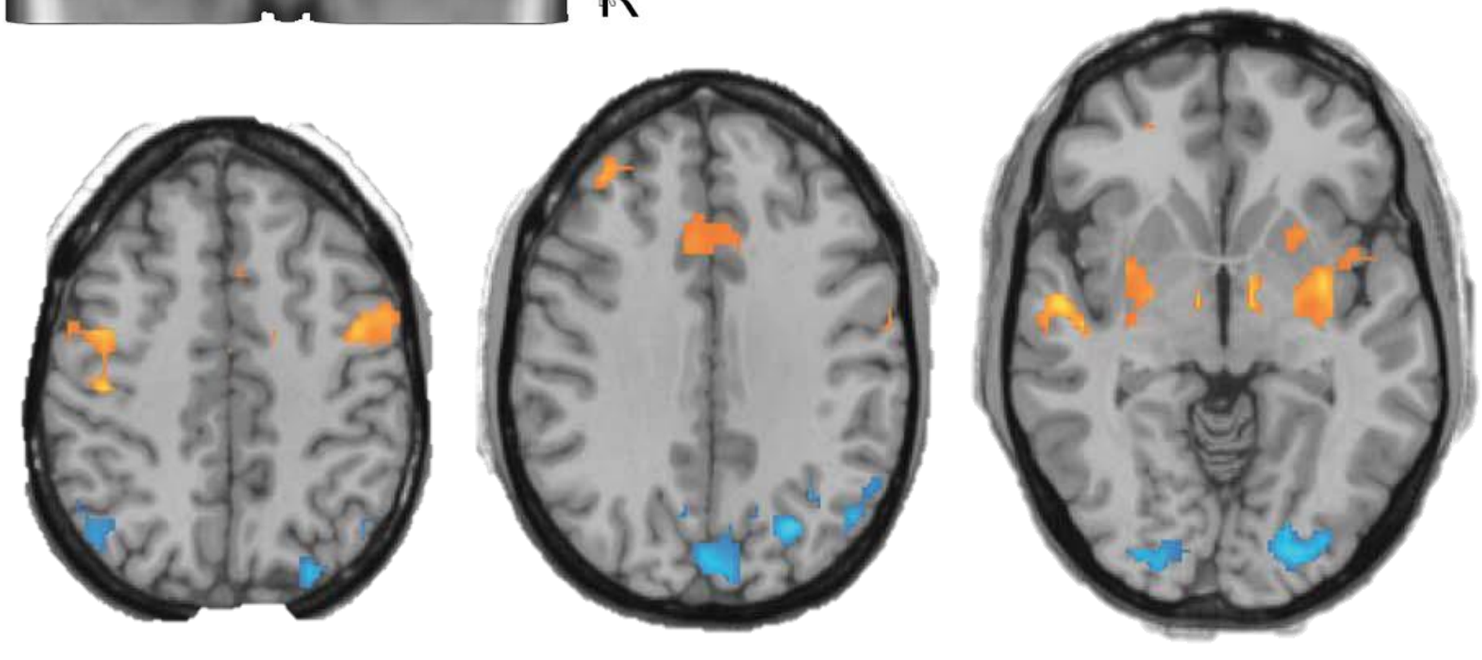
The results at the second-level analysis showed an increased neuronal activity, in the **premotor-striatal network**.

Discussion-II



GSWD in Glut1-DS

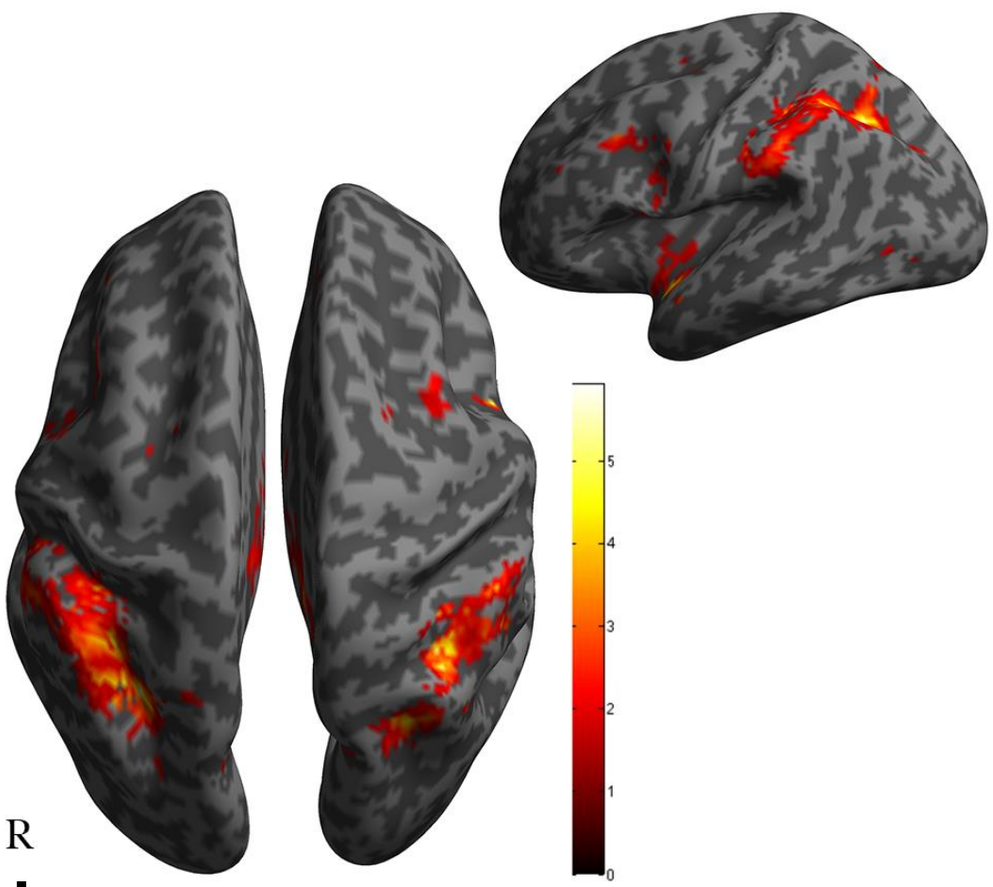
GSWD in
Myoclonic-Astatic Epilepsy

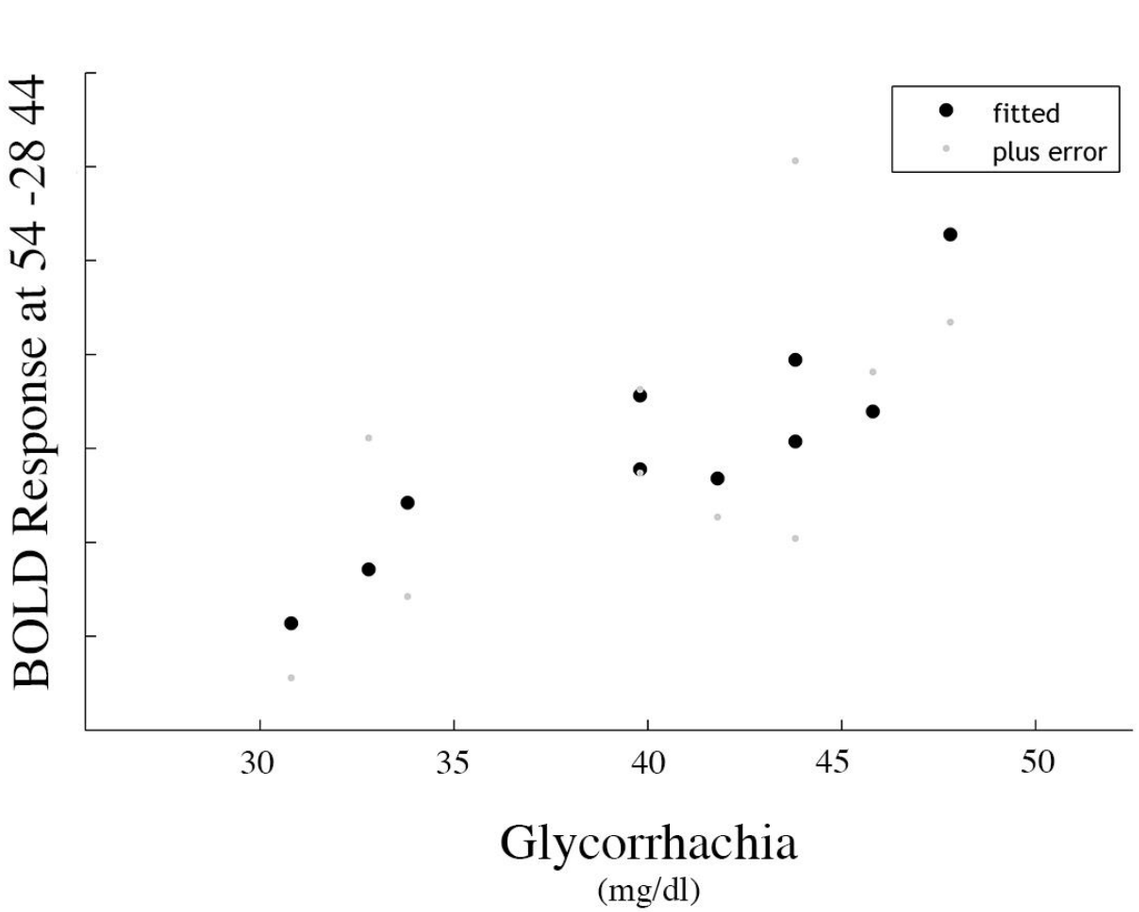


Moeller et al., 2014

BOLD maps and clinical measurements

Clinical Variables considered
-glycorrhachia
-Age at seizures' onset
-Ketogenic Diet (Y/N)
-QI
-Age





↓ Glycorrhachia at diagnosis-> reduced neuronal activity at the parietal and sensory-motor cortex

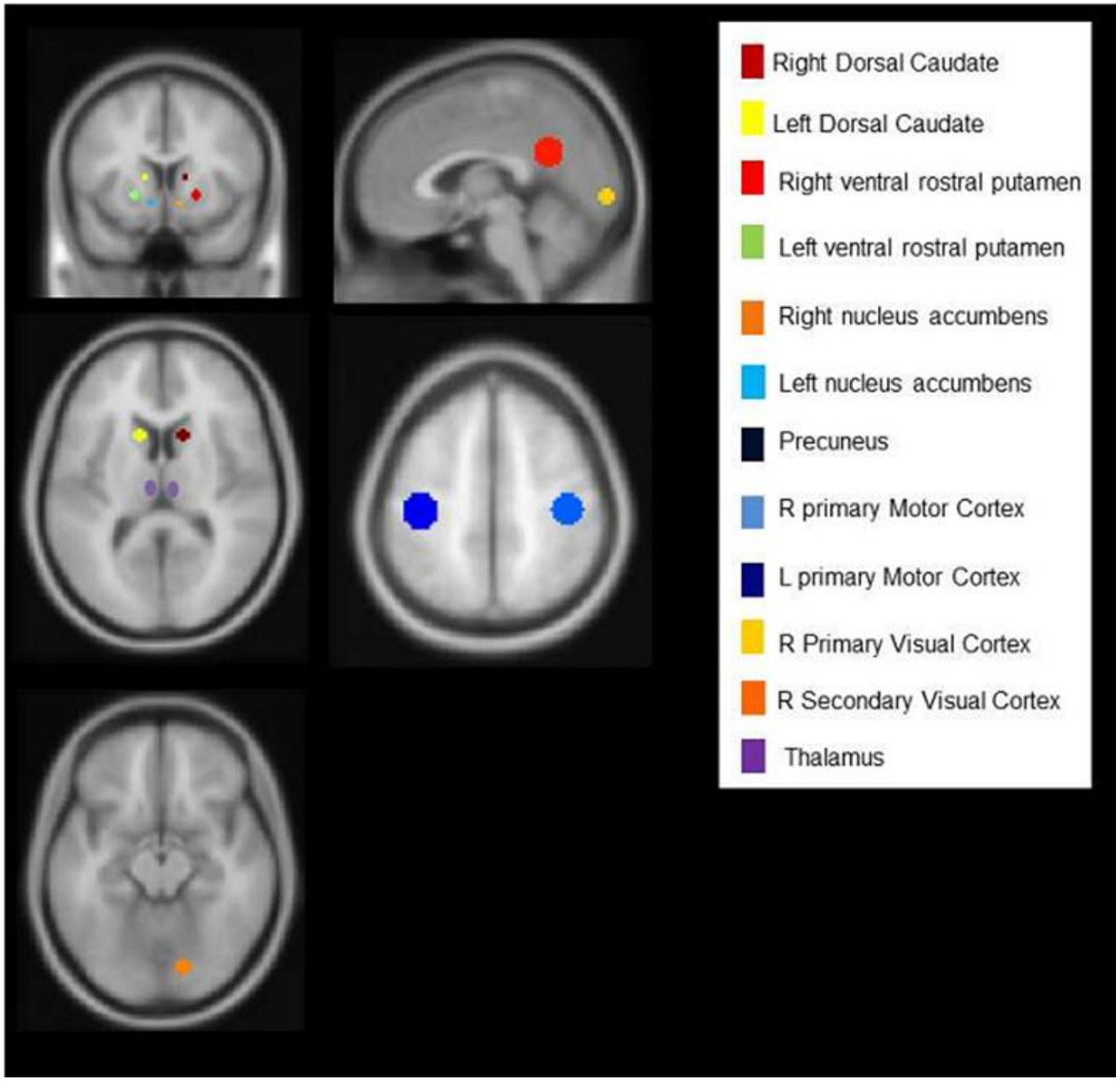
Discussion-III

2. Direct relationship between the level of glycorrhachia and cortical excitability

“brain glucose hypometabolism, present in infancy, leaves an imprint that persists even when the precipitating condition causing the hypoglycorrhachia is corrected” (Akman et al., 2015)

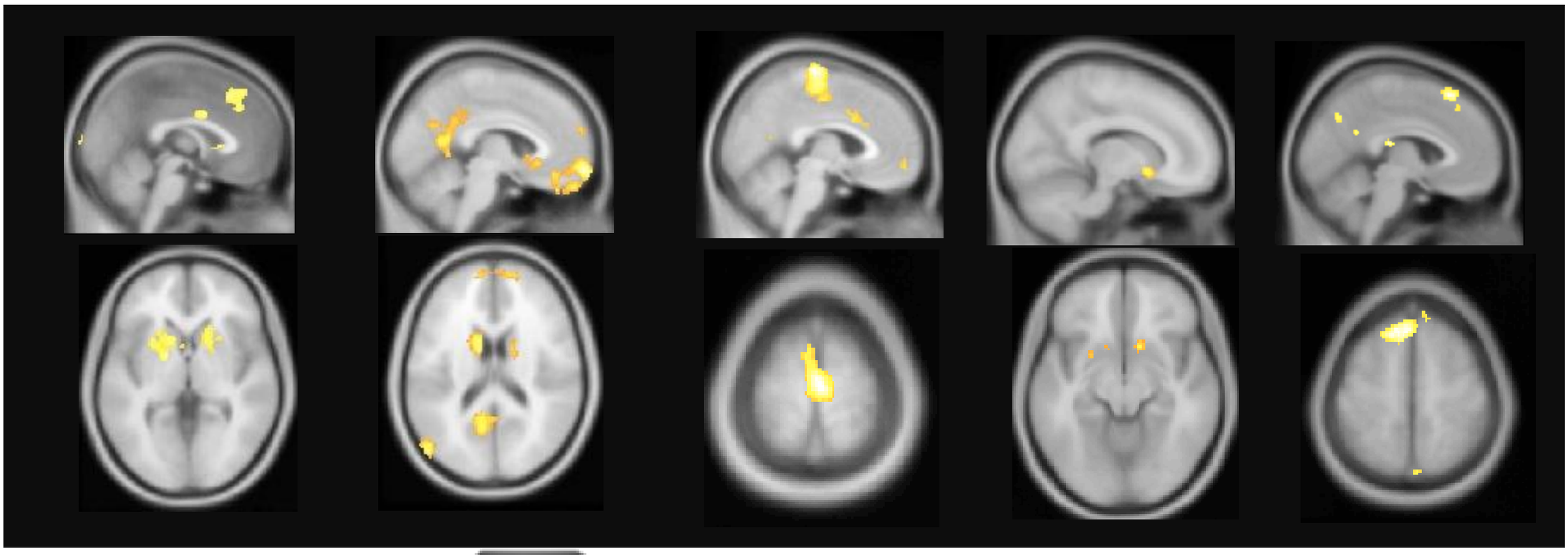
No effect of age and treatment

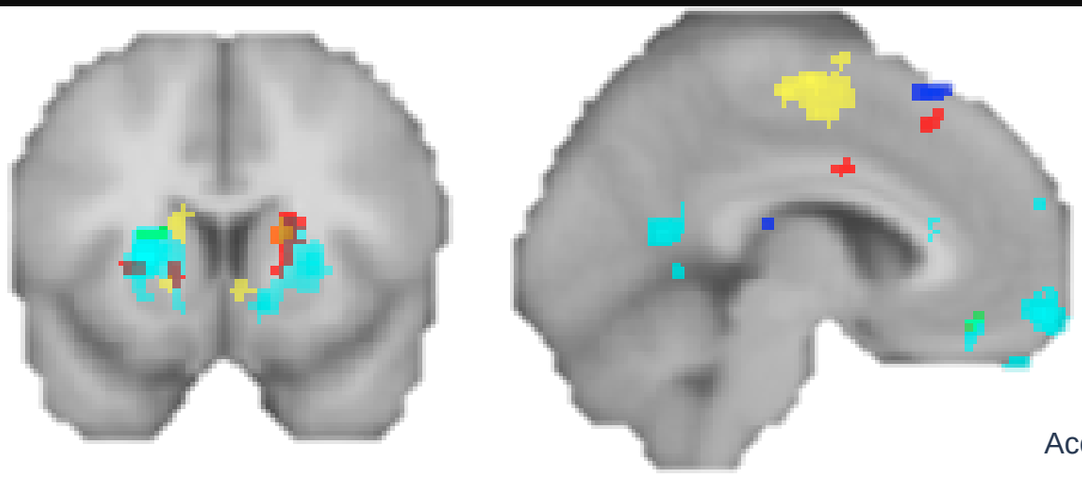
2. Resting State Networks in GLUT1



GLUT1 > controls

ACCUMBENS | **DORSAL CAUDATE** | **DORSAL CAUDAL PUTAMEN** | **VENTRAL ROSTRAL PUTAMEN** | **PCU**

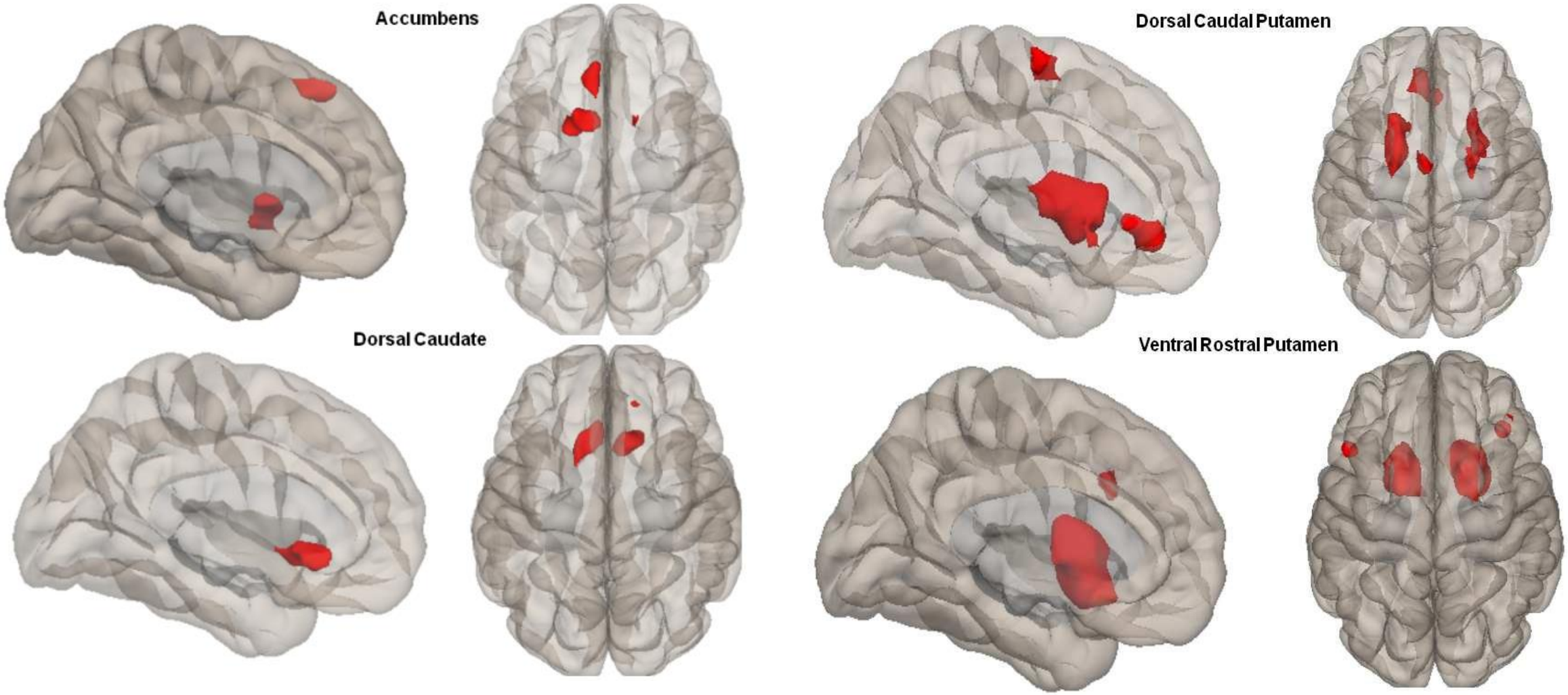




Vaudano et al., in preparation

Accumbens | Dorsal Caudate | Dorsal Caudal Putamen | Dorsal Rostral Putamen | PCU

GLUT 1 Children *vs* healthy children



↑ Functional connectivity

Vaudano et al., in preparation

PET imaging in GLUT1

- **the <u>thalami</u> displayed <u>hypometabolism</u> comparable to the degree of cortical depression**
- **the <u>caudate and bilateral lentiform nuclei</u> exhibited a relative <u>increase</u> in uptake.**

- Glucose metabolism was relatively preserved also in occipital, prefrontal and mesialfrontal cortices.

- findings were <u>independent of the severity of the disease, age or epileptic history.</u>

Pascual et al., 2002; Suls et al., 2008

Conclusion:

Preliminary data
At present: no clinical implication

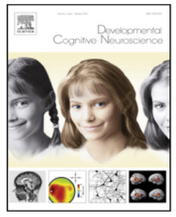
- But:
  - fMRI non invasive
  - In IGE with early onset/atypical features the findings of atypical BOLD findings related to GSW is a red flag to think to GLUT1
  - In GLUT1: functional connectivity of resting state-networks could be used in near future to evaluate prospectively single patients

Why PED/dystonia during adolescence?

Contents lists available at ScienceDirect

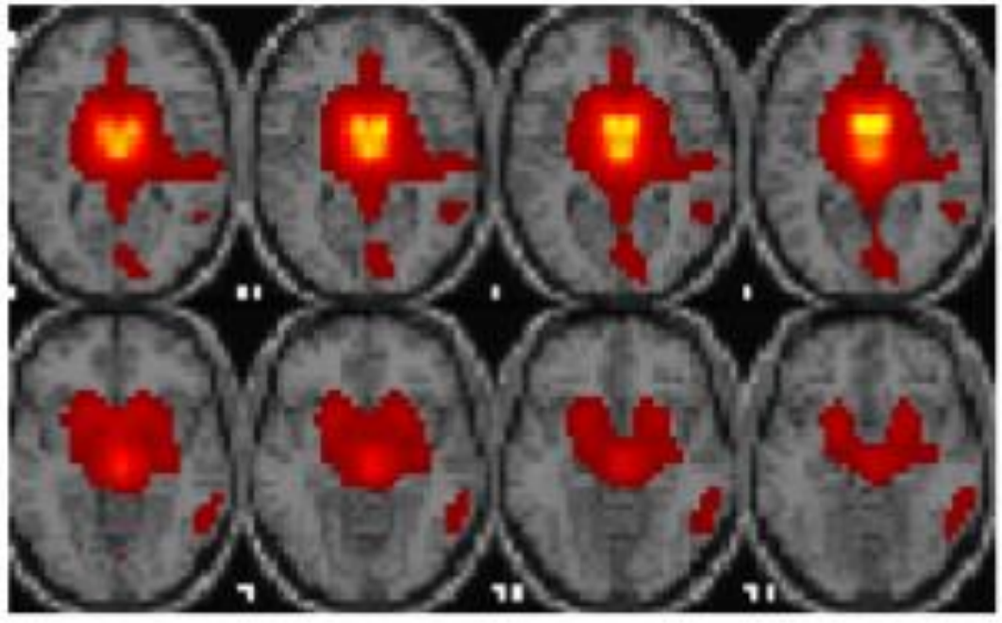
Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn



Intrinsic connectivity networks from childhood to late adolescence: Effects of age and sex

Cristina Solé-Padullés[a], Josefina Castro-Fornieles[a,b,c,d], Elena de la Serna[d], Rosa Calvo[a,b,d], Inmaculada Baeza[a,b,d], Jaime Moya[a,b], Luisa Lázaro[a,b,c,d], Mireia Rosa[b], Nuria Bargalló[d,e,f], Gisela Sugranyes[a,b,*]



Grazie per l’attenzione

Modena

Pavia

Anna E Vaudano MD, PhD

Andrea Ruggieri PhD student

Giulia Monti MD, PhD student

Laura Mirandola MD

Giada Giovannini MD

Prof. Pierangelo Veggiotti
Dr.ssa Sara Olivotto
Dr.ssa Valentina De Giorgis

Pavia – IRCCS Mondino

Patients & Families

Funding

UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

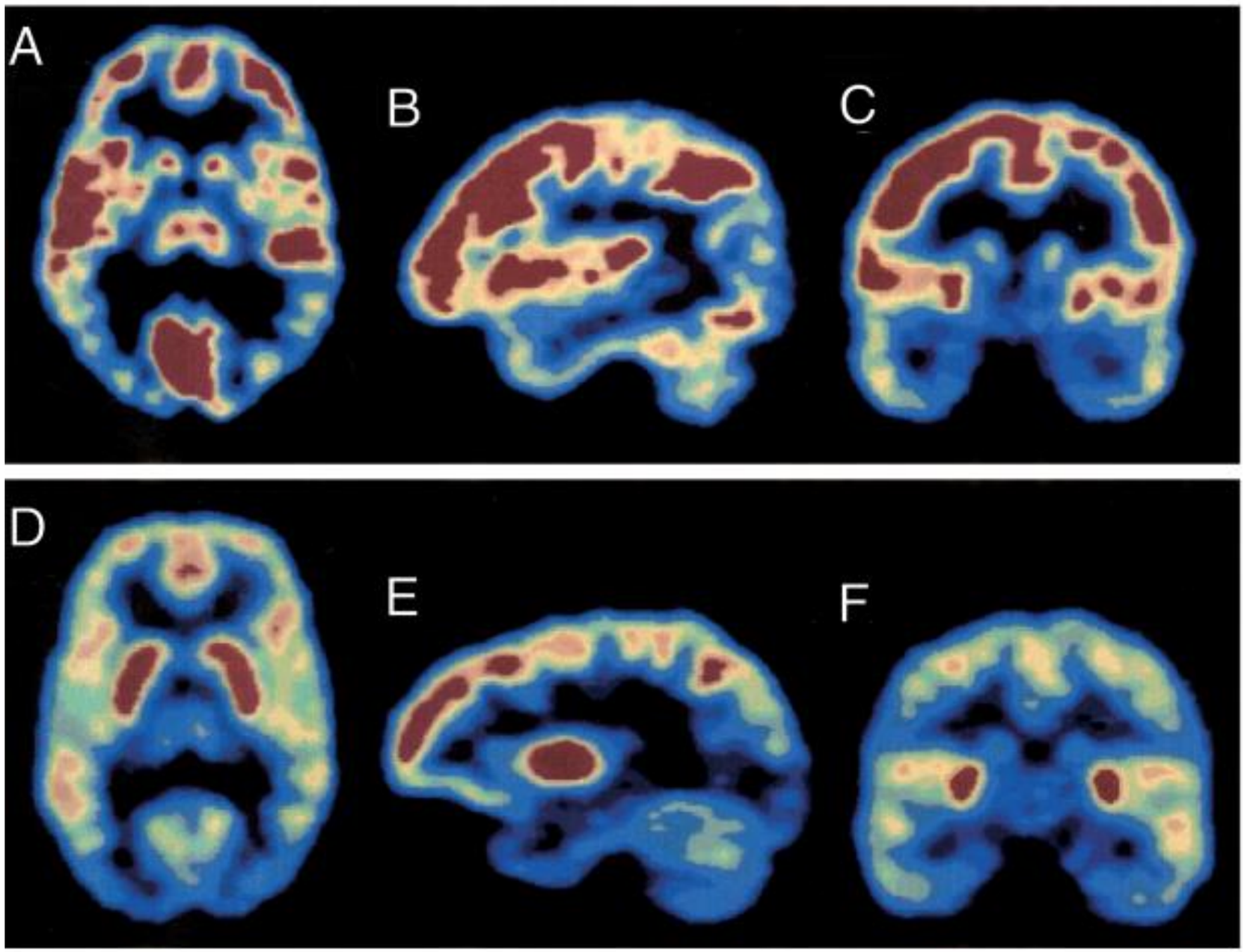
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena

Ministero della Salute

LICE
Lega Italiana contro l'Epilessia

FONDAZIONE
Cassa di Risparmio di Modena

PET imaging



ABC: control
DEF: GLUT-1DS

The radiotracer distribution appears globally diminished in comparison with the normal subject, except for an apparently increased uptake by the basal ganglia.