Radboud University Nijmegen

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MIRA

Donders Institute for Brain, Cognition and Behaviour

FMRIB
Oxford Centre for Functional MRI of the Brain

The brain at 'rest': investigating spontaneous activity in BOLD fMRI using Independent Component Analysis

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SPM 2011 — 14. Kurs zur funktionellen Bildgebung

The 'resting' condition

"The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is far from restful"

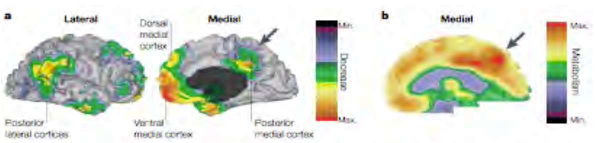
Seneca the younger, ~65A.D.

- *Poorly characterised experimental condition:*

"a behavioural condition characterised by quiet repose usually with eyes closed but occasionally, in the experimental setting, with eyes open with or without visual fixation."

Raichle, M, Trends Cogn Sci 2010

'Default Mode' of Brain Activity



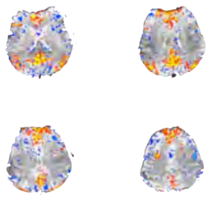
- Meta-analysis of 9 functional PET studies (N=132): consistent decreases during performance of attention demanding cognitive tasks
- Glucose metabolism in N=22 subjects under rest measured using FDG-PET

Shulman et al., J Cog Neurosci 1997 *Gusnard et al., NRN 2001* *Raichle et al., PNAS 2001*

Brain connectivity

Functional Connectivity
- temporal correlations between spatially remote neurophysiological events

Resting-State Networks
- *Multiple spatial patterns of correlated temporal dynamics*, resembling activation map



RSN analysis

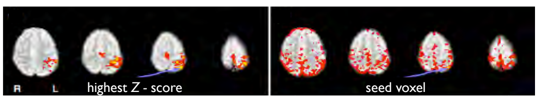
Need to estimate whole-brain temporal correlations...

Two popular approaches for RSN analysis:

•Seed-based correlation (Biswal, Raichle/Fox)

•ICA-based analysis (Kiviniemi, Beckmann, Calhoun)

Seed-based analysis



Activation maps from a finger tapping experiment

Correlation maps from a resting state experiment

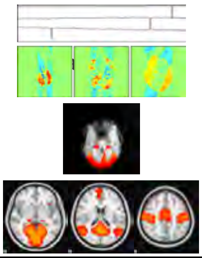
- Biswal (1995) first studied resting correlations through reference time course:

Functional Connectivity maps

Biswal et al. (1995) MRM

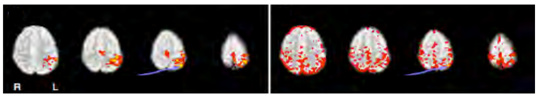
ICA

- Data-driven multivariate analysis.
- Good for finding:
  - Scanner and physiological
  - Activation with unknown characteristics
  - Resting state networks



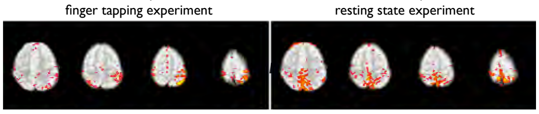
RSN analysis

- Biswal (1995) first studied resting correlations through reference time course



Activation maps from a finger tapping experiment

Correlation maps from a resting state experiment

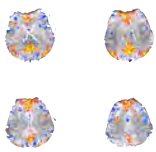


Spatial maps from an ICA decomposition

"Resting-State" Networks

Multiple spatial patterns of correlated temporal dynamics, resembling activation maps

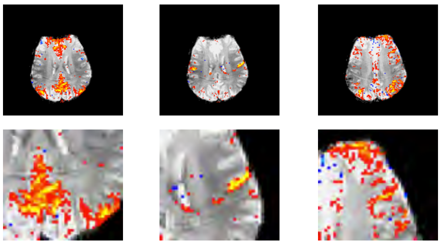
- can be found in FMRI data (BOLD & ASL) obtained at rest *and* in activation data
- characterised by (apparent) low frequency power spectra...
- seen when awake/sleep/anaesthesia, human/animals



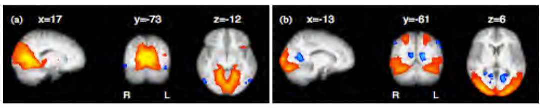
Also referred to as: "low-frequency correlations", "default activity", "default mode", "spontaneous network correlations", "intrinsic connectivity networks" ...

Spatial characteristics

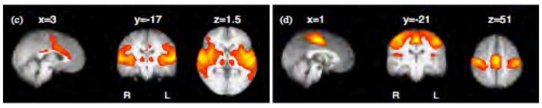
- RSNs are grey-matter networks



Spatial characteristics

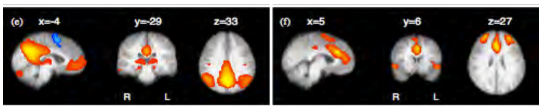


Medial visual cortex | Lateral Visual Cortex

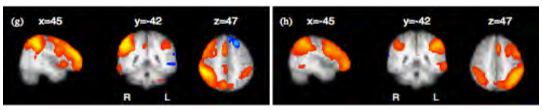


Auditory system | Sensori-motor system

Spatial characteristics



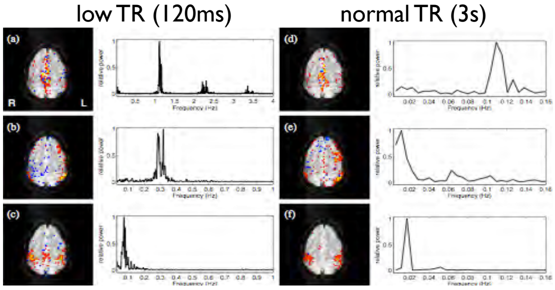
'default mode network' | Executive control



fronto-parietal

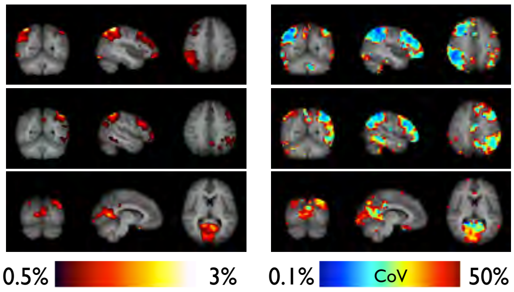
RSNs vs cardiac and respiraton

low TR (120ms) normal TR (3s)



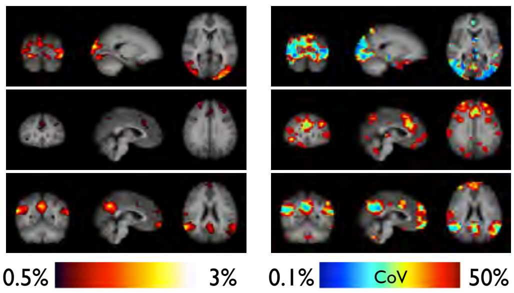
ICA separates RSNs from non-neural physiological and scanner artefacts (also see Birn, Human Brain Mapping, 2007)

RSN consistency



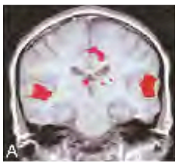
Damoiseaux et al., PNAS 2006

RSN consistency

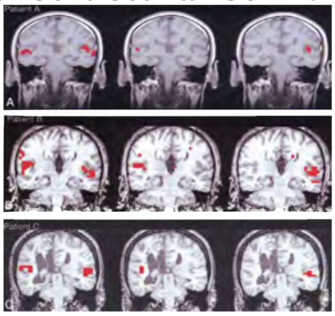


Damoiseaux et al., PNAS 2006

functional & structural conn.



control

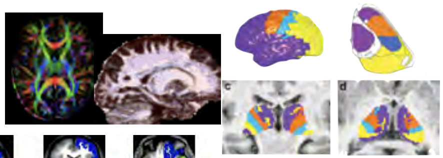


task seed R seed L

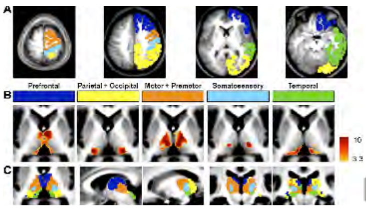
- absent contra-lateral connectivity in agenesis of CC

Quigley et al., Am J Neuroradiol, 2003

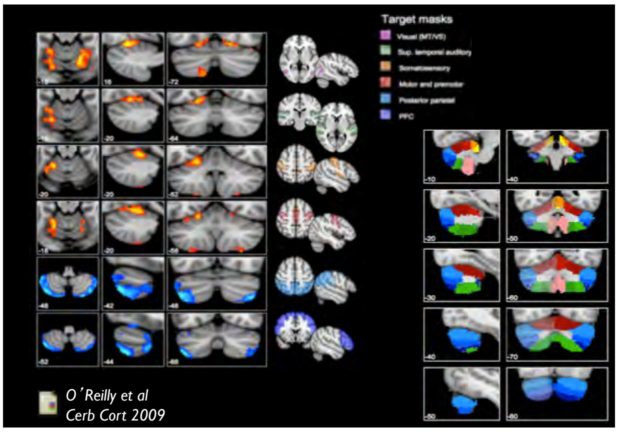
Parcellation of Thalamus



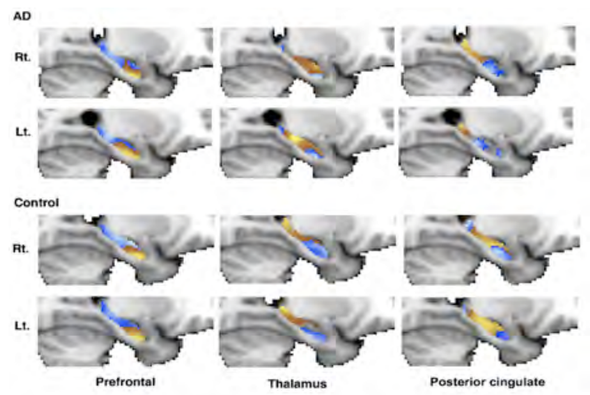
Behrens et al. Nat Neurosci 2003



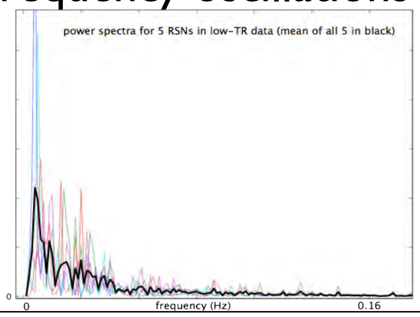
Zhang et al. J Neurophysiol 2008



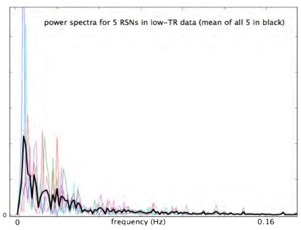
O'Reilly et al Cerb Cort 2009

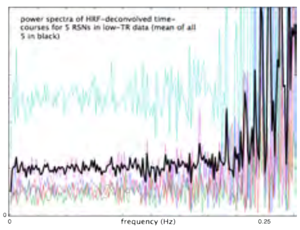


RSNs are 'low-frequency oscillations'?



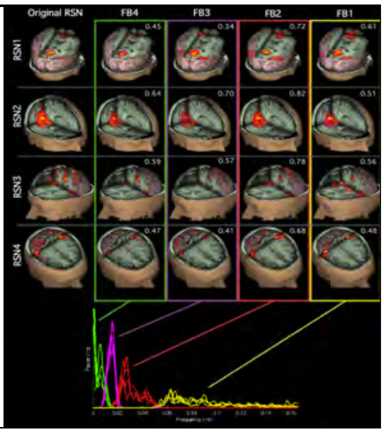
Temporal characteristics

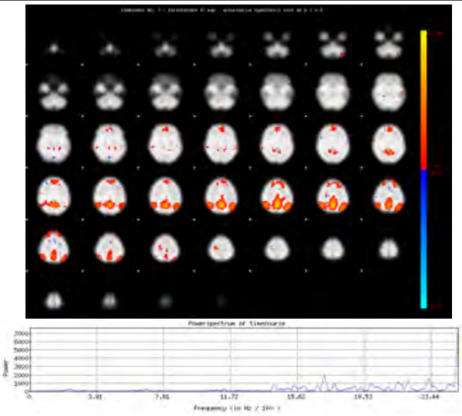




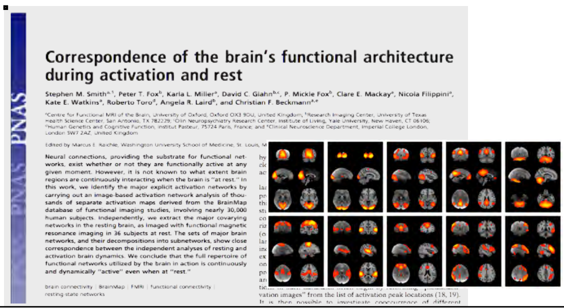
- Resting-state Networks are broadband processes!
- no 1/f characteristics!

Niazy, R et al. (2010)





The *functional* architecture of the human brain



Correspondence of the brain's functional architecture during activation and rest

Stephen M. Smith, Peter T. Fox, Karla L. Miller, David C. Glahn, P. Mickle Fox, Clare E. Mackay, Nicola Filippini, Kate E. Watkins, Roberto Toro, Angela R. Laird, and Christian F. Beckmann

The *functional* architecture of the human brain:

Correspondence between resting FMRI and task-activation studies

BrainMap, RIC, San Antonio

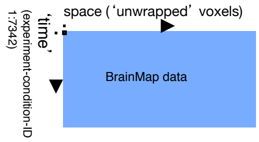
Data
- 1687 FMRI / PET activation studies (19% of all published activation imaging studies)
- 7342 separate activation conditions/contrasts
- 29,671 human subjects
- 66 "Behavioural domains" (gross paradigm classifications)

Resting FMRI data

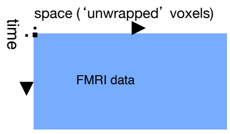
Data
- 36 healthy subjects, age 20-35
- Subjects at rest, eyes open, fairly dark scanner room
- 6 minutes FMRI, standard BOLD, 3x3x3.5mm

Data & Methods

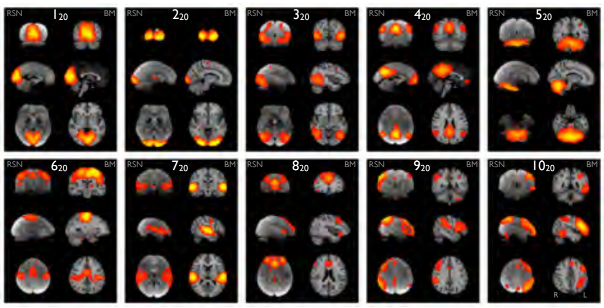
BrainMap, RIC, San Antonio



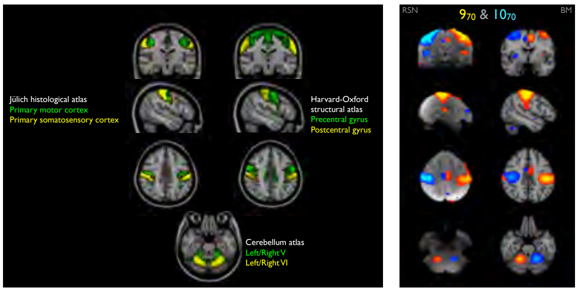
Resting FMRI data



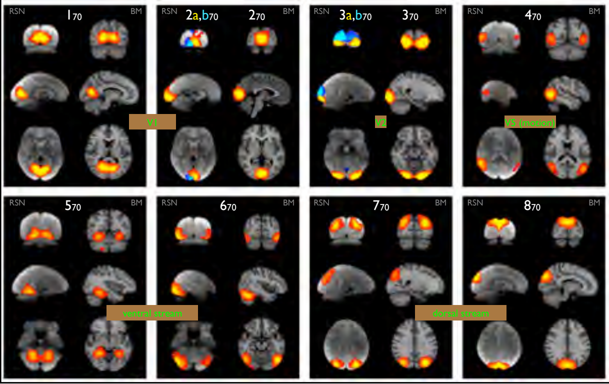
Pairings between RSN maps (left of each pair) and BrainMap maps (right) at ICA dimensionality of 20



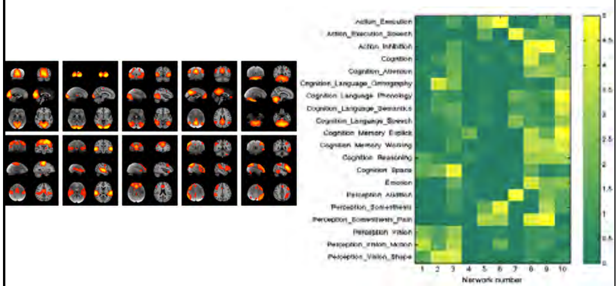
Pairings between RSN maps (left of each pair) and BrainMap maps (right) in the sensori-motor cortex, at ICA dimensionality of 70



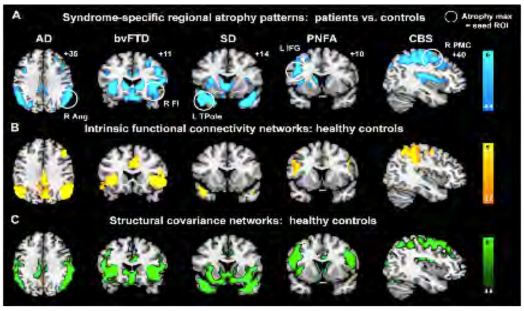
Pairings between RSN maps (left of each pair) and BrainMap maps (right) in visual areas, at ICA dimensionality of 70



Mapping the 10 paired maps back onto BrainMap "Behavioural Domains"



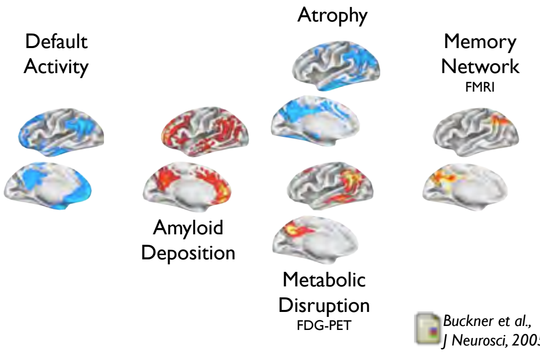
RSNs & neuro-degeneration



Neurodegenerative diseases target large-scale human brain networks

Seeley et al. (2009) Neuron

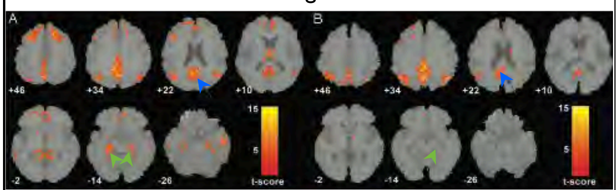
DMN in AD



Buckner et al., J Neurosci, 2005

DMN in healthy aging vs AD

Resting FMRI

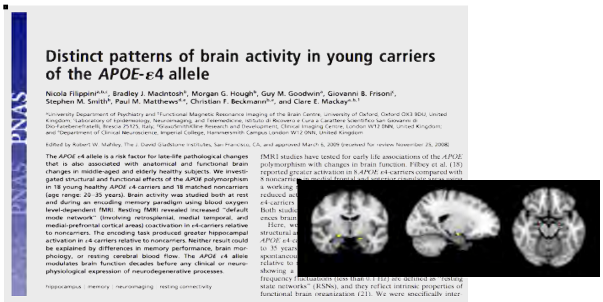


Controls

AD (CDR: 0.5-1)

Greicius et al., PNAS, 2004

Altered functional connectivity in young, healthy carriers of APOE-ε4


PNAS

Distinct patterns of brain activity in young carriers of the *APOE*-ε4 allele

Nicola Filippini[a,b,c], Bradley J. MacIntosh[b], Morgan G. Hough[b], Guy M. Goodwin[a], Giovanni B. Frisoni[c], Stephen M. Smith[b], Paul M. Matthews[d,e], Christian F. Beckmann[b,e], and Clare E. Mackay[a,b,1]

[a]University Department of Psychiatry and [b]Functional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, Oxford OX3 9DU, United Kingdom; [c]Laboratory of Epidemiology, Neuroimaging, and Telemedicine, Istituto di Ricovero e Cura a Carattere Scientifico San Giovanni di Dio-Fatebenefratelli, Brescia 25125, Italy; [d]GlaxoSmithKline Research and Development, Clinical Imaging Centre, London W12 0NN, United Kingdom; and [e]Department of Clinical Neuroscience, Imperial College, Hammersmith Campus London W12 0NN, United Kingdom

Edited by Robert W. Mahley, The J. David Gladstone Institutes, San Francisco, CA, and approved March 6, 2009 (received for review November 25, 2008)

The *APOE* ε4 allele is a risk factor for late-life pathological changes that is also associated with anatomical and functional brain changes in middle-aged and elderly healthy subjects. We investigated structural and functional effects of the *APOE* polymorphism in 18 young healthy *APOE* ε4-carriers and 18 matched noncarriers (age range: 20–35 years). Brain activity was studied both at rest and during an encoding memory paradigm using blood oxygen level-dependent fMRI. Resting fMRI revealed increased "default mode network" (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) coactivation in ε4-carriers relative to noncarriers. The encoding task produced greater hippocampal activation in ε4-carriers relative to noncarriers. Neither result could be explained by differences in memory performance, brain morphology, or resting cerebral blood flow. The *APOE* ε4 allele modulates brain function decades before any clinical or neurophysiological expression of neurodegenerative processes.

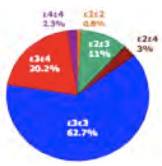
hippocampus | memory | neuroimaging | resting connectivity

fMRI studies have tested for early life associations of the *APOE* polymorphism with changes in brain function. Filbey et al. (18) reported greater activation in 8 *APOE* ε4-carriers compared with 8 noncarriers ...

... frequency fluctuations (less than 0.1 Hz) are defined as "resting state networks" (RSNs), and they reflect intrinsic properties of functional brain organization (21). We were specifically inter-

apolipoprotein E - *APOE*

- lipid transport protein coded on chromosome 19
- ε 4 allele first studied as risk factor for cardiovascular disease
- ε 4 Identified as risk for AD in 1993
  - Increased prevalence
  - decreased age of onset
  - gene dose effect



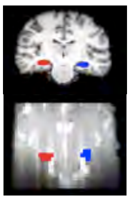
Menzel et al., 1983

What is NOT different

Structure - Whole brain GM, WM and hippocampal ROIs & VBM not different

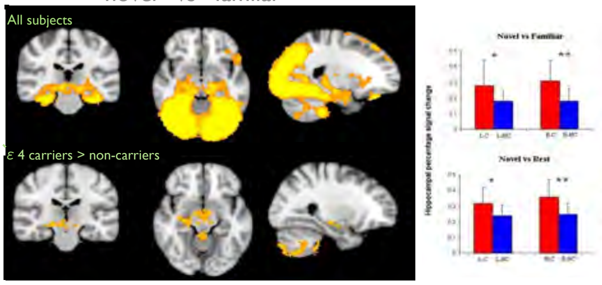
Cerebral blood flow - ASL in hippocampal and lobe ROIs and whole brain not different

Memory performance and reaction time not different

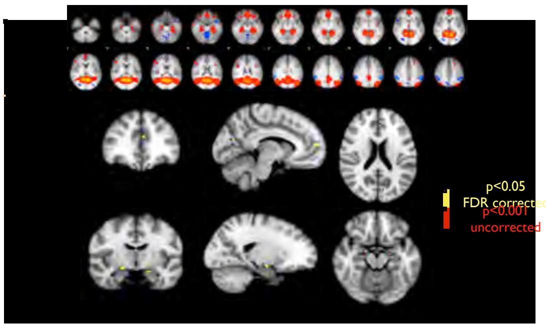


fMRI memory encoding

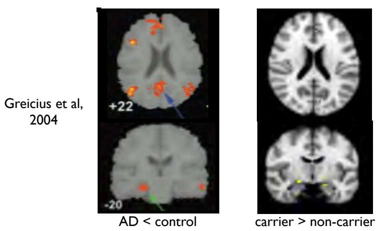
'novel' vs 'famliar'



Resting data - DMN



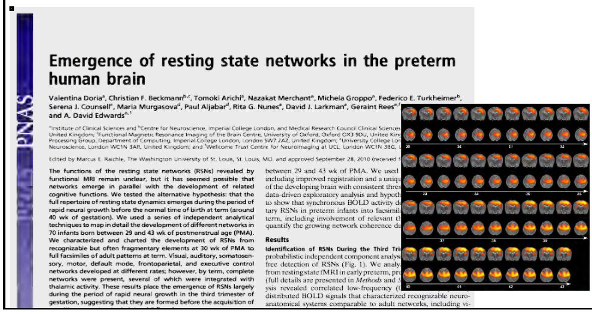
Tentative interpretation



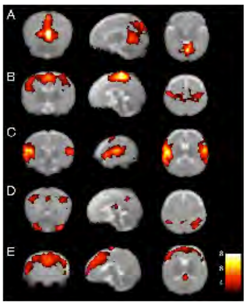
- Could AD be caused by overactivity of the hippocampus leading to premature 'wearing out'?

Filippini et al., PNAS '09

Development of RSNs during gestation



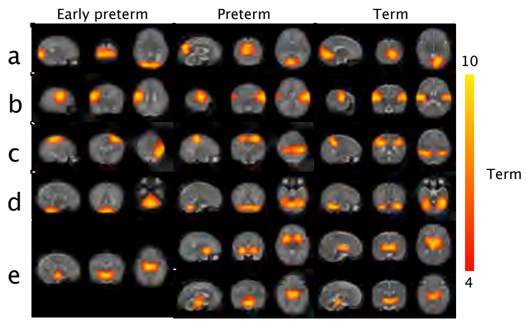
RSNs & early development

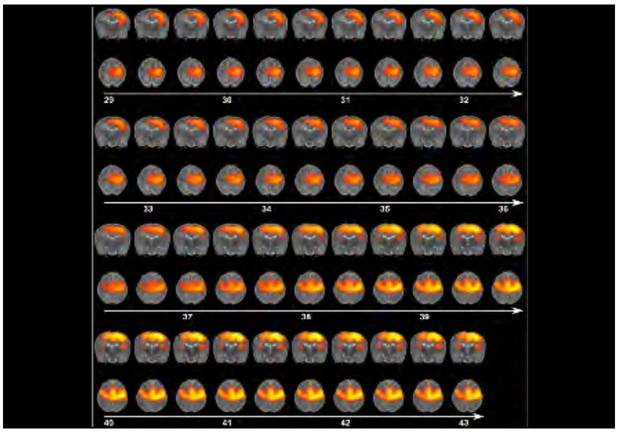


- some RSNs present in infants
- DMN (introspection / self-referencing...) missing

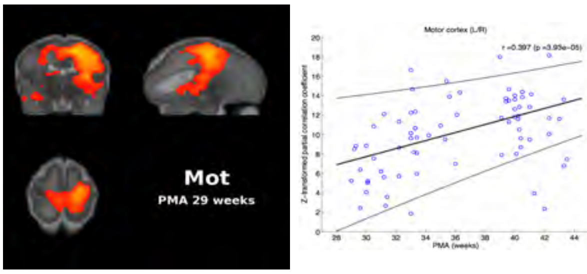
Fransson et al. PNAS 2007

RSNs in infants



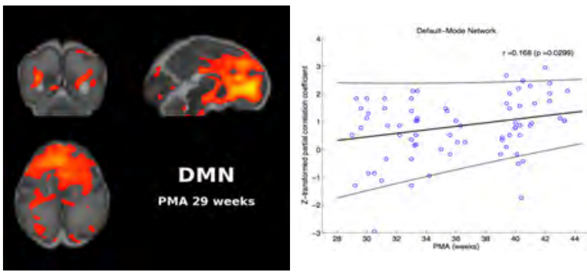


Dynamics of RSNs



Doria,V. et al, PNAS 2010

Dynamics of RSNs



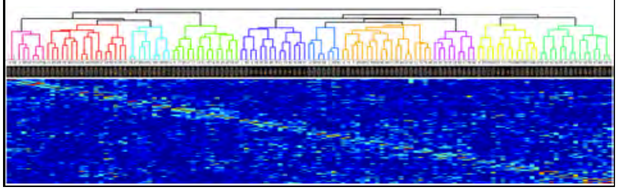
Doria,V. et al, PNAS 2010

Hierarchy of patterns

- RSNs typically characterised by 2-10 components/clusters/networks
- relatively low-dimensional 'splitting' of the data
- consider more detailed hierarchy of functional connectivity by increasing ICA model order

Resting-FMRI Network

- 36-subjects' matrices (ICOV: direct functional connections)
- One-group t-test to give population-significant network matrix
- Will threshold at $p<0.05$ (corrected for all possible connections)
- Feed into hierarchical clustering to reorder matrix and find (e.g) 10 functional sub-networks



"One man's noise is another man's signal"

- Resting-state FMRI promising technique, particularly in the clinical domain:
- does not require task compliance
- does not only probe specific cognitive functions but simultaneously investigates major *functional networks* which link to behaviour

Acknowledgements

- Steve Smith, Clare Mackay, Nicola Filippini, Mark Woolrich, Tim Behrens, Heidi Johansen-Berg (FMRIB Oxford)
- David Cole, Tomoki Arichi, David Edwards, Valentina Doria (Imperial College London)
- Serge Rombouts(LUMC Leiden)
- Rami Niazy (Rijad)
- Peter Fox, Angie Laird (RIC San Antonio)