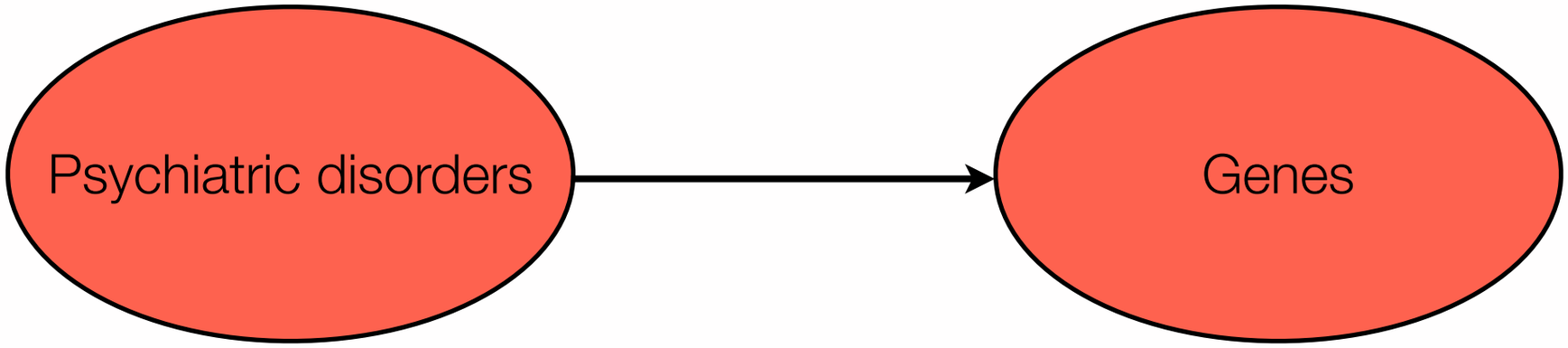
Studying neurodevelopmental disorders: from gene and brain development to endophenotype and finally back to clinical practice

Prof. Stephan Eliez, M.D.
Mrs. Maude Schneider, Ph.D
Mrs. Marie Schaer, M.D. Ph.D

Madrid, 21/06/2015
ESCAP Academy

How to explore the genetic bases of mental illness?



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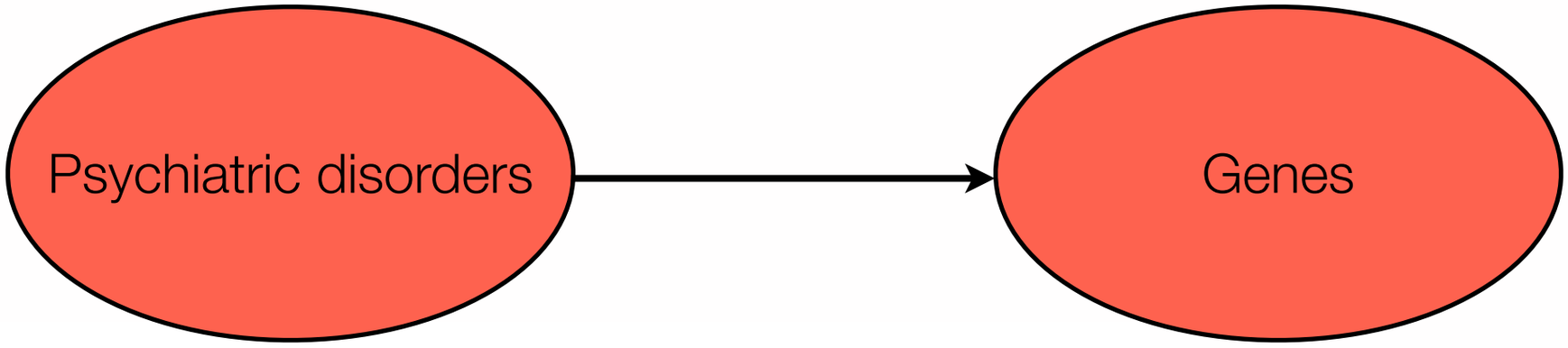

Molecular Psychiatry (2014) 19, 1085–1094

www.nature.com/mp

ORIGINAL ARTICLE

A genome-wide association study of anorexia nervosa

V Boraska[1,2,121], CS Franklin[1,121], JAB Floyd[1,3,121], LM Thornton[4,121], LM Huckins[1], L Southam[1], NW Rayner[1,5,6], I Tachmazidou[1], KL Klump[7], J Treasure[8], CM Lewis[9], U Schmidt[8], F Tozzi[4], K Kiezebrink[10], J Hebebrand[11], P Gorwood[12,13], RAH Adan[14,15], MJH Kas[14], A Favaro[16], P Santonastaso[16], F Fernández-Aranda[17,18], M Gratacos[19,20,21,22], F Rybakowski[23], M Dmitrzak-Weglarz[24], J Kaprio[25,26,27], A Keski-Rahkonen[25], A Raevuori[25,28], EF Van Furth[29,30], MCT Slof-Op 't Landt[29,31], JI Hudson[32], T Reichborn-Kjennerud[33,34], GPS Knudsen[33], P Monteleone[35,36], AS Kaplan[37,38], A Karwautz[39], H Hakonarson[40,41], WH Berrettini[42], Y Guo[40], D Li[40], NJ Schork[43], G Komaki[44,45], T Ando[44], H Inoko[46], T Esko[47], K Fischer[47], K Männik[48,49], A Metspalu[47,48], JH Baker[4], RD Cone[50], J Dackor[51], JE DeSocio[52], CE Hilliard[4], JK O'Toole[53], J Pantel[54], JP Szatkiewicz[51], C Taico[4], S Zerwas[4], SE Trace[4], OSP Davis[9,55], S Helder[9], K Bühren[56], R Burghardt[57], M de Zwaan[58,59], K Egberts[60], S Ehrlich[61,62], B Herpertz-Dahlmann[56], W Herzog[63], H Imgart[64], A Scherag[65], S Scherag[11], S Zipfel[66], C Boni[12], N Ramoz[12], A Versini[12], MK Brandys[14,15], UN Danner[15], C de Kovel[67], J Hendriks[14], BPC Koeleman[67], RA Ophoff[68,69], E Strengman[67], AA van Elburg[15,70], A Bruson[71], M Clementi[71], D Degortes[16], M Forzan[71], E Tenconi[16], E Docampo[19,20,21,22], G Escaramís[19,20,21,22], S Jiménez-Murcia[17,18], J Lissowska[72], A Rajewski[73], N Szeszenia-Dabrowska[73], A Slopien[24], J Hauser[24], L Karhunen[74], I Meulenbelt[31], PE Slagboom[31,75], A Tortorella[35], M Maj[35], G Dedoussis[76], D Dikeos[77], F Gonidakis[78], K Tziouvas[76], A Tsitsika[79], H Papezova[80], L Slachtova[81], D Martaskova[80], JL Kennedy[37,38], RD Levitan[37,38], Z Yilmaz[4,37], J Huemer[39], D Koubek[39], E Merl[39], G Wagner[39], P Lichtenstein[82], G Breen[9], S Cohen-Woods[9], A Farmer[9], P McGuffin[9], S Cichon[83,84,85], I Giegling[86], S Herms[83,85], D Rujescu[86], S Schreiber[87], H-E Wichmann[88,89], C Dina[90], R Sladek[91], G Gambaro[92], N Soranzo[1], A Julia[93], S Marsal[93], R Rabionet[19,20,21,22], V Gaborieau[94], DM Dick[95], A Palotie[1,96,97], S Ripatti[96,98], E Widén[96,98], OA Andreassen[99], T Espeseth[99,100], A Lundervold[101,102,103], I Reinvang[100], VM Steen[104,105], S Le Hellard[104,105], M Mattingsdal[99], I Ntalla[76], V Bencko[106], L Foretova[107], V Janout[108], M Navratilova[107], S Gallinger[109,110], D Pinto[111], SW Scherer[112], H Aschauer[113], L Carlberg[113], A Schosser[113], L Alfredsson[114], B Ding[114], L Klareskog[115], L Padyukov[115], P Courtet[116,117], S Guillaume[116,117], I Jaussent[116,117], C Finan[1], G Kalsi[9], M Roberts[9], DW Logan[1], L Peltonen[1], GRS Ritchie[1,118], JC Barrett[1] The Wellcome Trust Case Control Consortium 3[122], X Estivill[19,20,21,22,123], A Hinney[11,123], PF Sullivan[4,51,124], DA Collier[9,119,124], E Zeggini[1,124] and CM Bulik[4,120,124]

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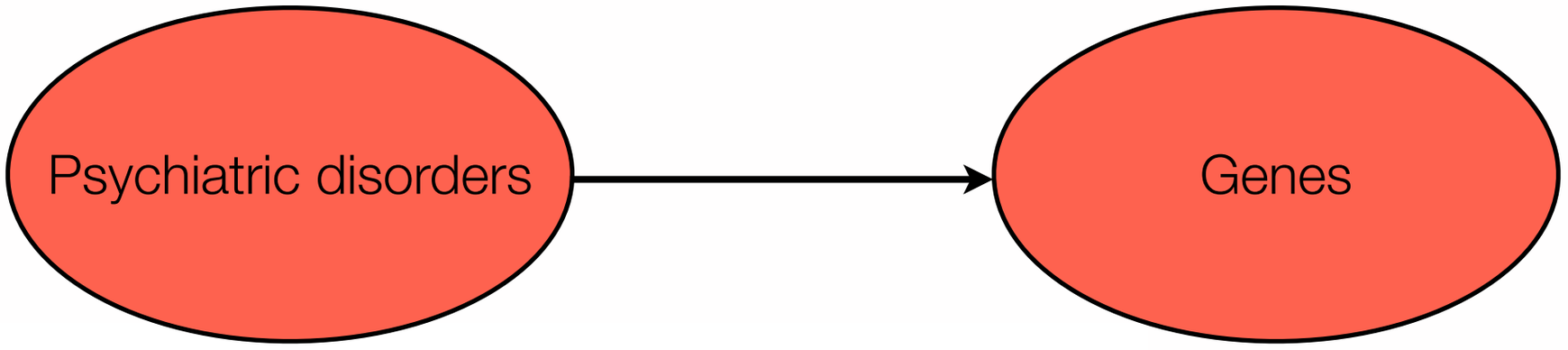

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A Fava
A Kesk
GPS Kr
G Kom
CE Hill
M de Z
C Boni
E Stren
G Esca
L Karhu
A Tsitsi
E Merl
D Ruje
R Rabi
A Lund
V Jano
B Ding
DW Lo
A Hinn

Research

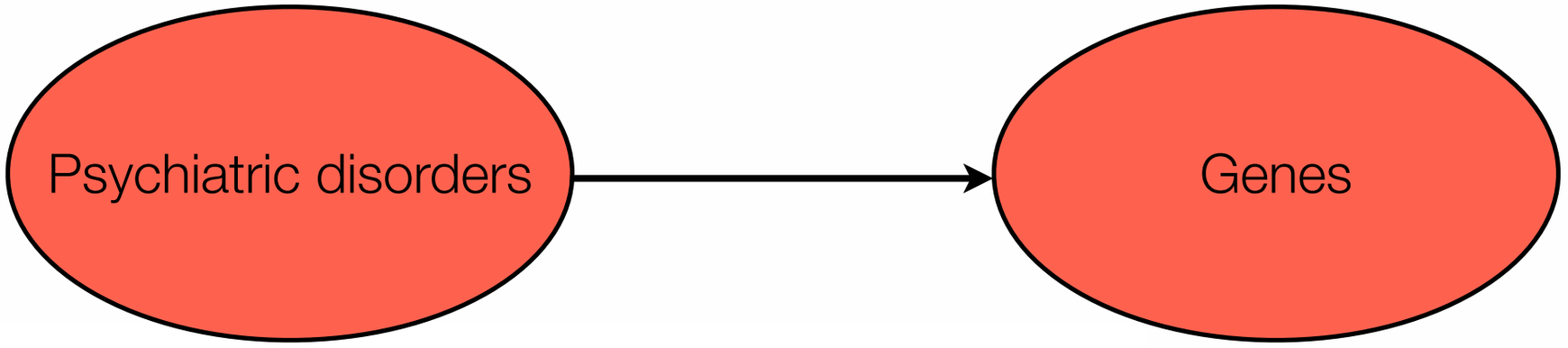
Original Investigation

Meta-analysis of Genome-wide Association Studies for Neuroticism, and the Polygenic Association With Major Depressive Disorder

Genetics of Personality Consortium

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2015.0554
Published online May 20, 2015.

How to explore the genetic bases of mental illness?



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Original Investigation

Meta-analysis of Genom for Neuroticism, and the With Major Depressive I

Genetics of Personality Consortium

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2015.0554
Published online May 20, 2015.

Genome-Wide Analysis Shows Increased Frequency of Copy Number Variation Deletions in Dutch Schizophrenia Patients

Jacobine E. Buizer-Voskamp, Jan-Willem Muntjewerff, Genetic Risk and Outcome in Psychosis (GROUP) Consortium, Eric Strengman, Chiara Sabatti, Hreinn Stefansson, Jacob A.S. Vorstman, and Roel A. Ophoff

Background: Since 2008, multiple studies have reported on copy number variations (CNVs) in schizophrenia. However, many regions are unique events with minimal overlap between studies. This makes it difficult to gain a comprehensive overview of all CNVs involved in the etiology of schizophrenia. We performed a systematic CNV study on the basis of a homogeneous genome-wide dataset aiming at all CNVs ≥50 kilobase pair. We complemented this analysis with a review of cytogenetic and chromosomal abnormalities for schizophrenia reported in the literature with the purpose of combining classical genetic findings and our current understanding of genomic variation.

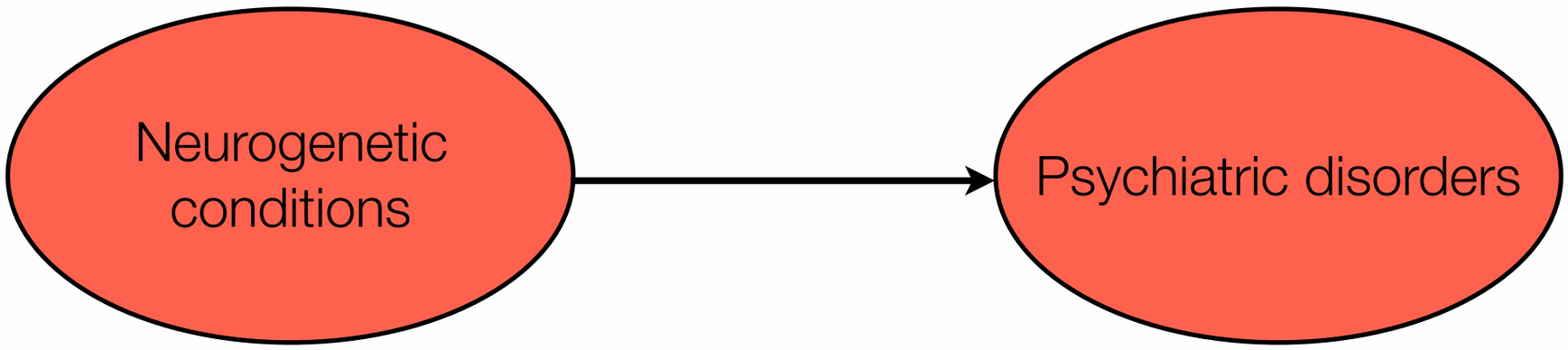
Methods: We investigated 834 Dutch schizophrenia patients and 672 Dutch control subjects. The CNVs were included if they were detected by QuantiSNP (http://www.well.ox.ac.uk/QuantiSNP/) as well as PennCNV (http://www.neurogenome.org/cnv/penncnv/) and contain known protein coding genes. The integrated identification of CNV regions and cytogenetic loci indicates regions of interest (cytogenetic regions of interest [CROIs]).

Results: In total, 2437 CNVs were identified with an average number of 2.1 CNVs/subject for both cases and control subjects. We observed significantly more deletions but not duplications in schizophrenia cases versus control subjects. The CNVs identified coincide with loci previously reported in the literature, confirming well-established schizophrenia CROIs 1q42 and 22q11.2 as well as indicating a potentially novel CROI on chromosome 5q35.1.

Conclusions: Chromosomal deletions are more prevalent in schizophrenia patients than in healthy subjects and therefore confer a risk factor for pathogenicity. The combination of our CNV data with previously reported cytogenetic abnormalities in schizophrenia provides an overview of potentially interesting regions for positional candidate genes.

BIOL PSYCHIATRY 2011;70:655–662

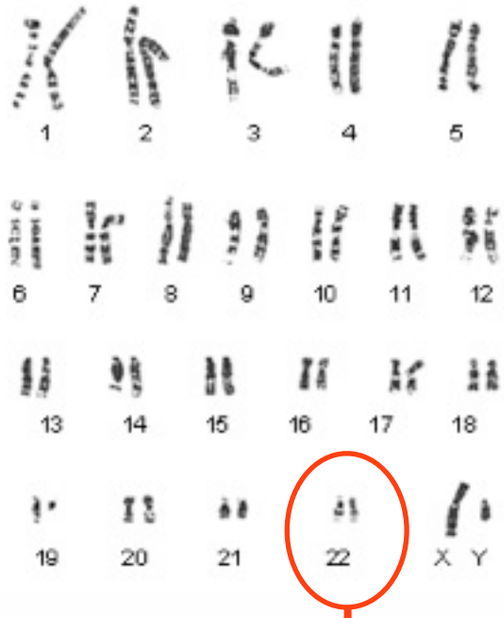
Studying rare neurogenetic conditions: a window for the exploration of the genetic bases of psychiatric disorders

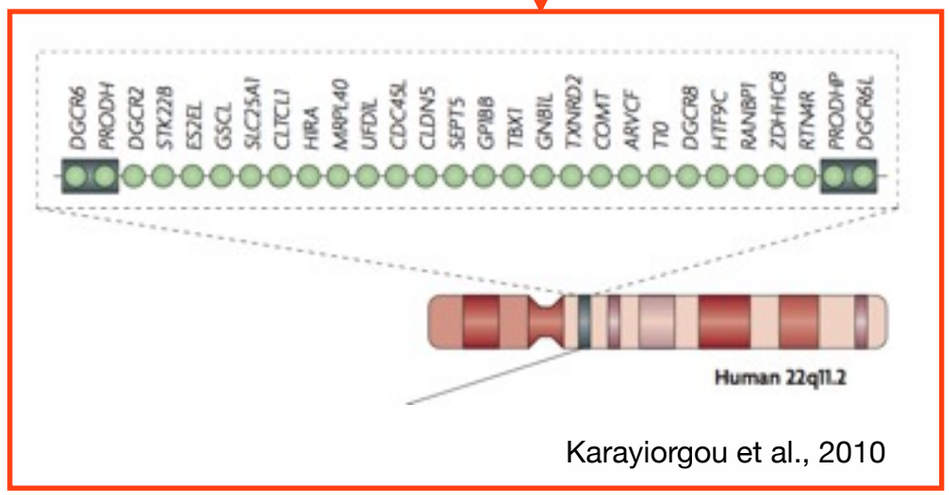


Down Syndrome and Alzheimer Disease
Prader-Willi Syndrome and hyperphagia
Shank 3 and autism
22q11.2DS and schizophrenia
...

22q11.2 microdeletion (22q11.2DS)

www.VCFSEF.org





Karayiorgou et al., 2010

- Prevalence: 1/4000 live birth
- In 90% of cases: *de novo* microdeletion
- Physical phenotype
  - Conotruncal cardiac defects
  - Velopharyngeal insufficiency and/or submucous cleft palate
  - Immune deficits
  - ...
- Cognitive phenotype
  - borderline intellectual functioning (mIQ = 70)

22q11.2 microdeletion (22q11.2DS)

Reviews and Overviews

Mechanisms of Psychiatric Illness

Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

Maude Schneider, M.Sc.
Martin Debbané, Ph.D.
Anne S. Bassett, M.D., F.R.C.P.C.
Eva W.C. Chow, M.D., F.R.C.P.C.
Wai Lun Alan Fung, M.D., Sc.D.
Marianne B.M. van den Bree, Ph.D.
Michael Owen, M.D., Ph.D.
Kieran C. Murphy, M.D., Ph.D.
Maria Niarchou, Ph.D.
Wendy R. Kates, Ph.D.
Kevin M. Antshel, Ph.D.
Wanda Fremont, M.D.
Donna M. McDonald-McGinn, M.S., C.G.C.
Raquel E. Gur, M.D., Ph.D.
Elaine H. Zackai, M.D.
Jacob Vorstman, M.D., Ph.D.
Sasja N. Duijff, Ph.D.
Petra W.J. Klaassen, M.Sc.
Ann Swillen, Ph.D.
Doron Gothelf, M.D.
Tamar Green, M.D.
Abraham Weizman, M.D.
Therese Van Amelsvoort, M.D., Ph.D.
Laurens Evers, M.D.
Erik Boot, M.D., Ph.D.
Vandana Shashi, M.D.
Stephen R. Hooper, Ph.D.
Carrie E. Bearden, Ph.D.
Maria Jalbrzikowski, Ph.D.
Marco Armando, M.D., Ph.D.
Stefano Vicari, M.D.
Declan G. Murphy, M.D.
Opal Ousley, Ph.D.
Linda E. Campbell, Ph.D.
Tony J. Simon, Ph.D.
Stephan Eliez, M.D.
for the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

Objective: Chromosome 22q11.2 deletion syndrome is a neurogenetic disorder associated with high rates of schizophrenia and other psychiatric conditions. The authors report what is to their knowledge the first large-scale collaborative study of rates and sex distributions of psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome. The associations among psychopathology, intellect, and functioning were examined in a subgroup of participants.

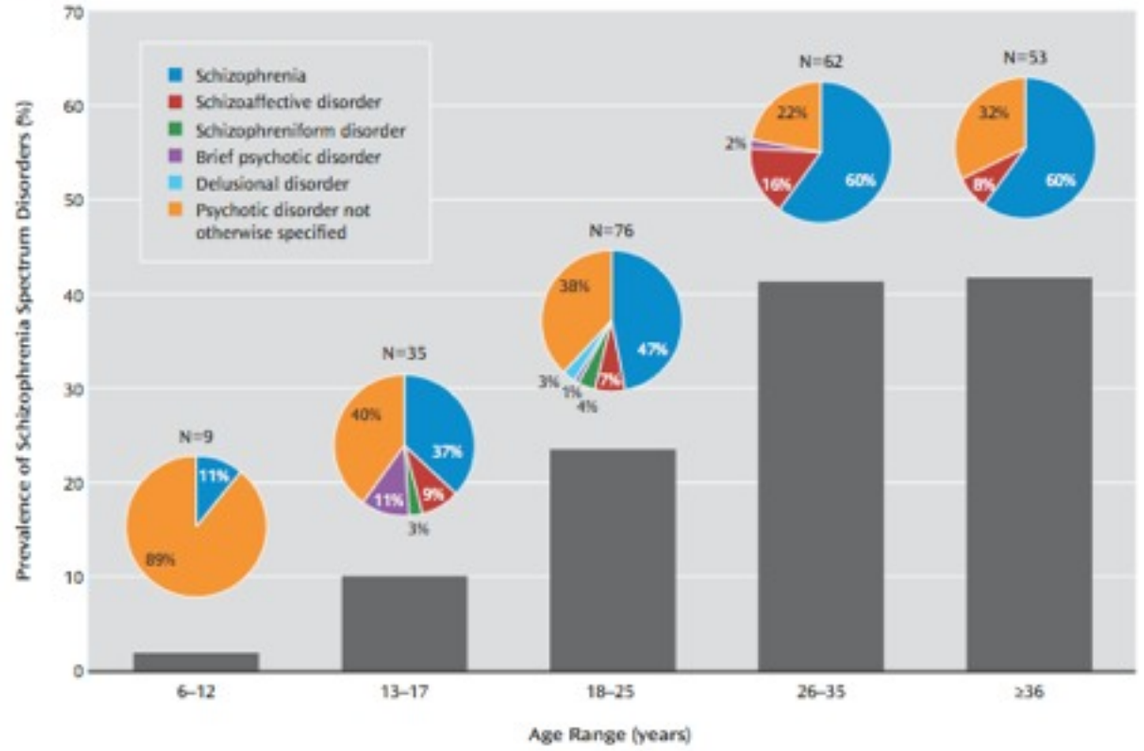
Method: The 1,402 participants with 22q11.2 deletion syndrome, ages 6–68 years, were assessed for psychiatric disorders with validated diagnostic instruments. Data on intelligence and adaptive functioning were available for 183 participants ages 6 to 24 years.

Results: Attention deficit hyperactivity disorder (ADHD) was the most frequent disorder in children (37.10%) and was overrepresented in males. Anxiety disorders were more prevalent than mood disorders at all ages, but especially in children and adolescents. Anxiety and unipolar mood disorders were overrepresented in females. Psychotic disorders were present in 41% of adults over age 25. Males did not predominate in psychotic or autism spectrum disorders. Hierarchical regressions in the subgroup revealed that daily living skills were predicted by the presence of anxiety disorders. Psychopathology was not associated with communication or socialization skills.

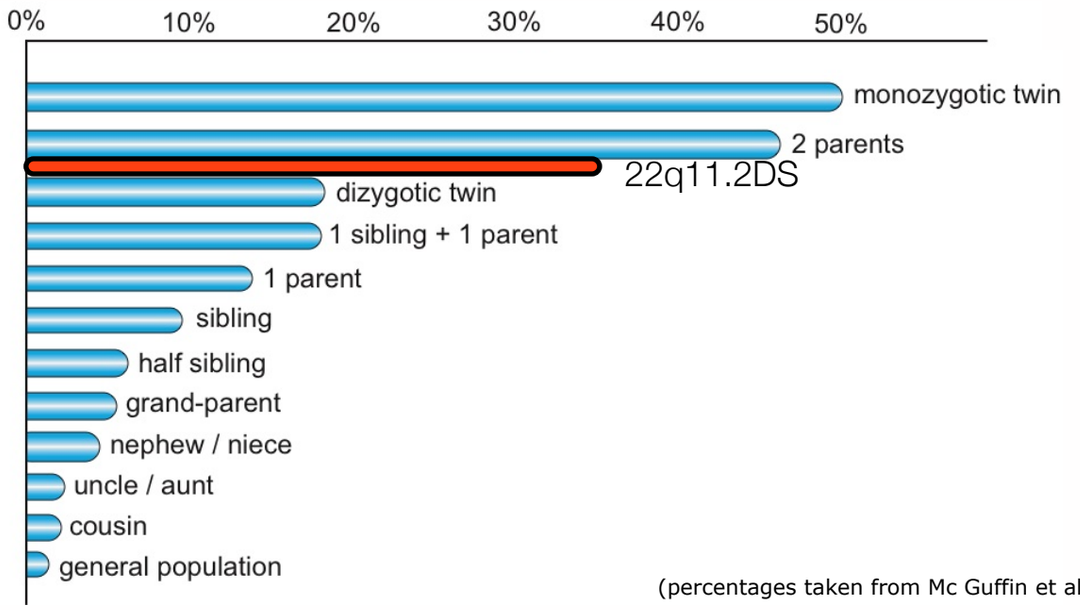
Conclusions: To the authors' knowledge, this is the largest study of psychiatric morbidity in 22q11.2 deletion syndrome. It validates previous findings that this condition is one of the strongest risk factors for psychosis. Anxiety and developmental disorders were also prevalent. These results highlight the need to monitor and reduce the long-term burden of psychopathology in 22q11.2 deletion syndrome.

Am. J Psychiatry (2014), 171 (6)

FIGURE 2. Prevalence of Schizophrenia Spectrum Disorders and Distribution of Specific Disorders by Age in Participants With 22q11.2 Deletion Syndrome[a]



Risk of schizophrenia based on familial history



(percentages taken from Mc Guffin et al, 1995)

The Geneva 22q11.2DS longitudinal study

2001 2003 2005 2007 2009 2011 2013 2015 2017

2001-2004
1st funding period

2004-2008
2nd funding period

2009-2013
3rd funding period

2013-2017
4th funding period

Visit 1

Visit 2

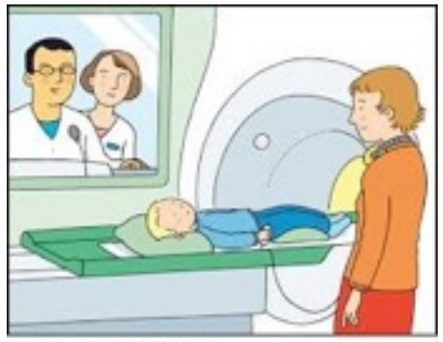
Visit 3

Visit 4

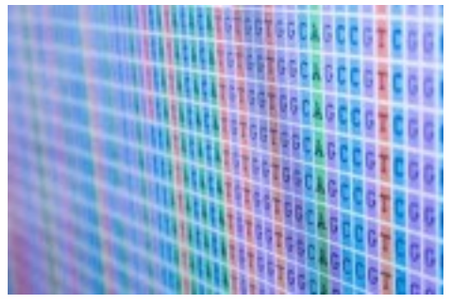
Neuropsychological testing

Clinical interviews

MRI



Genetic analyses



Collaboration with S. Antonarakis

EEG

Collaboration with C. Michel

Eye tracking

The Geneva 22q11.2DS longitudinal study

2001 2003 2005 2007 2009 2011 2013 2015 2017

2001-2004 1st funding period	**2004-2008** 2nd funding period	**2009-2013** 3rd funding period	**2013-2017** 4th funding period

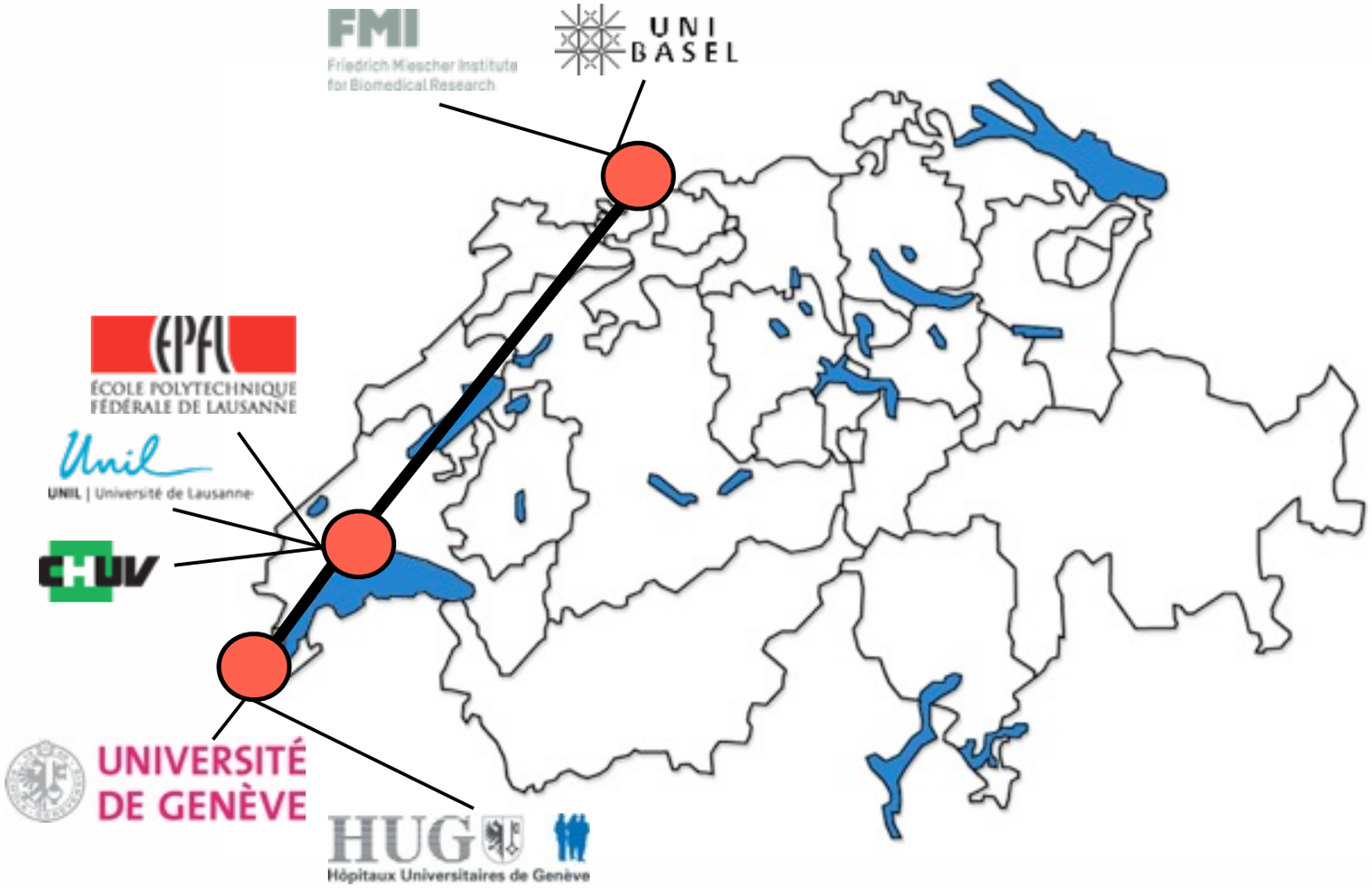
Genetics	Size of the deletion	Parental origin & COMT polymorphism		Combination of polymorphisms & WGS (with the 22q11.2DS Consortium)
Brain structure	Lobar volumetric measurements	Fractional anisotropy & 3D cortical thickness	Local gyrification index, tractography & connectome	Mixed model non-linear trajectory analyses
Brain activity		Task specific fMRI	Resting-state fMRI	Multimodal integration
Behavior	Standardized cognitive and diagnostic tools	Refining the assessment of psychotic symptoms & experimental cognitive tasks	Social cognitive tasks and eye-tracking	Ecological paradigms

The Geneva 22q11.2DS longitudinal study

2001 2003 2005 2007 2009 2011 2013 2015 2017

2010-2014
1st funding period

2014-2018
2nd funding period



Objectives

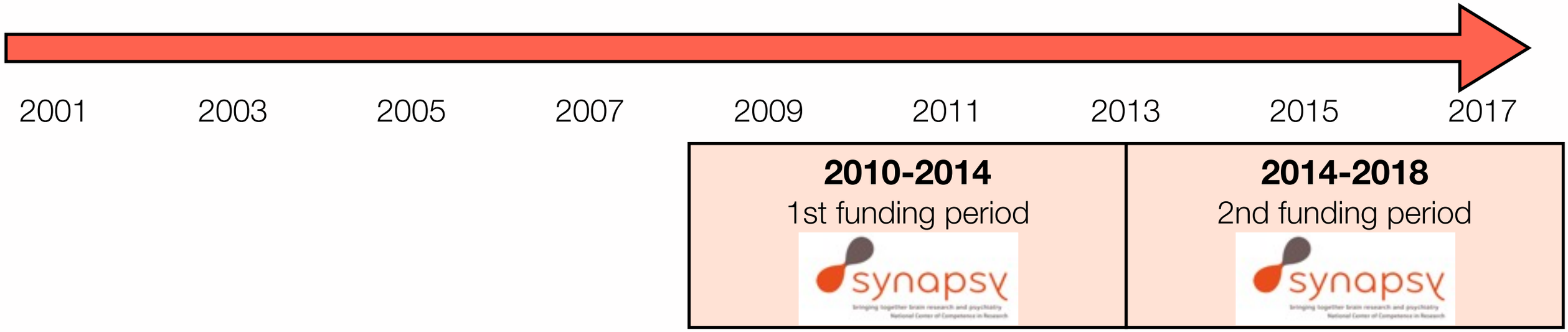
Contributing to the development of a Swiss network of excellence in psychiatric research

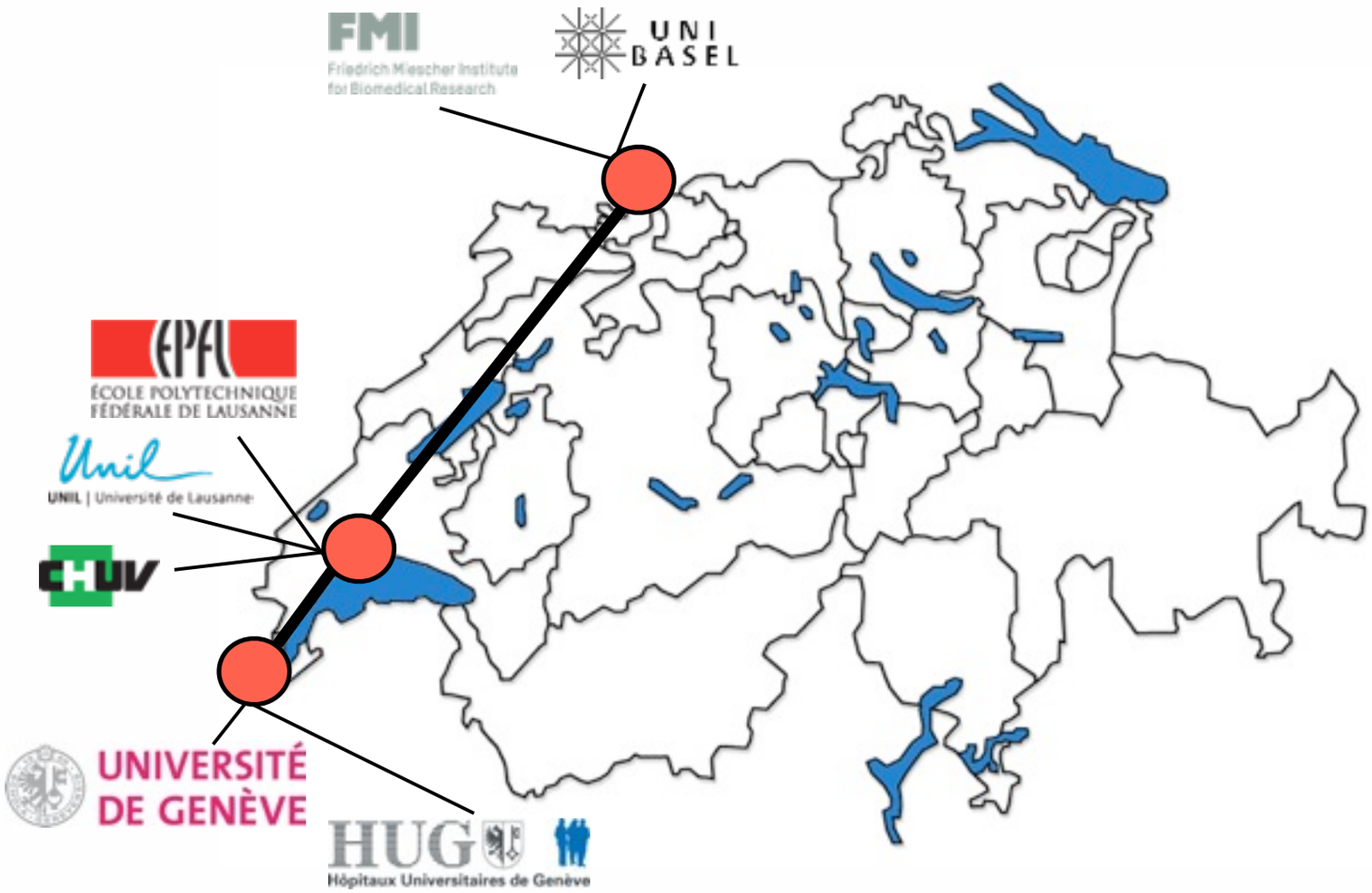
Identifying biological bases of certain psychiatric disorders

Bringing together fundamental and clinical research

Setting up translational studies between human cohorts and animal models

The Geneva 22q11.2DS longitudinal study





The 22q11.2DS project within SYNAPSY

Clinical research (patients with 22q11.2DS)

- Stephan Eliez
- Christoph Michel

Fundamental research (LgDel+/- mice)

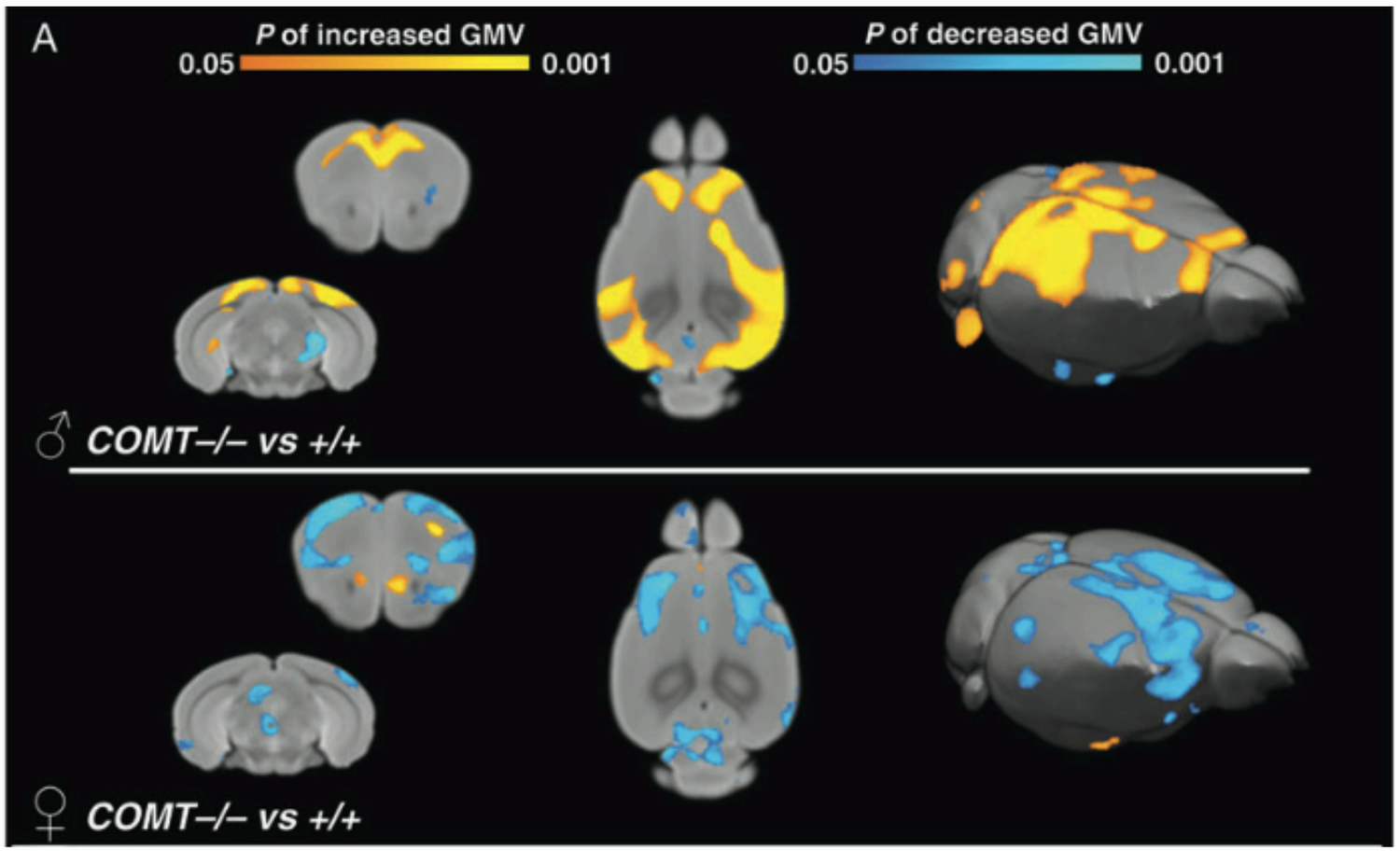
- Pico Caroni
- Stylianos Antonarakis
- Olaf Blanke
- Alan Carleton
- Christoph Michel
- Kathrin Hess Bellwald

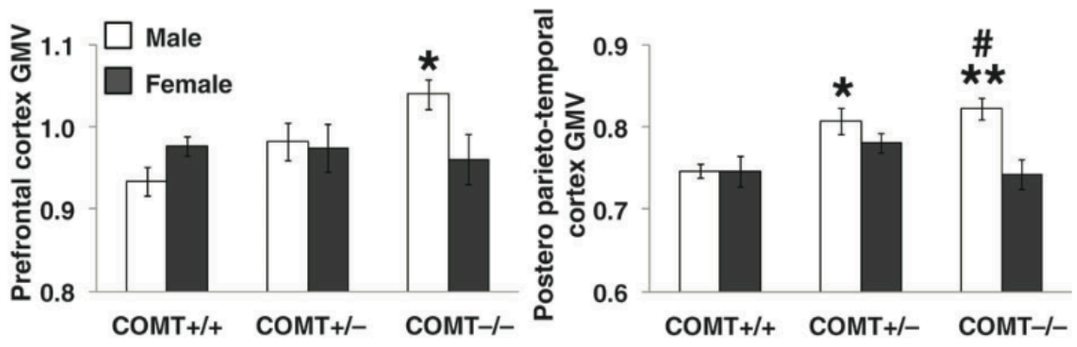
Example of an ongoing translational project

P.I. Stephan Eliez and Francesco Papaleo (IIT, Genova)

In mice...

Increased prefrontal and postero-parieto-temporal gray-matter volume in male but not female COMT knockout mice





CURRENT GOAL: replicate the finding that the level of COMT activity modulates brain volume in LgDel+/- mice

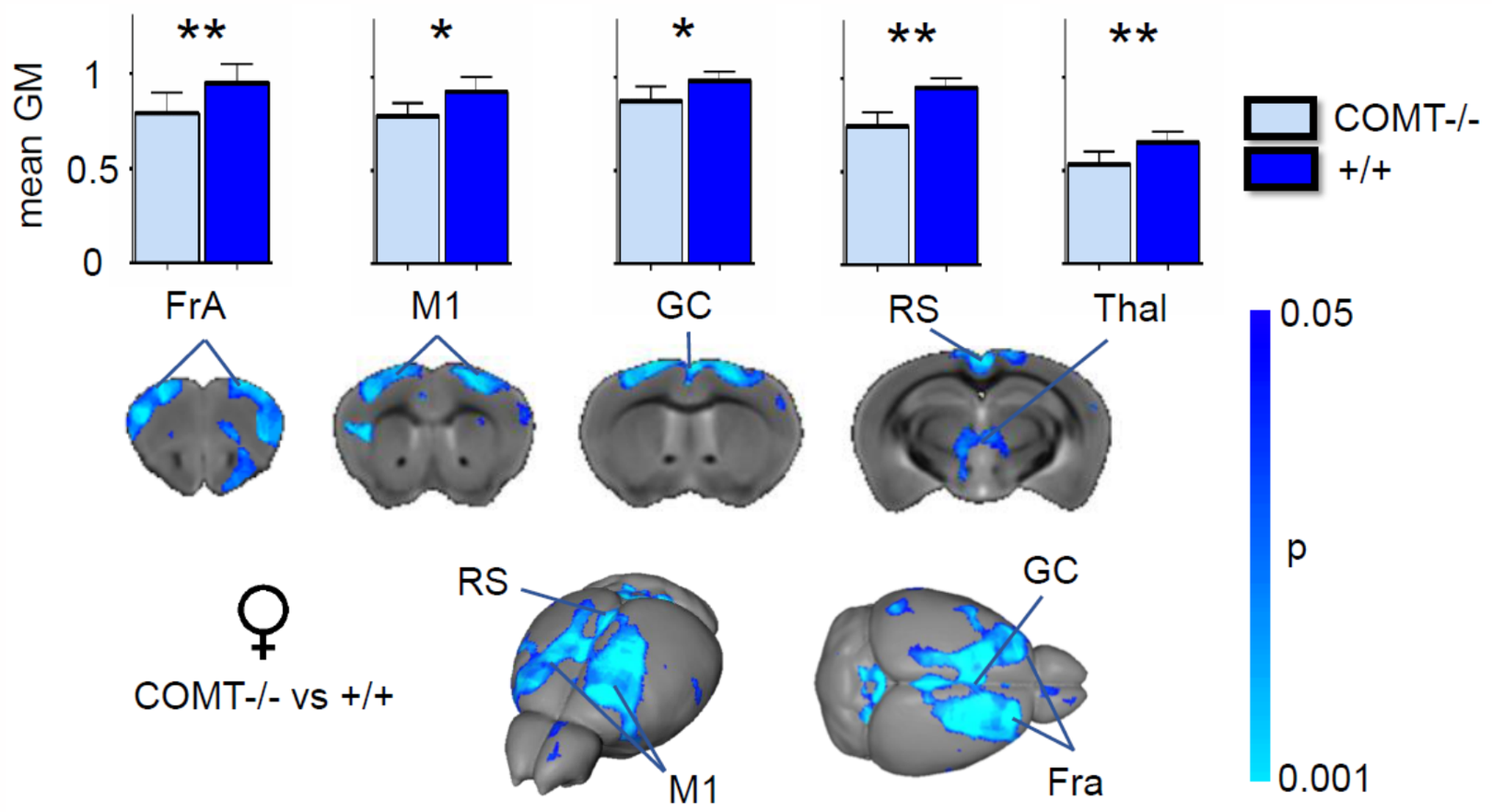
Sannino et al., 2014, Cerebral cortex

Example of an ongoing translational project

P.I. Stephan Eliez and Francesco Papaleo (IIT, Genova)

In mice...

Decreased grey matter volume in COMT -/- female mice



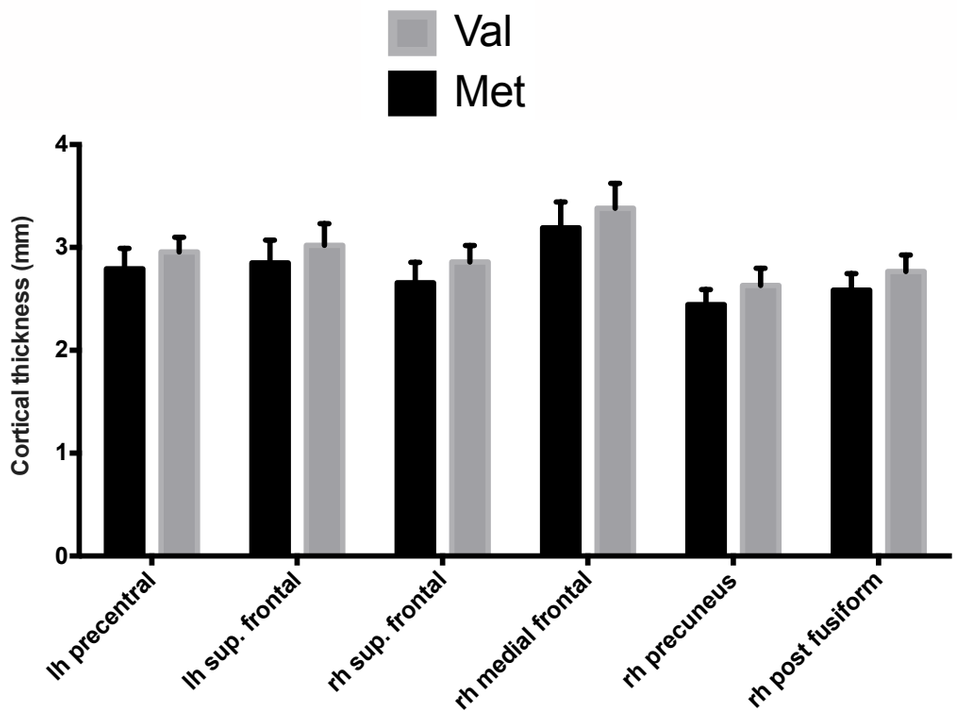
FrA= Associative frontal cortex
M1= Primary motor cortex
GC= Cingulate gyrus
RS= Retrosplenial cortex
Thal= Thalamus

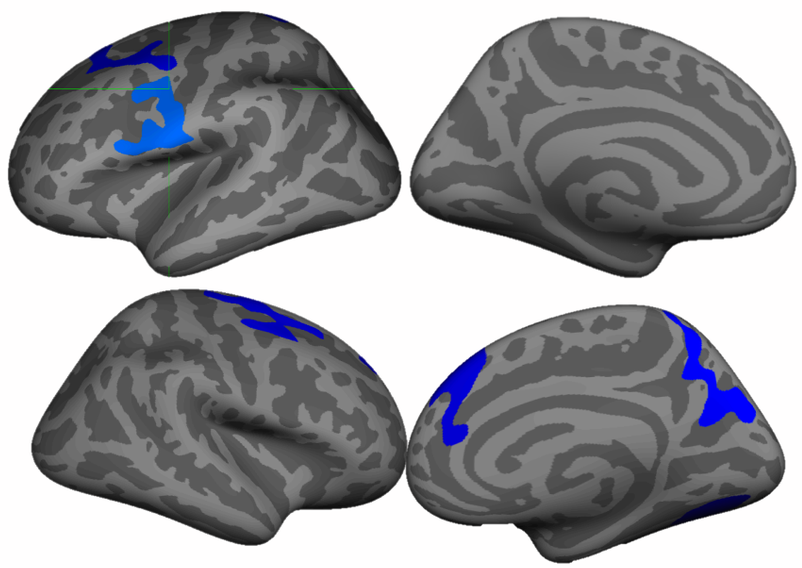
Example of an ongoing translational project

P.I. Stephan Eliez and Francesco Papaleo (IIT, Genova)

In humans...

Decreased cortical thickness in Met carriers (low enzyme activity & increased dopamine level) in frontal and parietal regions only in POST PUBERTY





Differences are mainly driven by females

Current work of Marica Padula,
Ph.D. Student

Studying the cognitive mechanisms associated with negative symptoms in 22q11.2DS

Maude Schneider, Ph.D.
(Maude.Schneider@unige.ch)

A few words about my carrer path

2004-2009

UNIVERSITÉ DE GENÈVE
FACULTÉ DE PSYCHOLOGIE ET DES SCIENCES DE L'ÉDUCATION

Bsc. and Msc. in Psychology at the University of Geneva

Introduction to cognitive psychopathology
Prof. M. Van der Linden

Internship at the psychiatric hospital in Lausanne
Unit specialized in early phases of psychosis

Nightwatch in a center specialized in rehabilitation of young adults with psychosis

Master thesis with Prof. S. Eliez and M. Debbané on 22q11.2DS

2009-2014

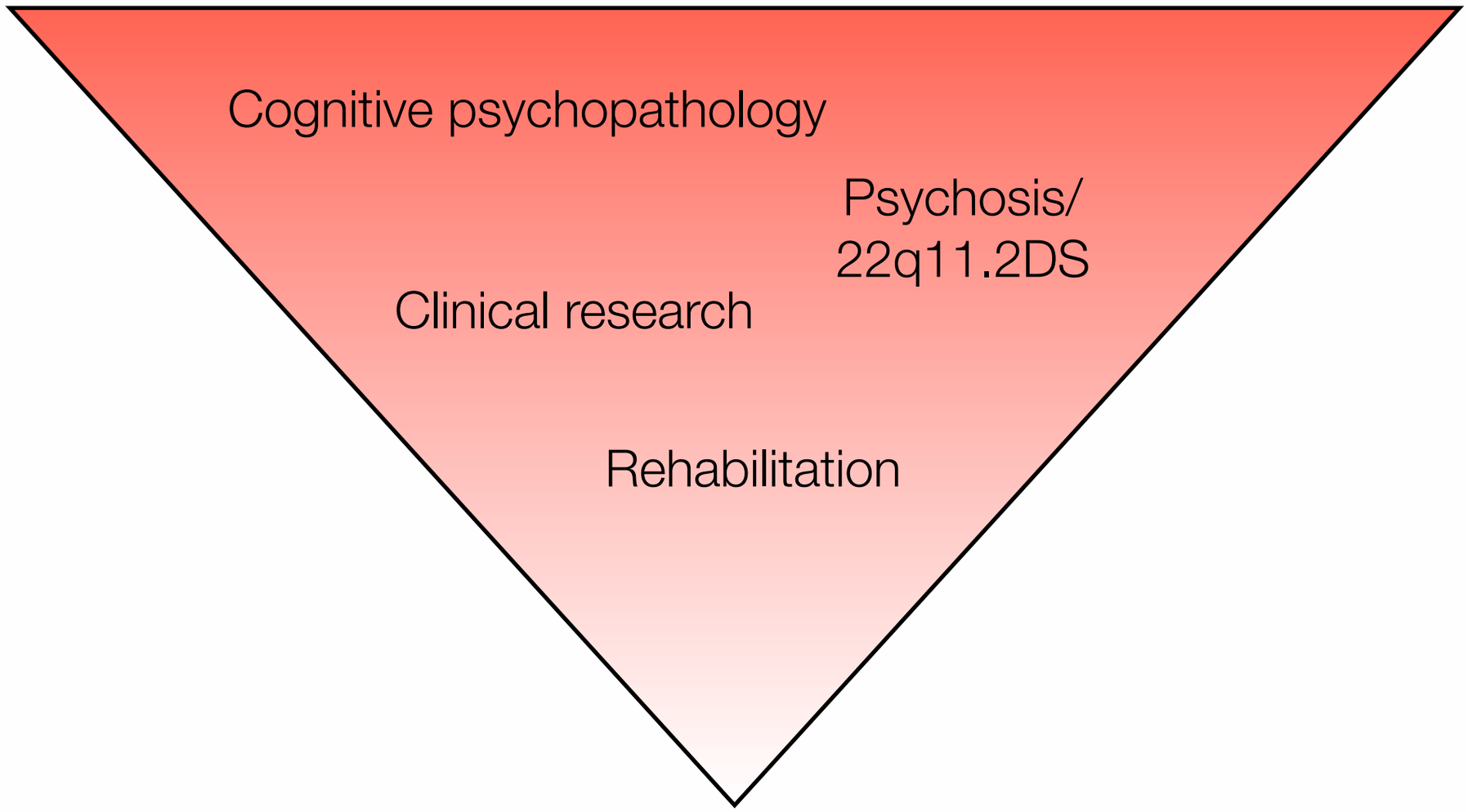
UNIVERSITÉ DE GENÈVE
FACULTÉ DE PSYCHOLOGIE ET DES SCIENCES DE L'ÉDUCATION

Ph.D. in Psychology under the mentorship of Prof. M. Van der Linden and Prof. S. Eliez

REPUBLIQUE ET CANTON DE GENEVE
POST TENEBRAS LUX

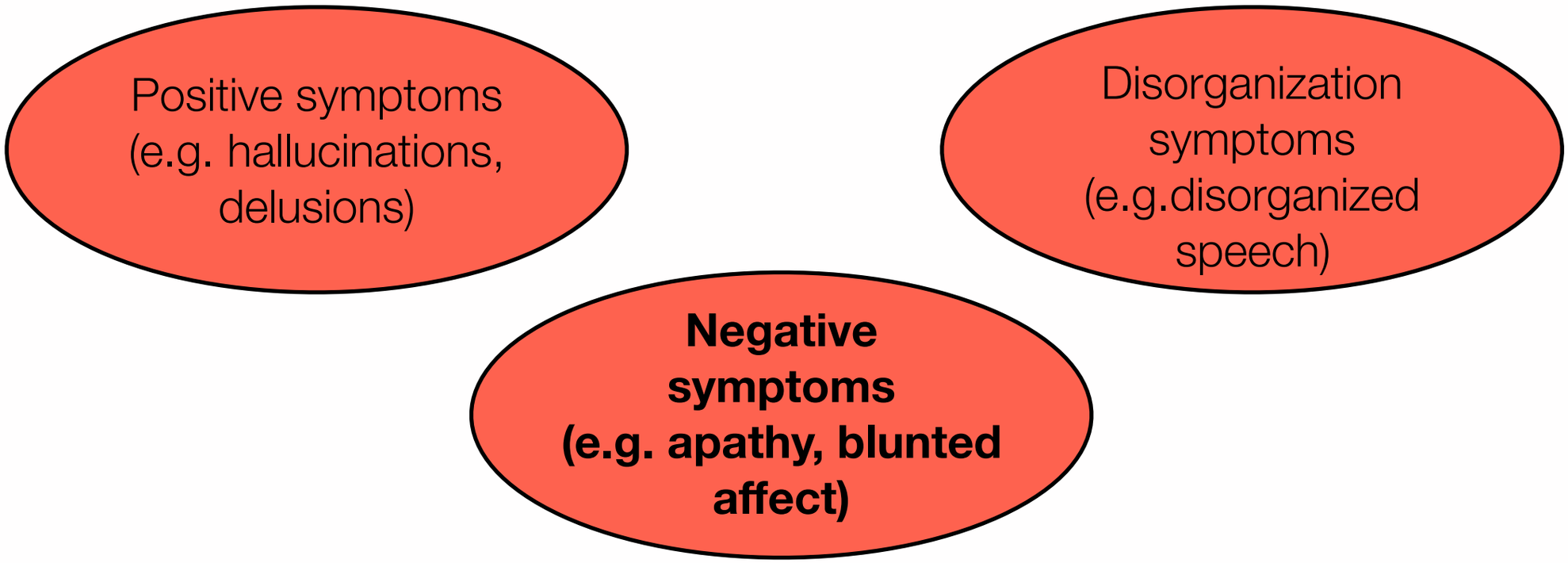
Clinical training in psychotherapy for children and adolescents at the Geneva outpatient state service (Office Médico-Pédagogique)

Building research objectives...



Studying the cognitive bases of negative symptoms
in adolescents and young adults with 22q11.2DS

Defining the clinical phenotype



Symptom	Factor 1	Factor 2
PANSS N6 Lack of spontaneity	**1.071**	
PANSS N1 Blunted affect	**0.866**	
PANSS N7 Stereotyped thinking	**0.784**	
SIPS N3 Expression of emotion	**0.776**	
PANSS N2 Emotional withdrawal	**0.775**	
PANSS G7 Motor retardation	**0.736**	
PANSS N5 Difficulty in abstract thinking	**0.698**	
SIPS N4 Experience of emotions and self	**0.412**	
SIPS N1 Social anhedonia		**0.997**
SIPS D4 Personal hygiene		**0.799**
PANSS G16 Active social avoidance		**0.797**
SIPS N2 Avolition		**0.722**
PANSS N4 Passive social withdrawal		**0.693**
PANSS N3 Poor rapport	0.446	**0.528**
SIPS N6 Occupational functioning		

Decreased emotional expressiveness

Decreased motivation and pleasure

Negative symptoms are present in the majority of adolescents and young adults with 22q11.2DS

Two distinct but correlated symptomatic dimensions

Strong association with daily-life functioning

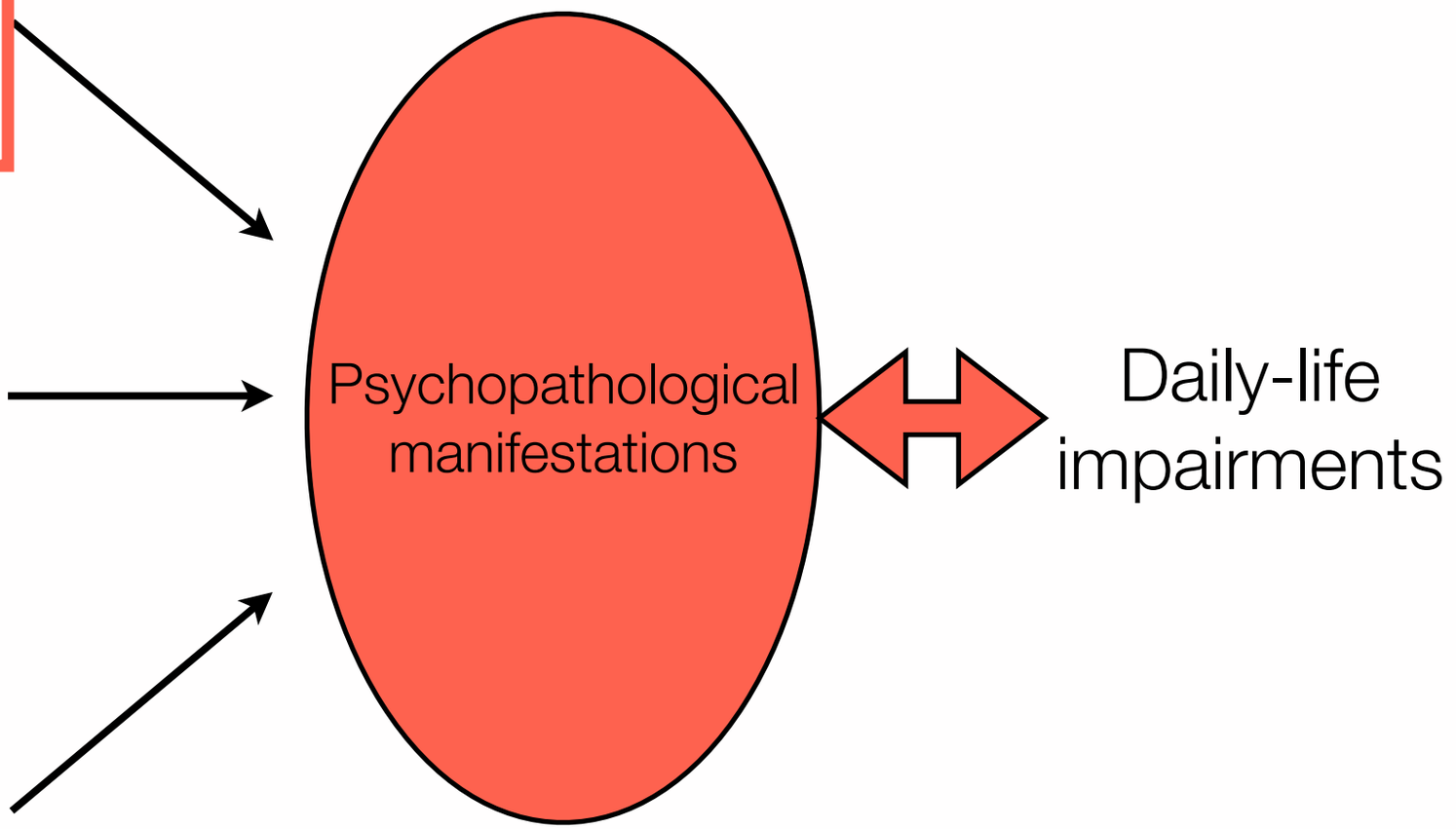
Schneider et al. (2012)
Psychiatry Research

Focus of cognitive psychopathology

Cognitive deficits
Inability to perform a given cognitive function (irrespective of context)

Cognitive biases
Preferential processing of a certain type of information at the cost of others

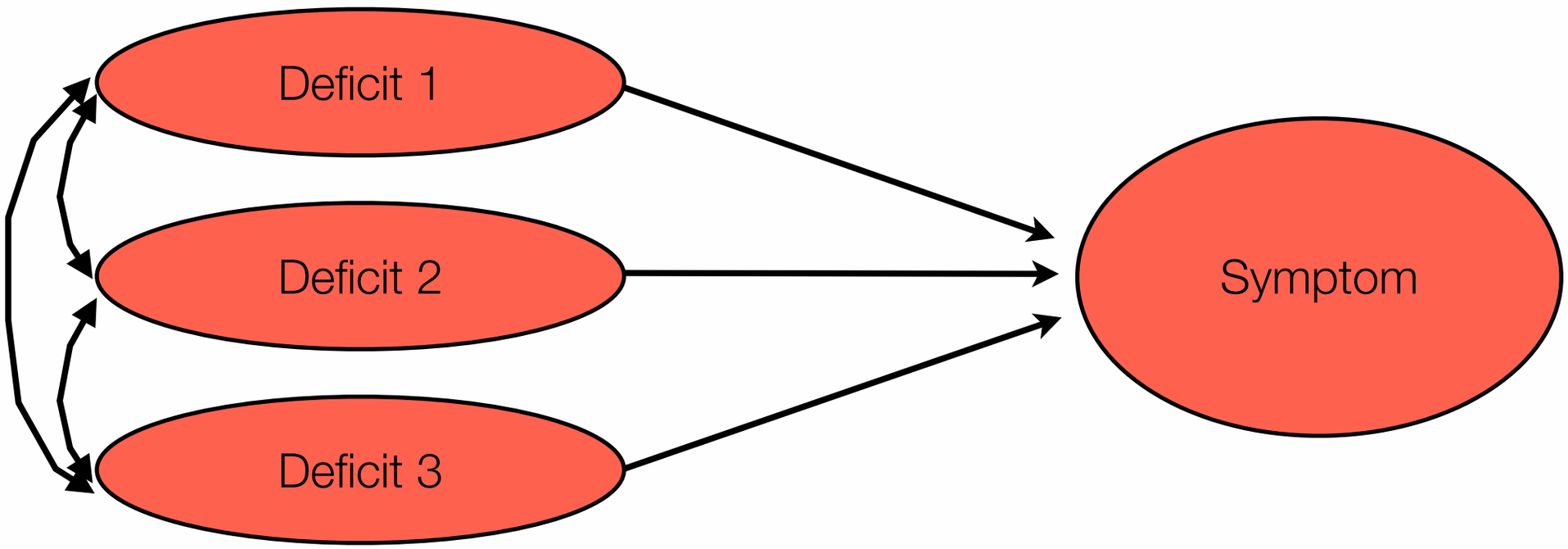
Dysfunctional beliefs
Particular ways of «reading» oneself, others, and the environment



Cognitive deficits associated with negative symptoms in 22q11.2DS

- Negative symptoms are a complex set of symptoms

- Their clinical expression is likely to result from different cognitive deficits and vary from one patient to another
  --> impact for clinical interventions!
  --> importance of focusing on deficits that have a significant impact on daily-life functioning



Cognitive deficits associated with negative symptoms in 22q11.2DS

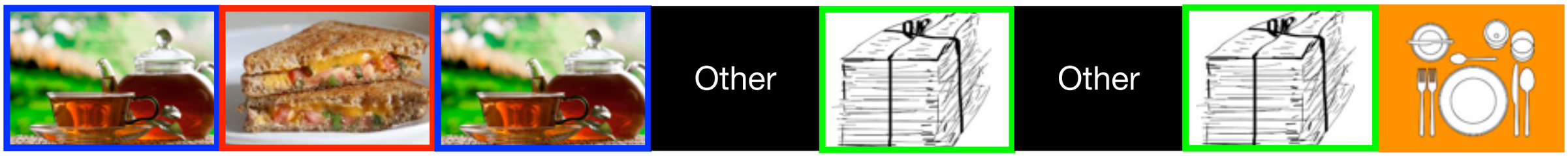
Investigation of multitasking abilities using an ecological paradigm

Multitasking = organization and accomplishment of several inter-related tasks in a given time

Multitasking characterizes many daily-life situations (e.g. cooking a meal) and cannot be examined using traditional neuropsychological tasks

Multitasking evaluation for adolescents

«You invite school friends at home to prepare a history project for school.You have to accomplish three tasks in 30 minutes:
- prepare sandwiches and hot tea
- set the table ready
- prepare a folder with a chapter from a history book.»



15’ 127’ 38’ 44’ 487’ 5’ 61’ 220’ ...

Schneider et al. (in press) *AJIDD*

Cognitive deficits associated with negative symptoms in 22q11.2DS

In comparison with typically developing controls, adolescents with 22q11.2DS are characterized by:

1. Performance
   - Increased number of ignored actions
   - Increased tendency to forget ongoing instructions

2. Sequencing
   - Lower number of sequences (i.e. less «switching» between activities)
   - Higher percentage of sequences allocated to «other» (i.e. non goal directed) activities

Variables associated with the severity of negative symptoms & functional alterations

- Indicators of inefficient planning abilities
- Indicator of prospective memory deficits
- Indicator of source switching deficits

Schneider et al. (in press) *AJIDD*

Cognitive deficits associated with negative symptoms in 22q11.2DS

Putative mechanism

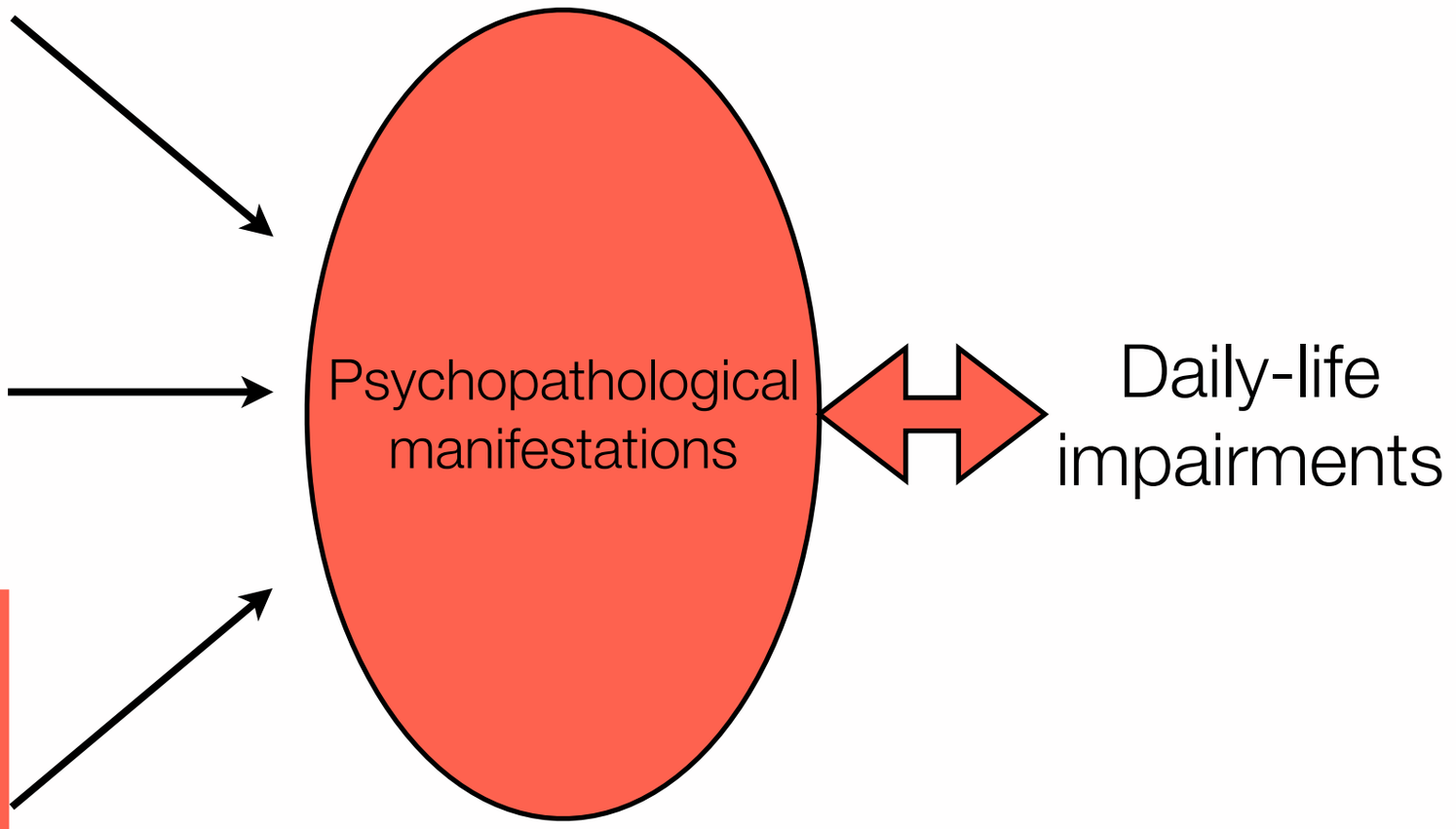
Planning & source switching deficits → Multitasking impairments → Daily-life impairments in g.-d. activities → Reduced motivation & pleasure to perform g.-d. activities

Focus of cognitive psychopathology

Cognitive deficits
Inability to perform a given cognitive function (irrespective of context)

Cognitive biases
Preferential processing of a certain type of information at the cost of others

Dysfunctional beliefs
Particular ways of «reading» oneself, others, and the environment

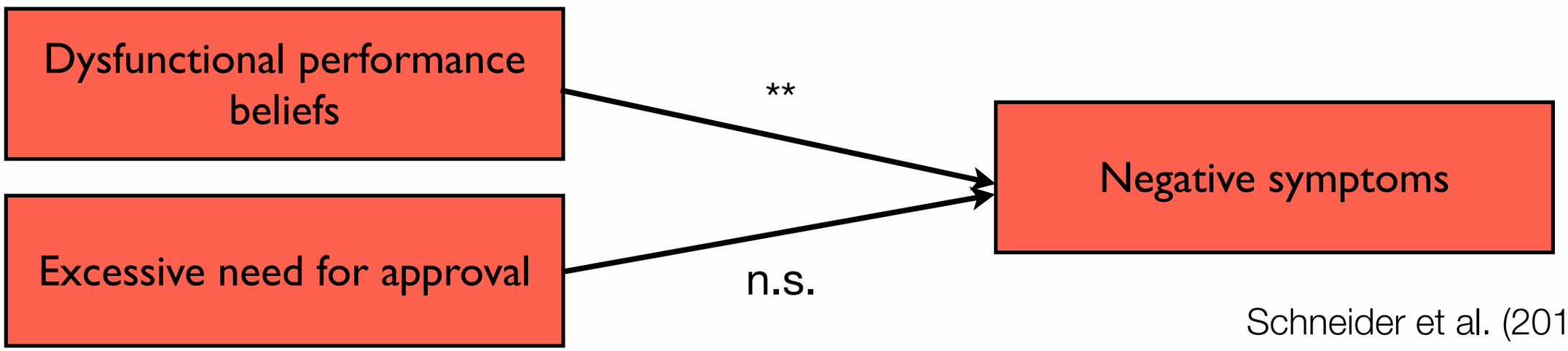


Dysfunctional beliefs associated with negative symptoms in 22q11.2DS

Dysfunctional performance beliefs

- Overly generalized negative conclusions regarding one's own task performance
- «If I fail partly, it is as bad as being a complete failure»
- Associated with cognitive deficits and past experiences of failures
- Vulnerability for the development/maintenance of negative symptoms
  → negative symptoms = unadaptive way of avoiding future negative experiences (e.g. social withdrawal)
- Other types of dysfunctional beliefs not associated with negative symptoms (e.g. excessive need for approval)

Beck et al. (2009)

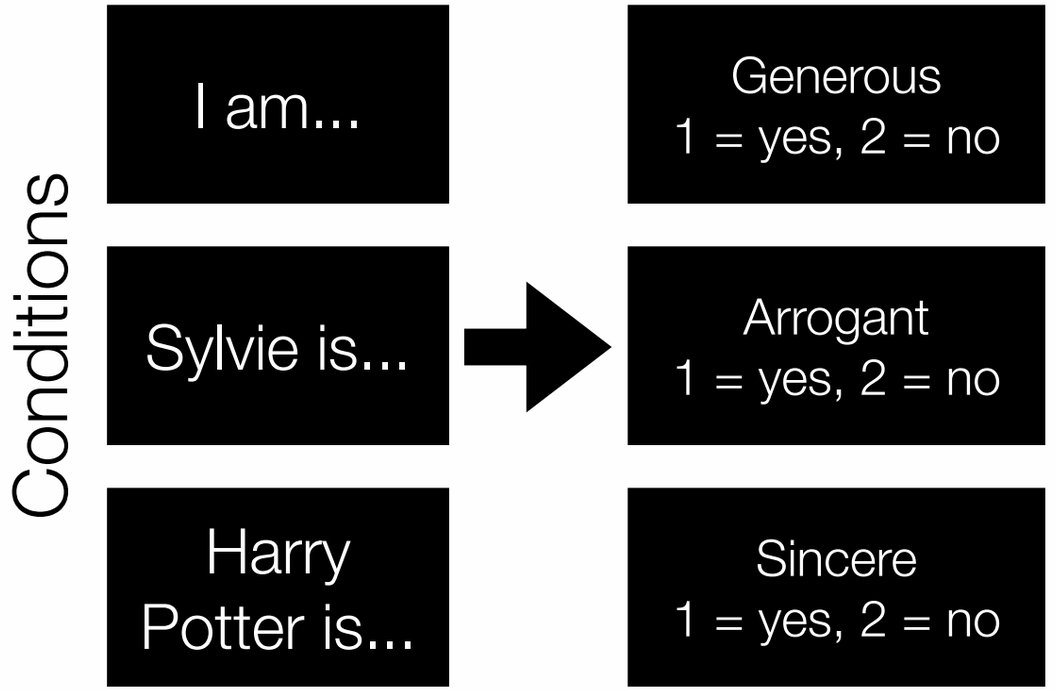


Schneider et al. (2015)
Early Intervention in Psychiatry

What about the brain?

Examining self- and other-representation in the brain

→ fMRI paradigm



In comparison with typically developing controls, adolescents with 22q11.2DS have lower level of activation in the caudate nucleus, the ACC, and the anterior prefrontal cortex during the self condition when contrasted over rest.

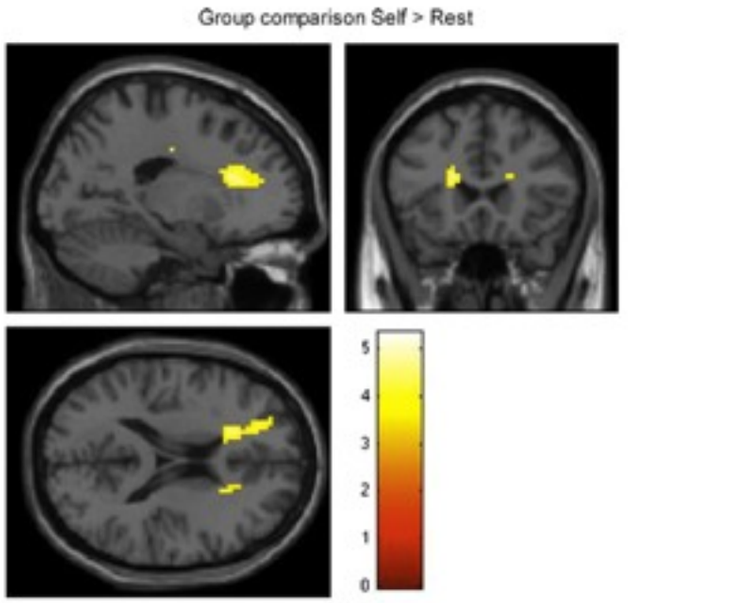


Fig. 4. Increased activations in typically developing adolescents compared to 22q11DS youths during the contrast self condition > rest.

Adolescents with 22q11.2DS are characterized by :
- difficulties in building an accurate representation of themselves
- atypical activation of the reward system during self-related processing

According to some authors (e.g. Nelson et al., 2009), this represents characteristics of schizophrenia which are associated with social dysfunctions

Schneider et al. (2012)
Developmental Cognitive Neurosciences

Towards research-based intervention techniques

A Skype-based social skills training for adolescents and young adults with 22q11.2DS

P.I. Bronwyn Glaser & Maude Schneider

- adapted from the SOSTA-FRA curriculum (Freitag et al., 2013, *Trials*)
- up to 4 participants / group
- 3 month program (12 sessions)
- 1 hour / session
- Content structured in three parts
    - good communication (e.g. initiating a discussion in different contexts)
    - emotions (e.g. recognizing emotions in oneself and others)
    - «complex» social skills (e.g. perspective taking, training for job interviews)

What was this all for?

From a research point of view…

- Clearer description of negative symptomatology in 22q11.2DS
- Better understanding of cognitive risk factors for negative symptoms

From a clinical point of view…

- Implications of our findings for clinical interventions in patients with negative symptoms
    - Cognitive remediation (e.g. social cognition)
    - Cognitive interventions (e.g. Goal management training)

From a personal point of view…

- Coherence: bringing together clinical concerns and research hypotheses
- Self-confidence: article writing, oral presentations, etc…
- Structure: formulating hypotheses, running structured interviews, etc…

What's next?

FROM GENEVA
TO
LEUVEN
(Prof. I. Myin-Germeys)

Ecological psychology: Experience sampling methodology (ESM)

Focus on psychosis

From neuroimaging in 22q11DS to early development in autism

Marie Schaer, M.D. Ph.D.
(Marie.Schaer@unige.ch)

Career Path

2005 **Medical Diploma**

PhD in neurosciences

2008 **MD-PhD**

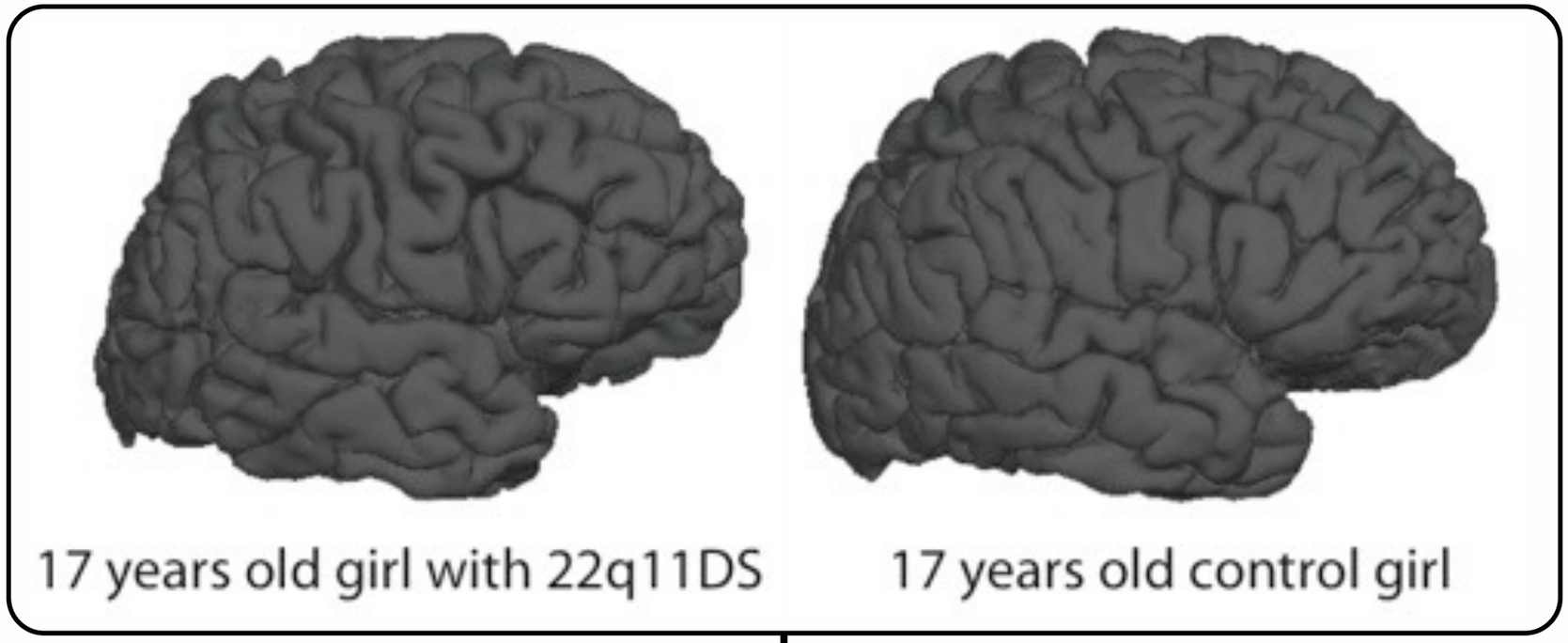
Clinical training

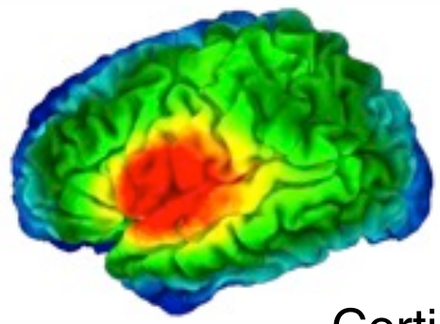
2013 **Started clinical research projects as a main investigator**
Left abroad to gain experience (Stanford University & UC Davis)

PhD in neurosciences: cortical morphology in 22q11DS

Advisors: Prof. Stephan Eliez (Child Psychiatry, Geneva) & Prof. Jean-Philippe Thiran (Signal Processing Laboratory, Swiss Federal Institute of Technology, Lausanne)

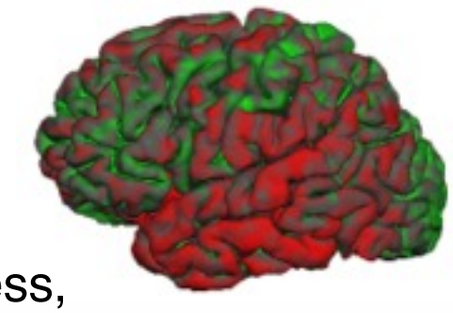
What can be learnt from brain structure in 22q11DS?





Cortical folding (gyrification),
a marker of early brain development

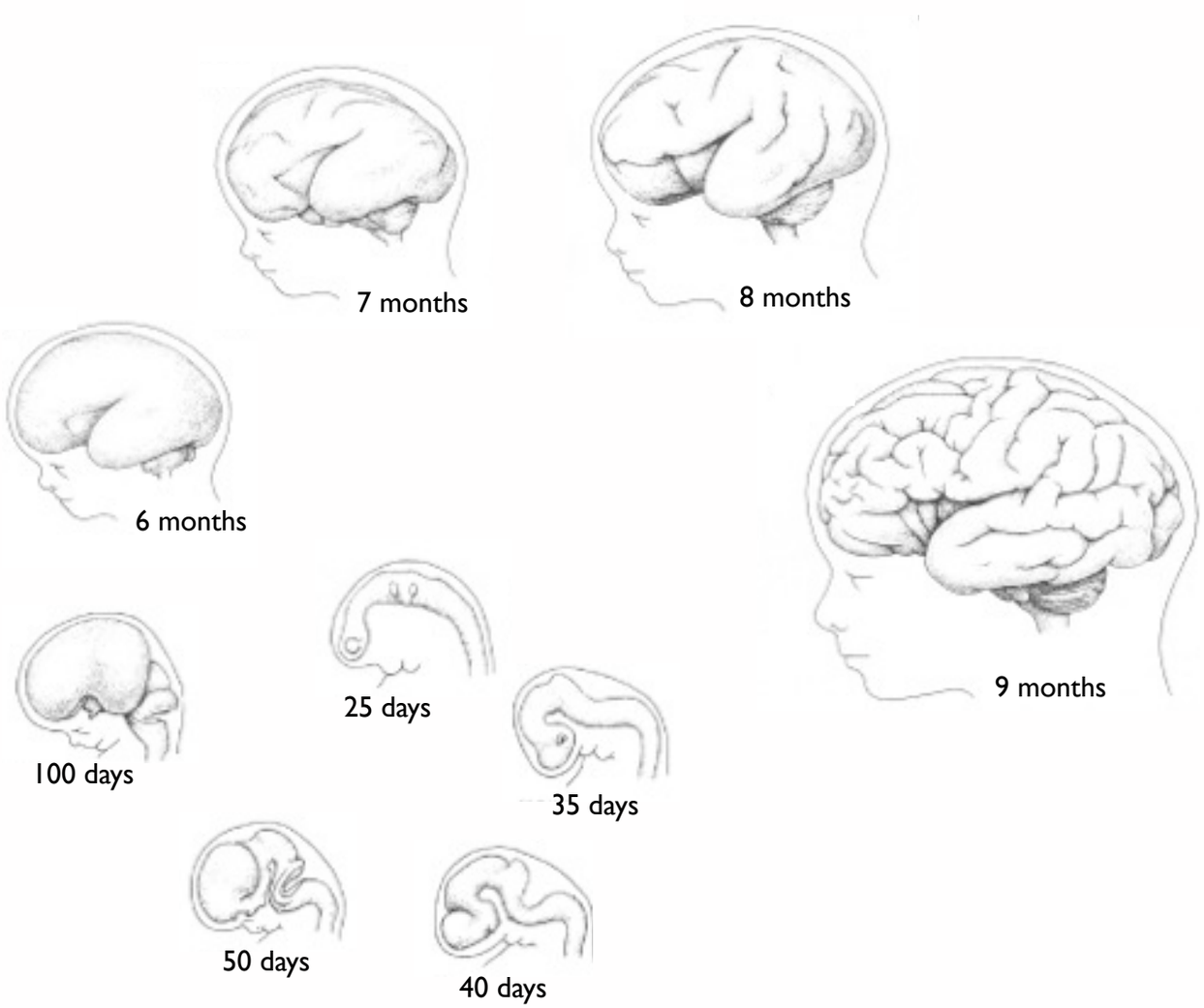
Schaer et al, IEE TMI 2008
http://surfer.nmr.mgh.harvard.edu/fswiki/LGI

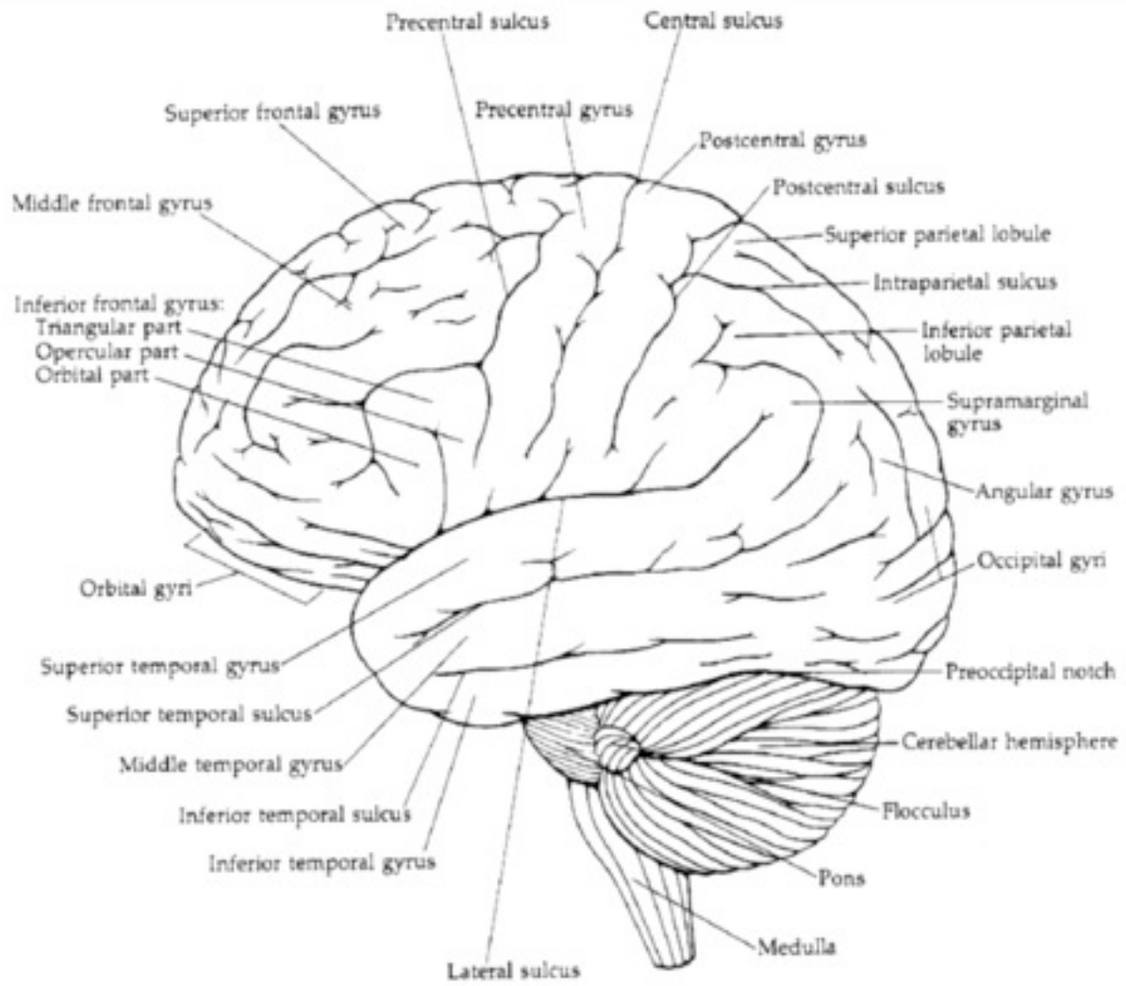


Cortical thickness,
an index of brain development

Fischl et al., PNAS 2009
http://surfer.nmr.mgh.harvard.edu/

Cortical folding (Gyrification)

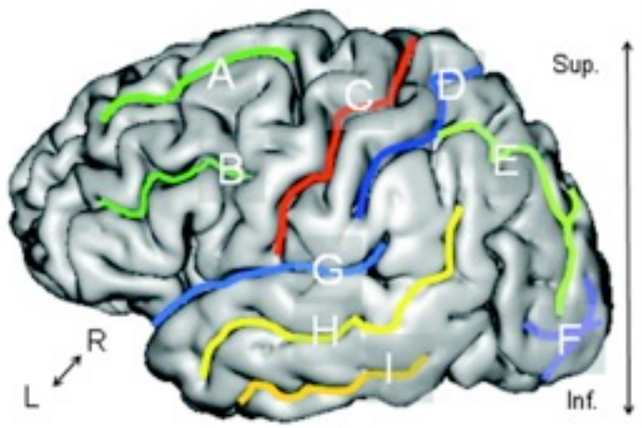




- Studying the patterns of cortical folding in grown-up children / adults reveal information on the early developmental processes

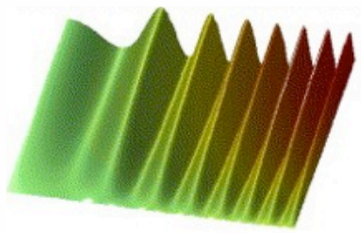
Measuring gyrification

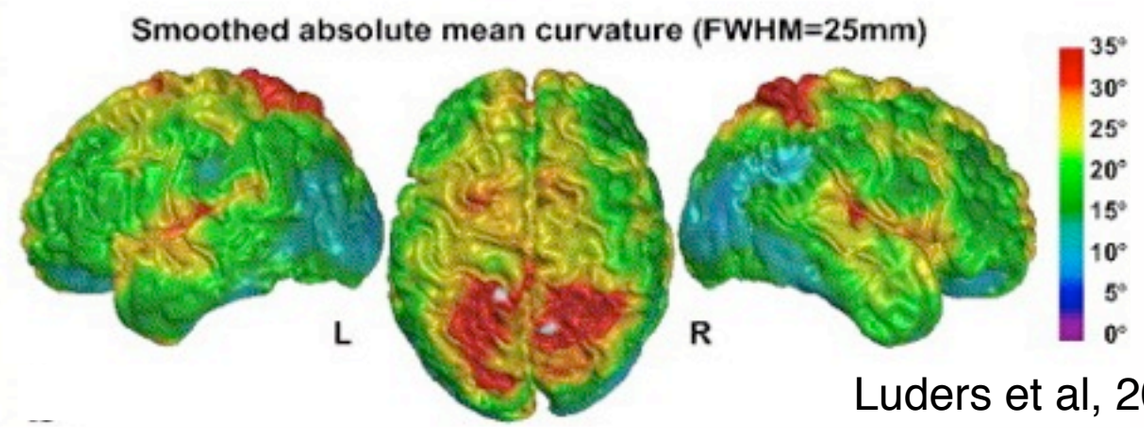
- Sulcal morphometry
  - ☑ *interpretability*
  - ☒ *one sulcus at a time*



Kochunov et al, 2005

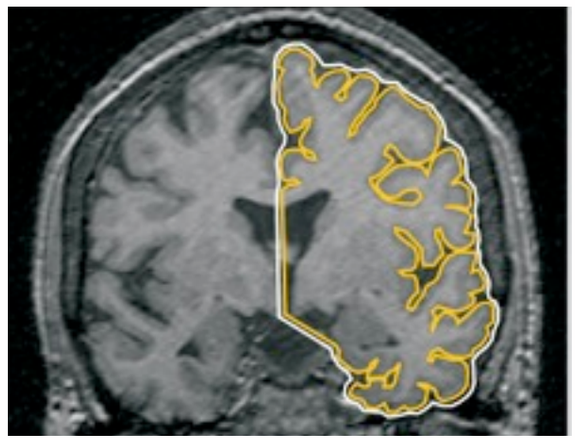
- Curvature-based
  - ☑ *resolution*
  - ☒ *interpretability*





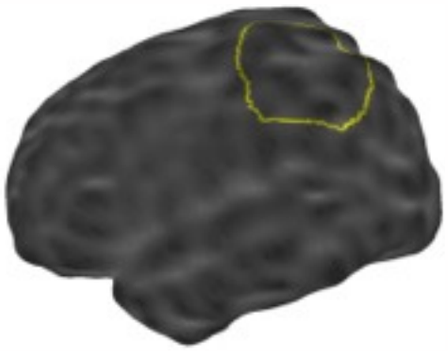
Luders et al, 2006

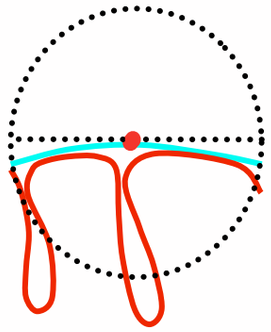
- Surface-based (Gyrification Index; Zilles et al, 1988)
  - ☑ *interpretability*
  - ☒ *resolution*

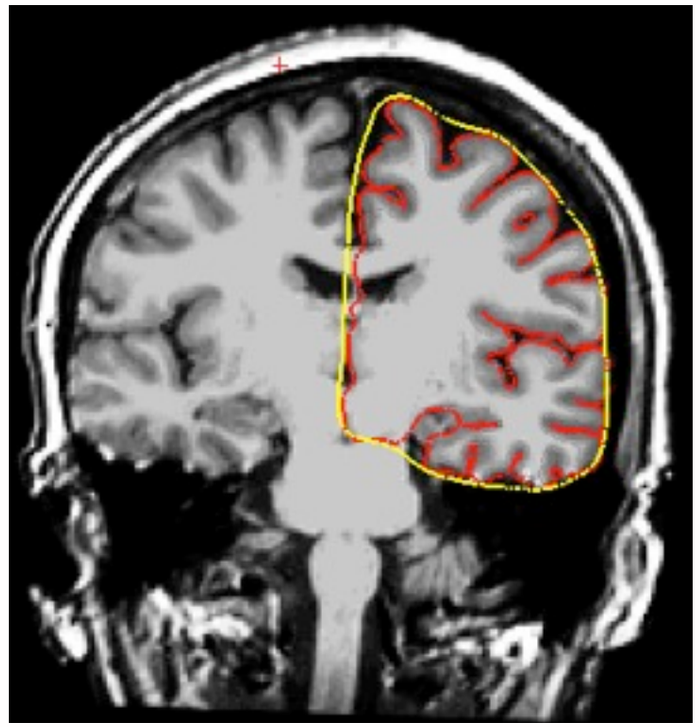


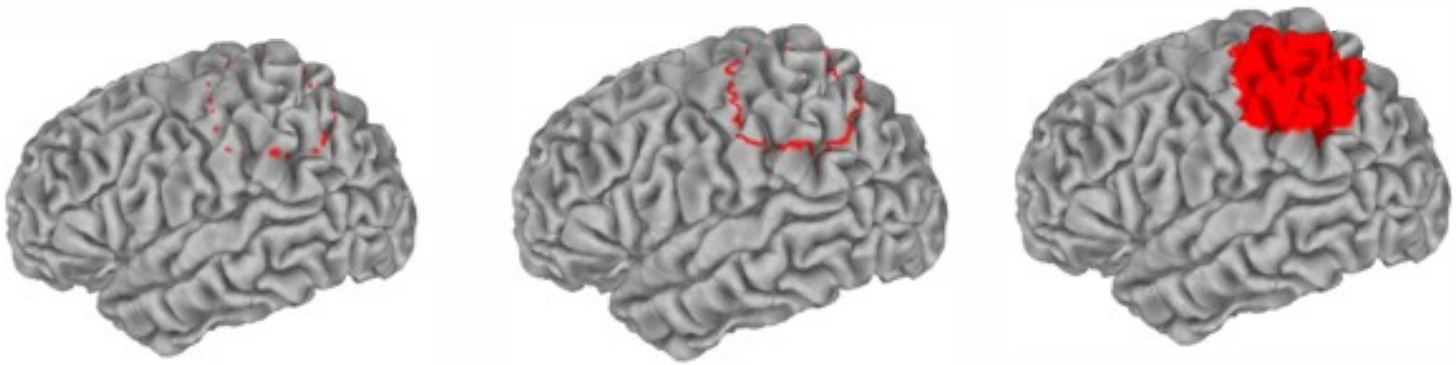
Sallet et al, 2003

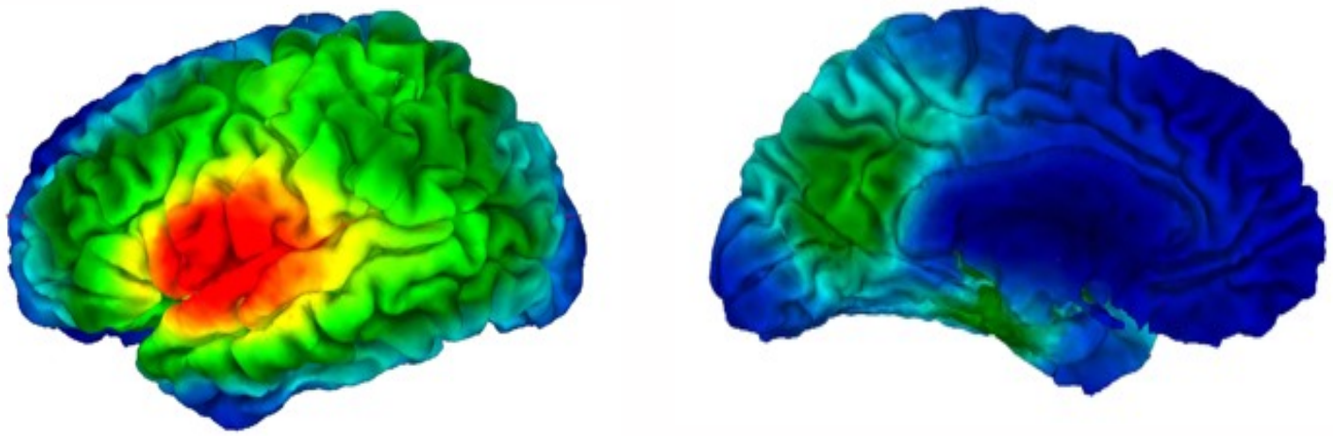
The local Gyrification Index











http://surfer.nmr.mgh.harvard.edu/fswiki/LGI

Schaer, Bach Cuadra, Tamarit, Lazeyras, Eliez, Thiran (2008) ***A surface-based approach to quantify local cortical gyrification***, IEEE Transactions on Medical Imaging 27(2):161-170

Altered gyrification pointing to early developmental disruption

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Congenital heart disease affects local gyrification in 22q11.2 deletion syndrome

MARIE SCHAER MD PHD[1,2] | BRONWYN GLASER MA[1] | MERITXELL BACH CUADRA PHD[2] | MARTIN DEBBANE PHD[1] | JEAN-PHILIPPE THIRAN PHD[2] | STEPHAN ELIEZ MD[1,3]

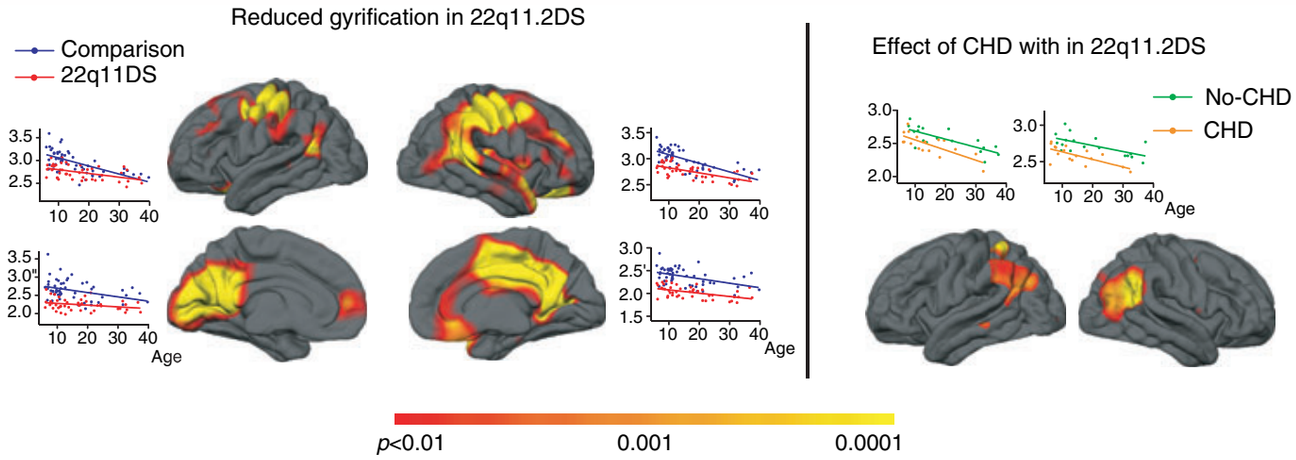


Figure 2: Statistical maps of the vertex-by-vertex local gyrification index (/GI) comparisons (colorbar shows *p* values). Left panel shows regions of decreased /GI in patients with 22q11.2DS compared with the comparison groups (FDR<0.01). No region of increased /GI was observed in 22q11.2DS compared with comparison groups. A detailed description of the clusters is provided in Table I. The right panel illustrates reduced /GI in the congential heart disease (CHD) compared to no-CHD subgroups (p<0.01). The cluster at the right parieto-temporo-occipital junction was more significant than the left one, and survived correction for multiple comparisons using FDR<0.05. No cluster of increased /GI value was observed in the subgroup with CHD compared with the subgroup without. Details of the mean /GI values per cluster are available in Table II. FDR, false discovery rate.

Psychological Medicine, Page 1 of 9. © Cambridge University Press 2011
doi:10.1017/S0033291711002315

ORIGINAL ARTICLE

Cortical folding in Broca's area relates to obstetric complications in schizophrenia patients and healthy controls

U. K. Haukvik[1,2*], M. Schaer[3], R. Nesvåg[1,2], T. McNeil[4,5], C. B. Hartberg[1,2], E. G. Jönsson[6], S. Eliez[3] and I. Agartz[1,6,7]

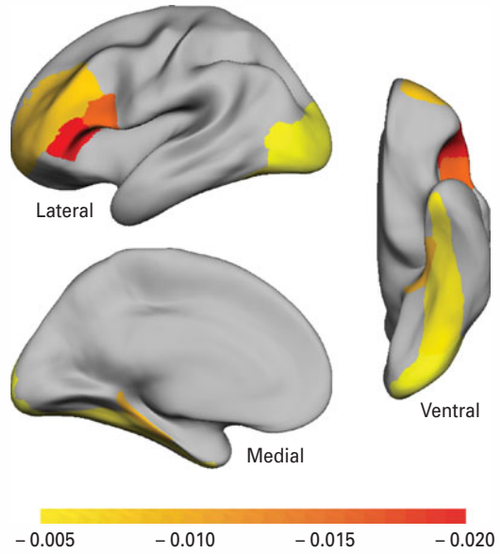
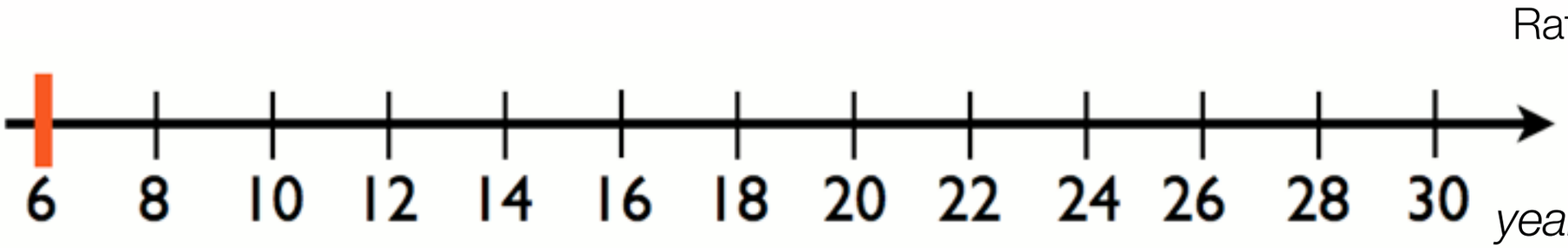
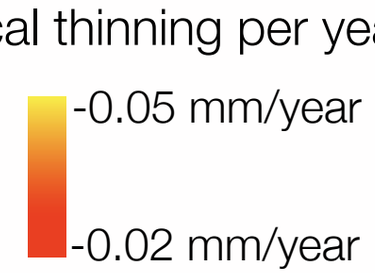


Fig. 1. The effect of increasing number of obstetric complications (OCs) on average local gyrification in pre-defined cortical areas in the left hemisphere significant at $p < 0.05$, from the linear regression model with age, diagnosis, gender and continuous OCs. The red area remains significant after Bonferroni correction for multiple tests. The colour map represents *B* values for OCs, with the corresponding *p* values listed in Supplementary Table S1.

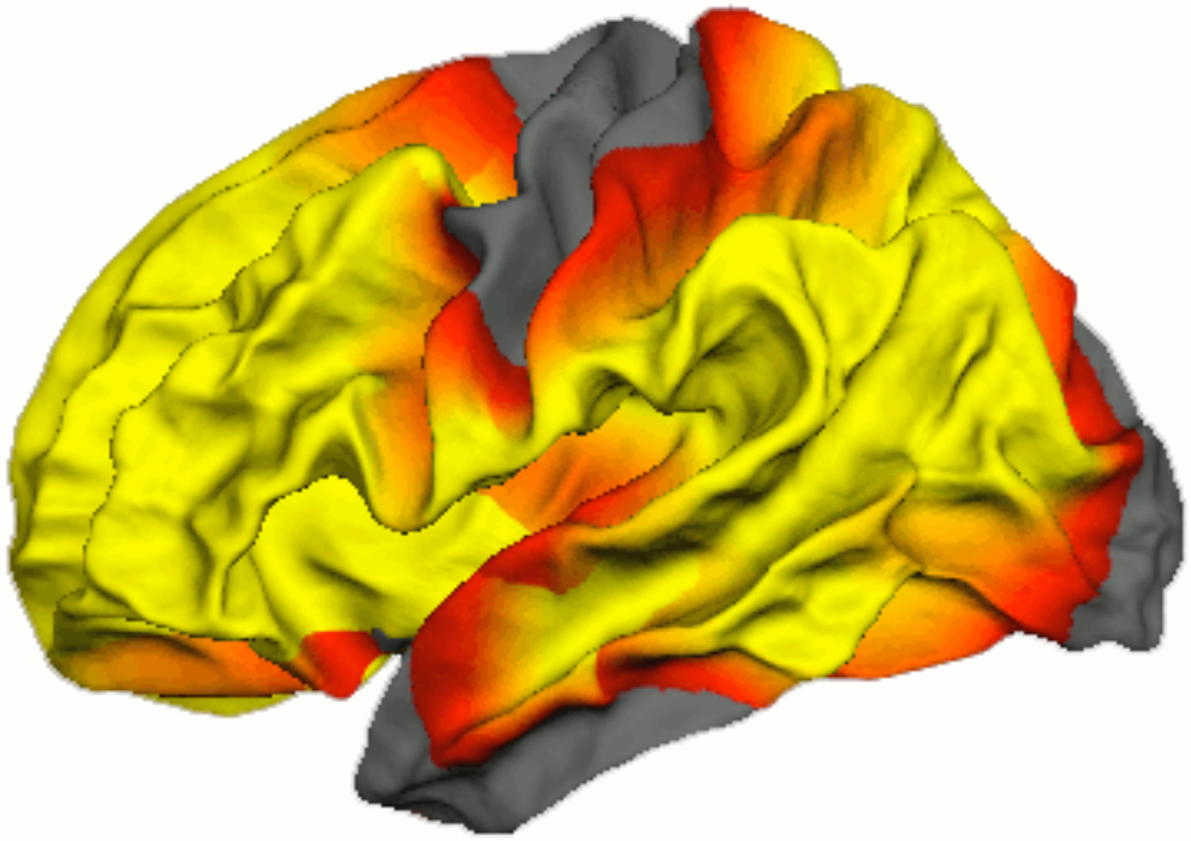
Cortical thickness in 22q11DS

Capturing movies of cortical thickness changes

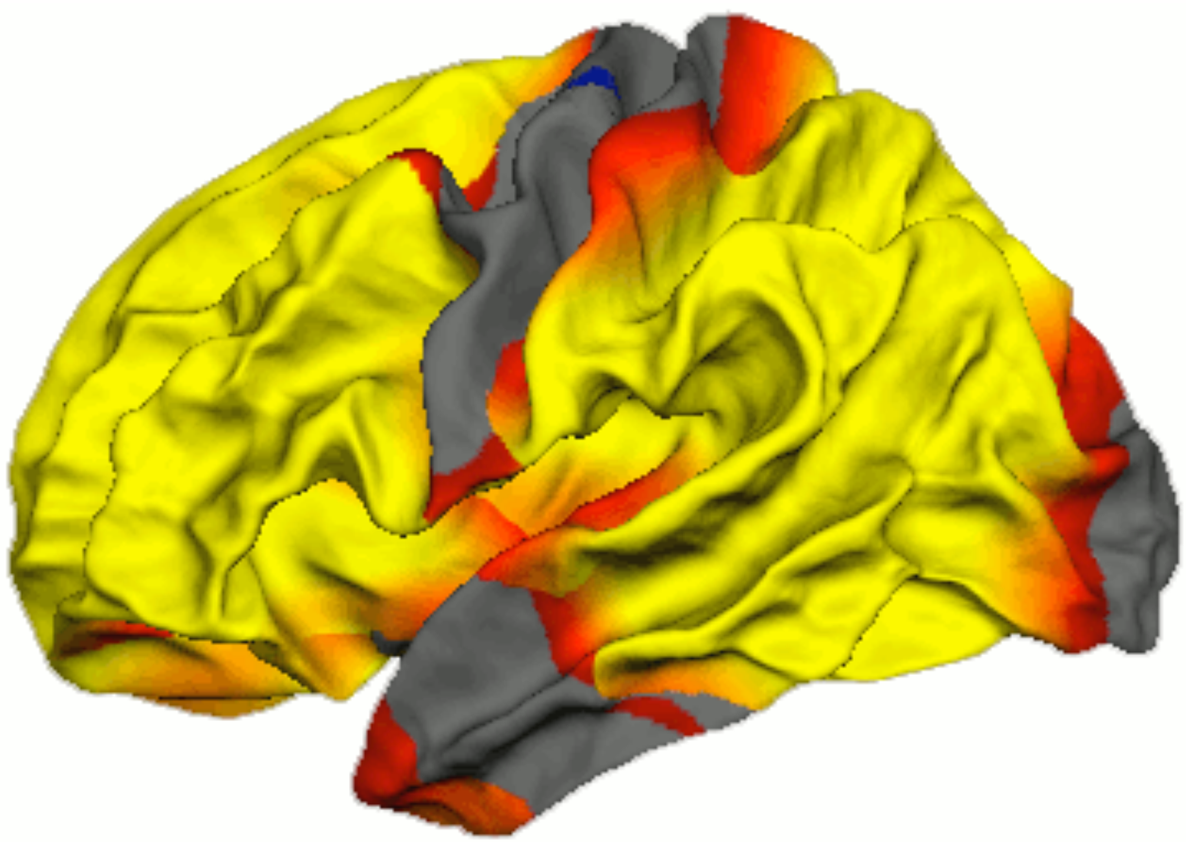




Controls



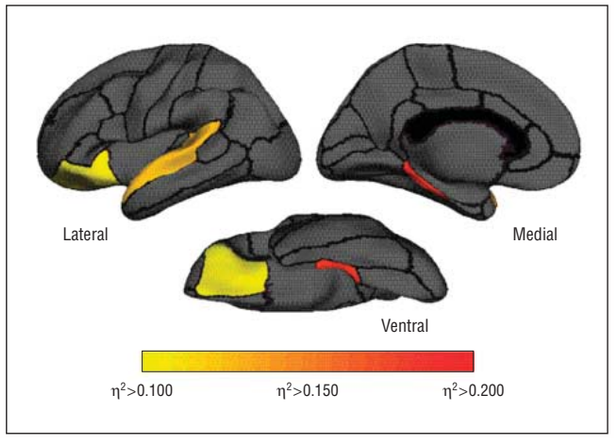
22q11DS



398 MR images: 209 from 137 typically developing individuals and 189 from 94 individuals affected with 22q11DS

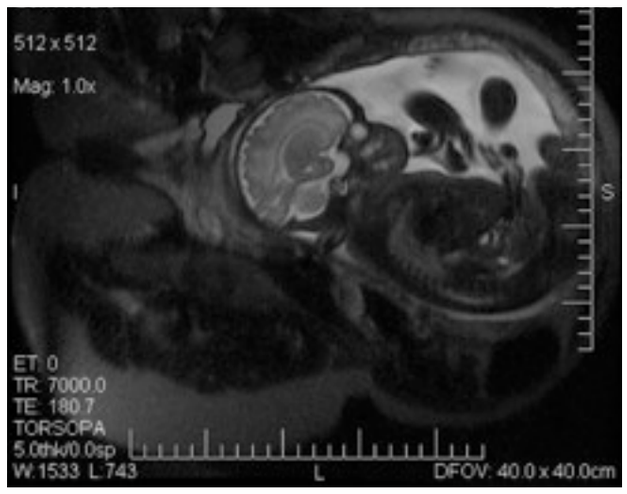
Side projects during my PhD

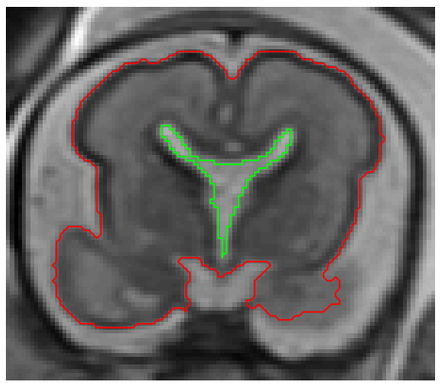
Other neurodevelopmental & neurodegenerative conditions



SH. Woodward, M. Schaer, DG Kaloupek, L. Cediel, S. Eliez (2009), ***Cerebral cortical volume is globally and regionally smaller in combat-related posttraumatic stress disorder***, Archives of General Psychiatry, 66(12):1373-82

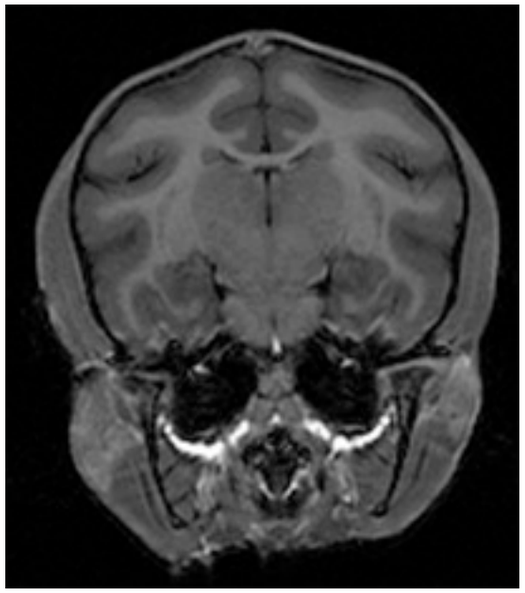
Fetal brain imaging

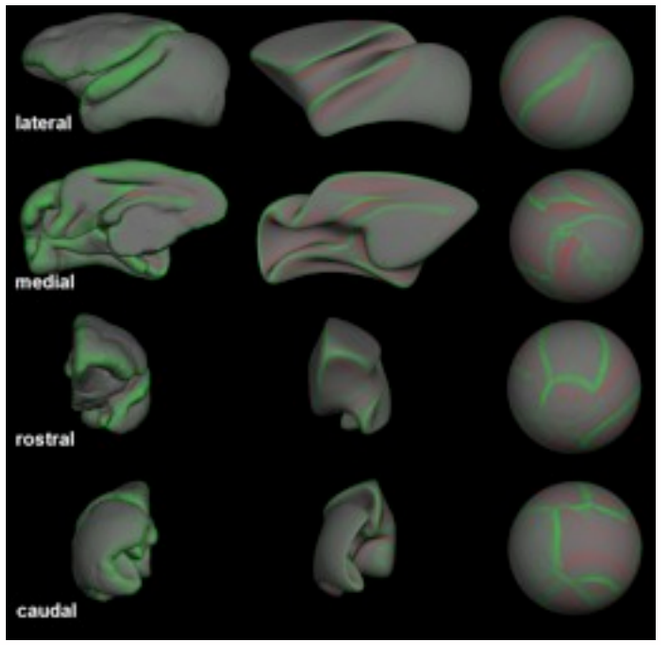




Ferrario, Bach Cuadra, Schaer, Houhou, Zosso, Eliez, Guibaud, Thiran (2008), ***Brain surface segmentation of magnetic resonance images of the fetus,*** EUSIPCO

Squirrel monkeys





Katz, Liu, Schaer, Parker, Epps, Ottet, Buckmaster, Bammer, Moseley, Schatzberg, Eliez, Lyons (2009) ***Prefrontal plasticity and stress inoculation-induced resilience***, Dev Neurosci, 31(4):293-9

Career Path

2005 **Medical Diploma**

PhD in neurosciences

2008 **MD-PhD**

Clinical training

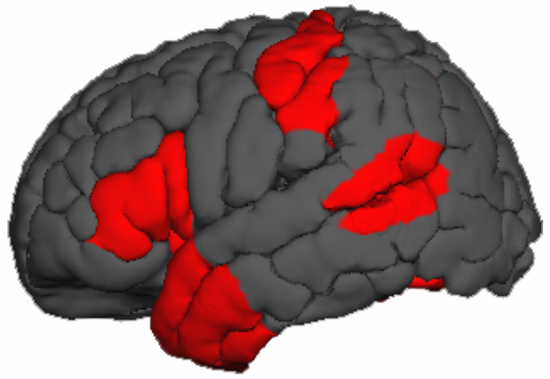
- Pre-requisites for the title of specialist in Child & Adolescent Psychiatry, including adult psychiatry and somatic medicine
- Critical to gain the required clinical experience to ask relevant research questions, and to get access to patients

2013 **Started clinical research projects as a main investigator**
Left abroad to gain experience (Stanford University & UC Davis)

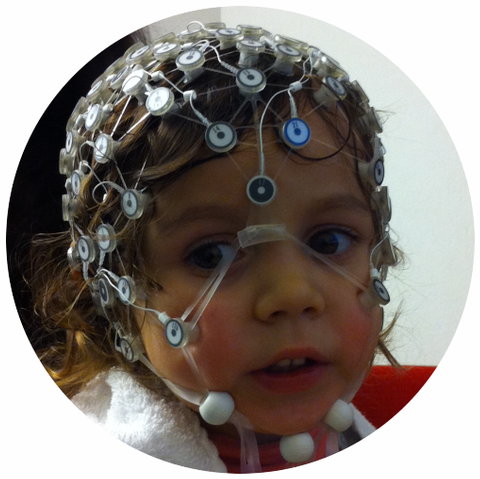
Combining research & clinical work

Starting as a main investigator, supported by the Swiss National Funds & the Fondation Pôle Autisme

- Validate biomarkers to aid early diagnosis of autism, to be able to intervene earlier



- Measure how early intensive intervention improves trajectories of development in preschool children with autism



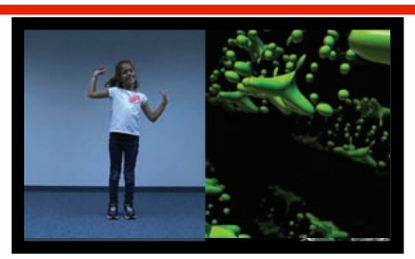
- Help defining subgroups of children with different responses to therapeutic interventions

synapsy
National Center of Competence in Research

A longitudinal research protocol

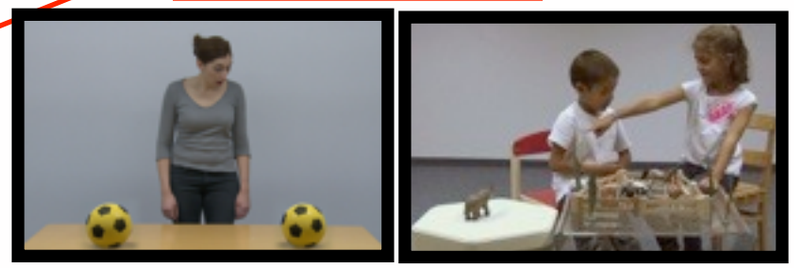
Standardized behavioral assessments and specifically-designed eye-tracking and EEG paradigms

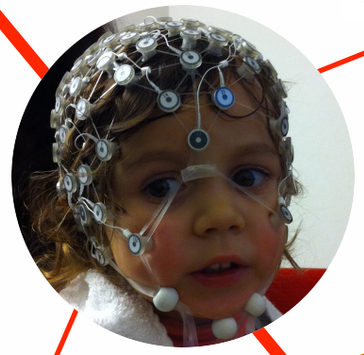
Social orienting



Neural bases of biological motion processing

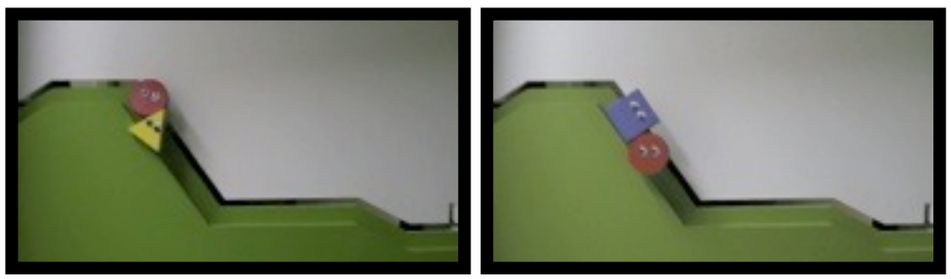
Joint attention





Understanding of goal-oriented actions and intentions

Development of moral judgment



Collaboration with K. Hamlin, University of British Columbia

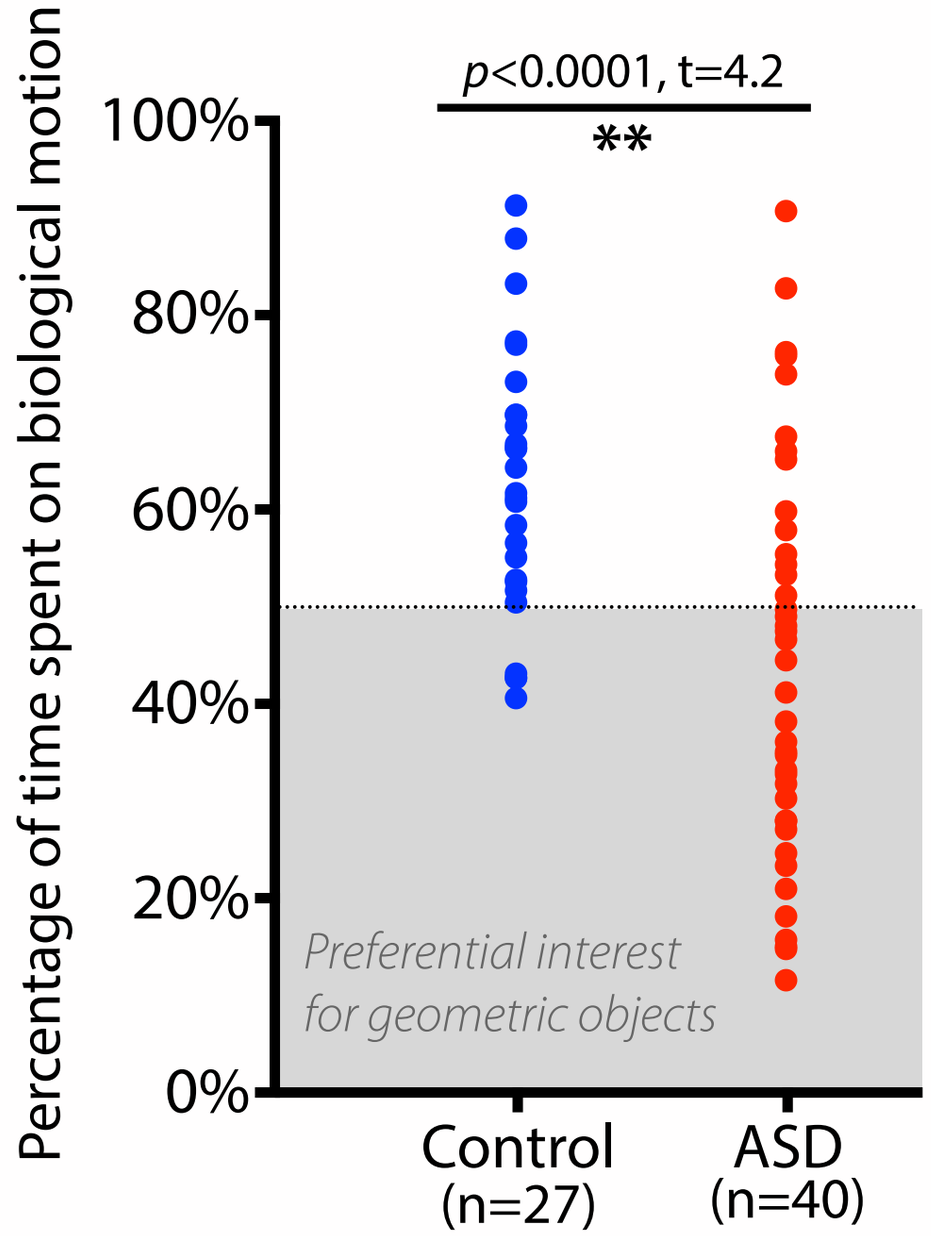
Representation of other's beliefs (theory of mind)

Progressive construction of interpersonal skills and empathy

Schaer, Franchini & Eliez, Swiss Archives of Neurology and Psychiatry 2014; 165(8):277-89

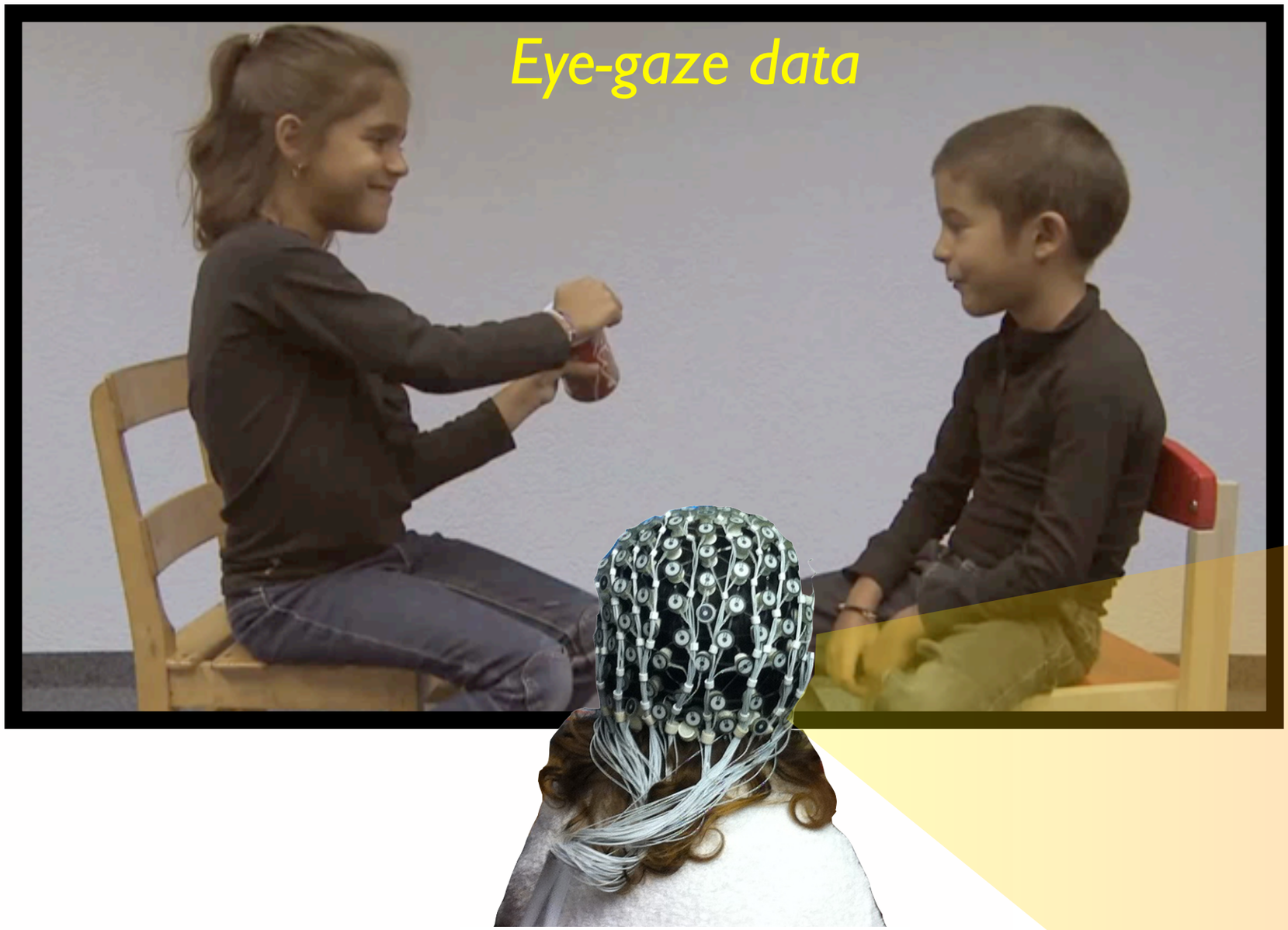
Measuring social orienting with eye-tracking

Measuring social orienting with eye-tracking



Franchini et al., in preparation

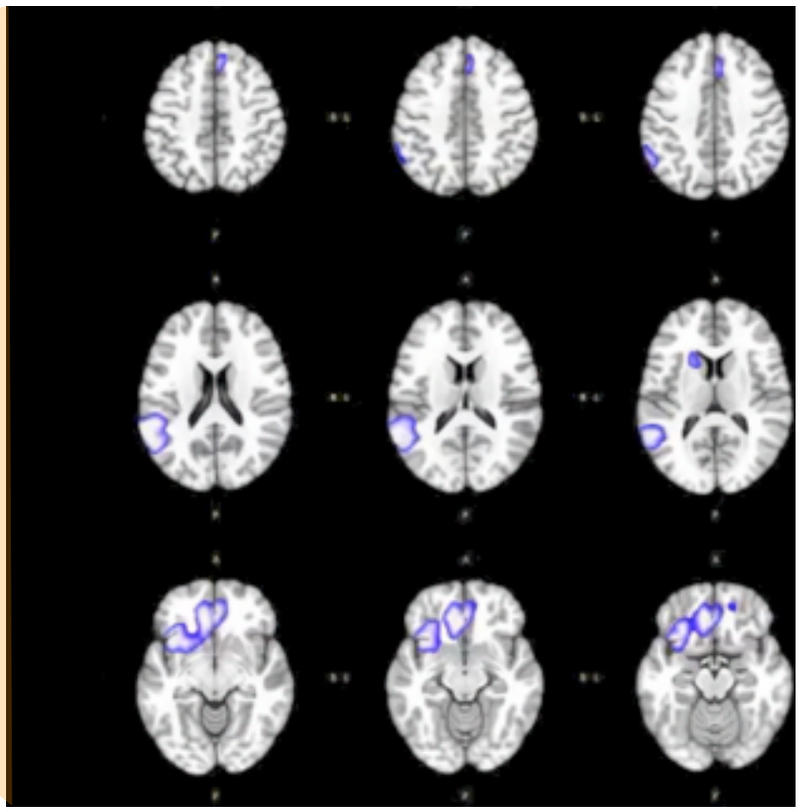
Combining EEG & eye-tracking to understand autism



EGI EEG system with 128 channels
synchronized at the ms with a Tobii TX300 system

Christoph Michel, Tonia Rihs, Reem Jan

Real-time source localization using high-resolution EEG

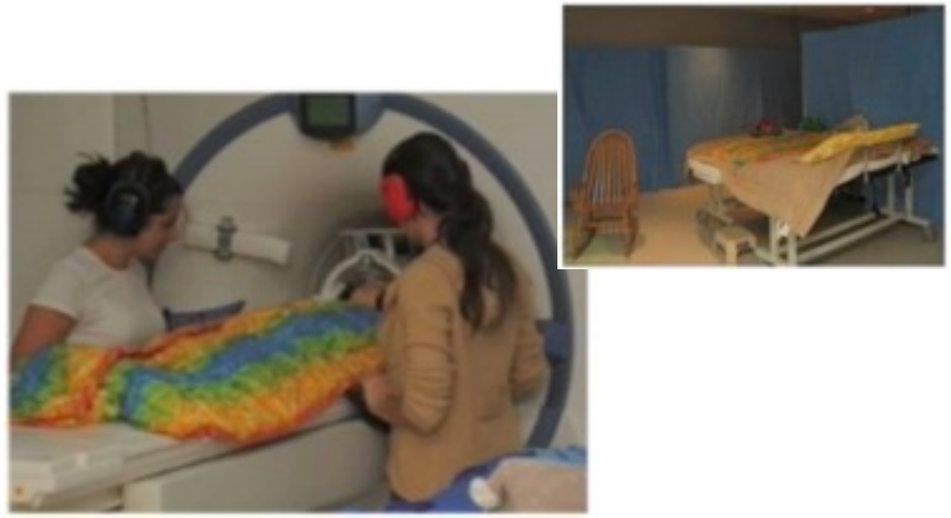


What's next?

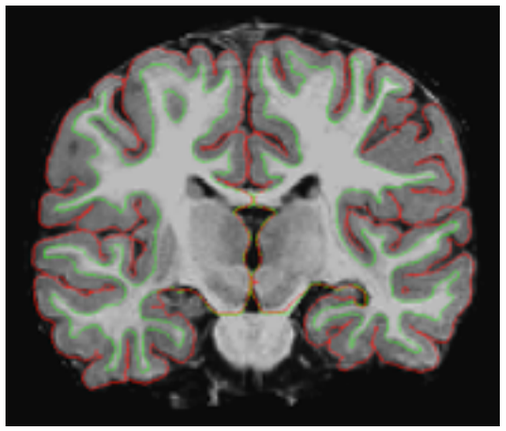
- Assess the feasibility of MRI in our cohort of children with ASD

- Use multimodal integration tolls, to delineate trajectories of brain systems involved with social processing

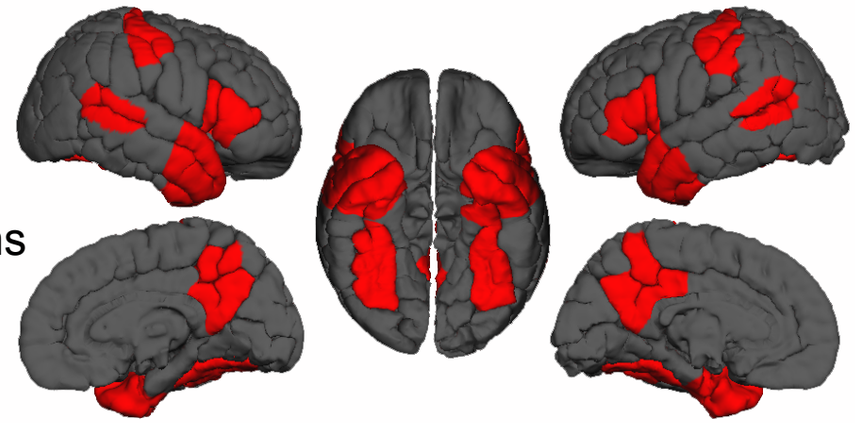
Child friendly scanning environment at the MIND Institute (UC Davis)



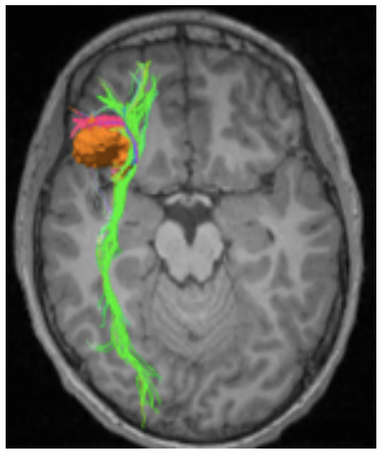
Collaboration with C. Nordahl, UC Davis

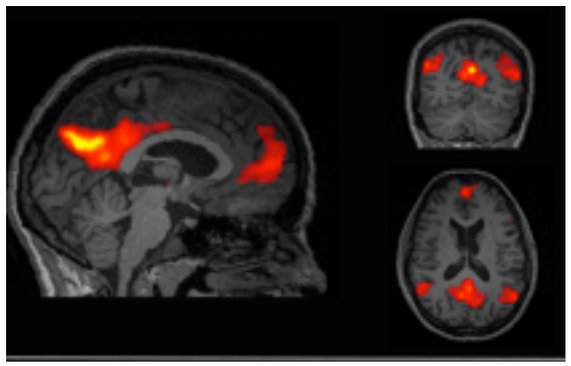


Example of cortical reconstructions in a 18 months old child



Morphometry of the social brain





Maturation of the DMN

A few suggestions

- For the PhD:
  - Carefully select your advisor, and a place where you can both acquire skills and be relatively independent
  - Remember that the PhD is a uniquely protected period to be academically productive

- During your clinical years:
  - Try not to loose contact with research

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