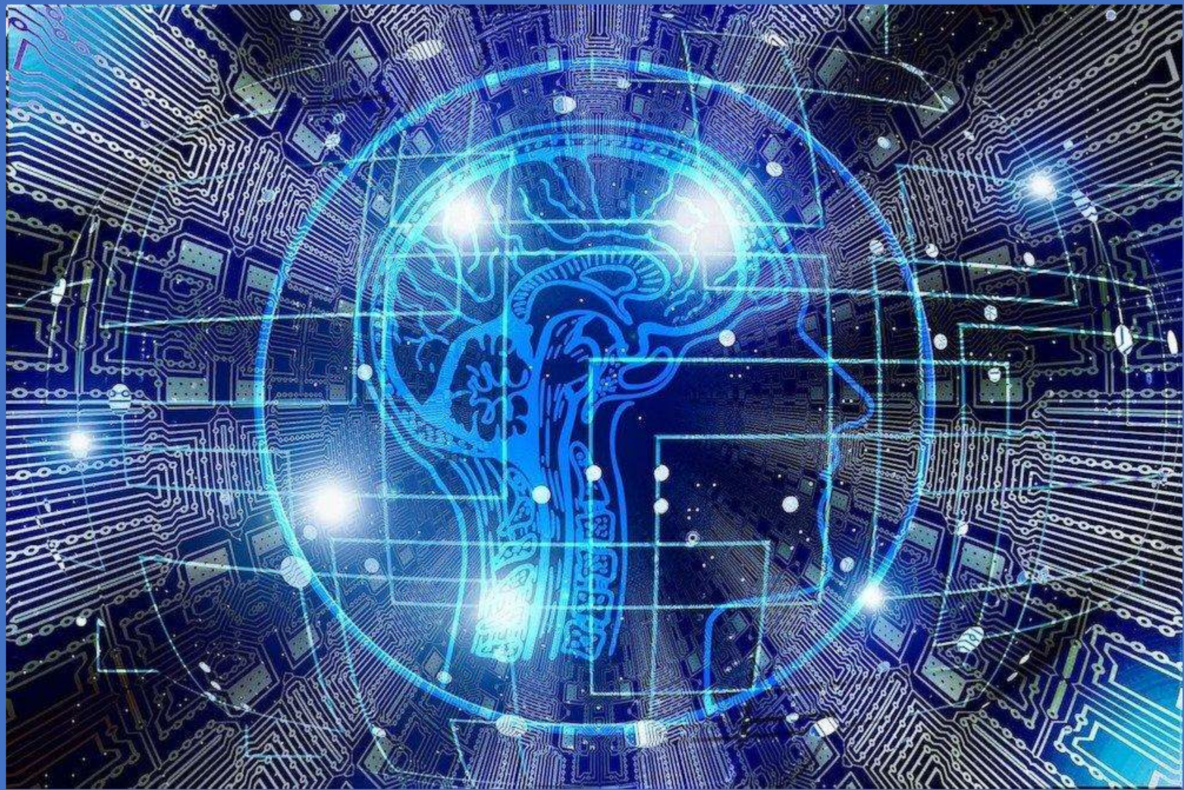
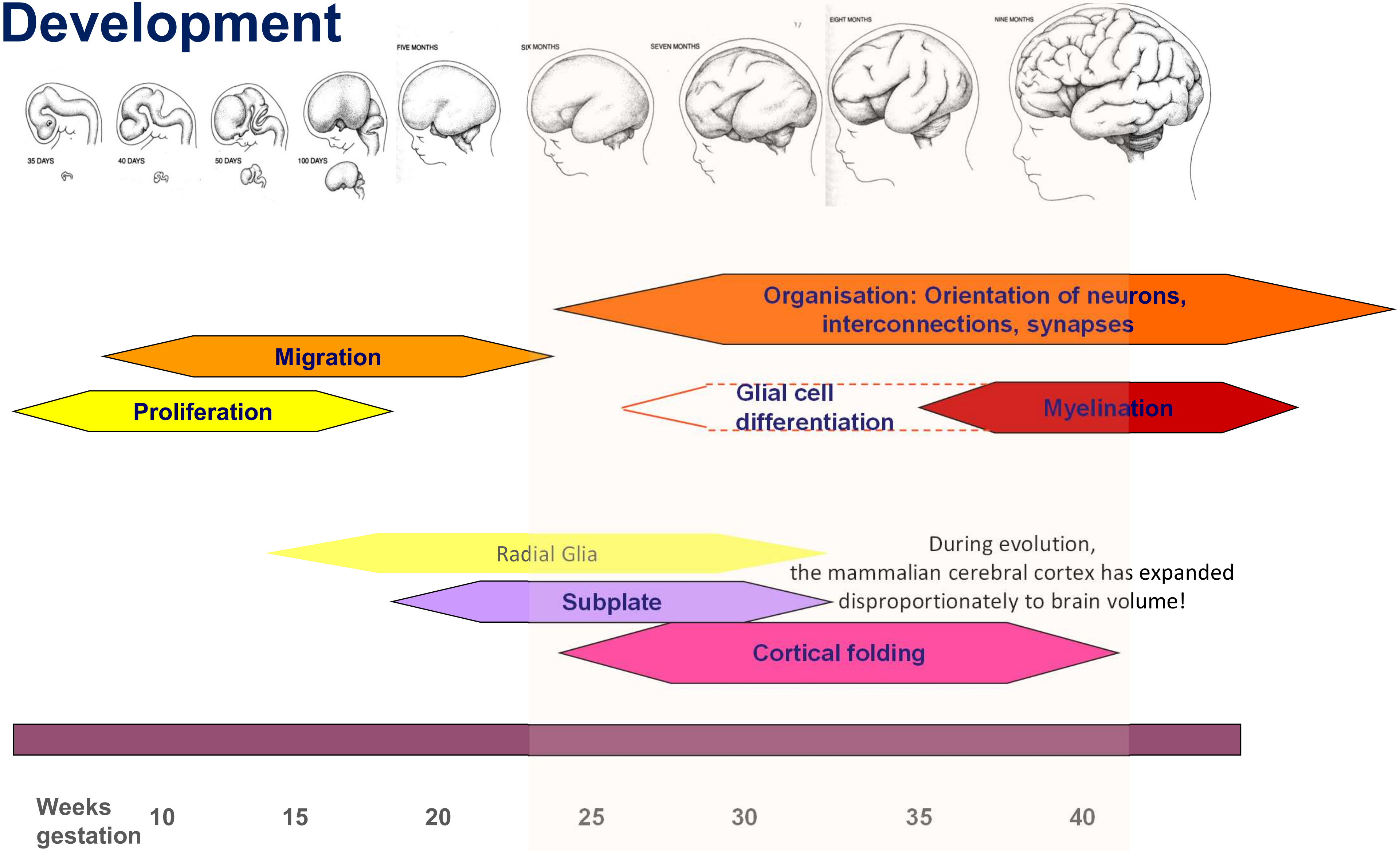
La rete delle reti: il connettoma implicazioni diagnostico-terapeutiche



Ettore Piro MD
Pediatra, Neuropsichiatra Infantile, Neuropediatra, Psicoterapeuta
Università degli Studi di Palermo

Tolman 24 ppt 5

Brain Development



CONNETTOMA

Methods

I. Computing Connection matrix

1. Register T1 over B0 (non-weighted diffusion image)
2. Over diffusion data, compute tractography

   over B0-registered T1 data:

   i. Register all subject in a common referential
   ii. Segment WM,GM and pial surfaces
   iii. Divide cortical surface in standardized regions of interest –subnetwork definition

1. For each pair of regions of the cortex:

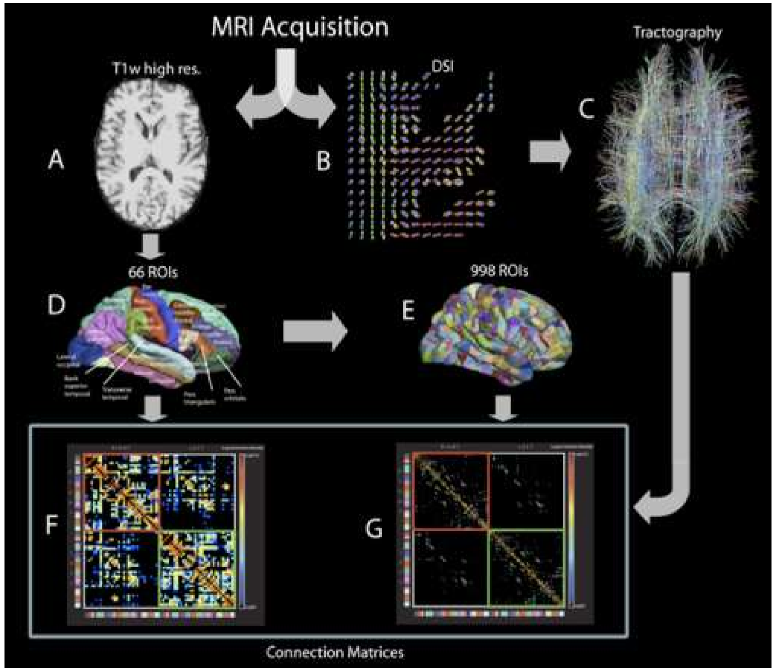
   i. Compute the density of the bundle connecting the 2 regions
   ii. Store the value in a matrix
   iii. Threshold density values for mean FA along the bundle connecting ROIs and eliminate self-connections

II. Wilcoxon rank-sum test for structural connectivity group differences

III. Correlation of strength of ALTERED connections with the scores achieved on socio-cognitive

Pearson's correlaton

http://www.brain-connect.eu/



Cammoun L., et al 2012. *J Neurosci Methods* 203: 386-397. **Hagmann P.**, et al 2008. *PLoS Biol* 6: e159. **Hagmann P.**, et al 2007. *PLoS One* 2: e597. **Meskaldji D.E.**, et al 2013. *Neuroimage* 80: 416-425. **Meskaldji D.E.**, et al 2013. *J arXiv preprint arXiv:1307.3286*

mappa delle connessioni neurali cerebrali

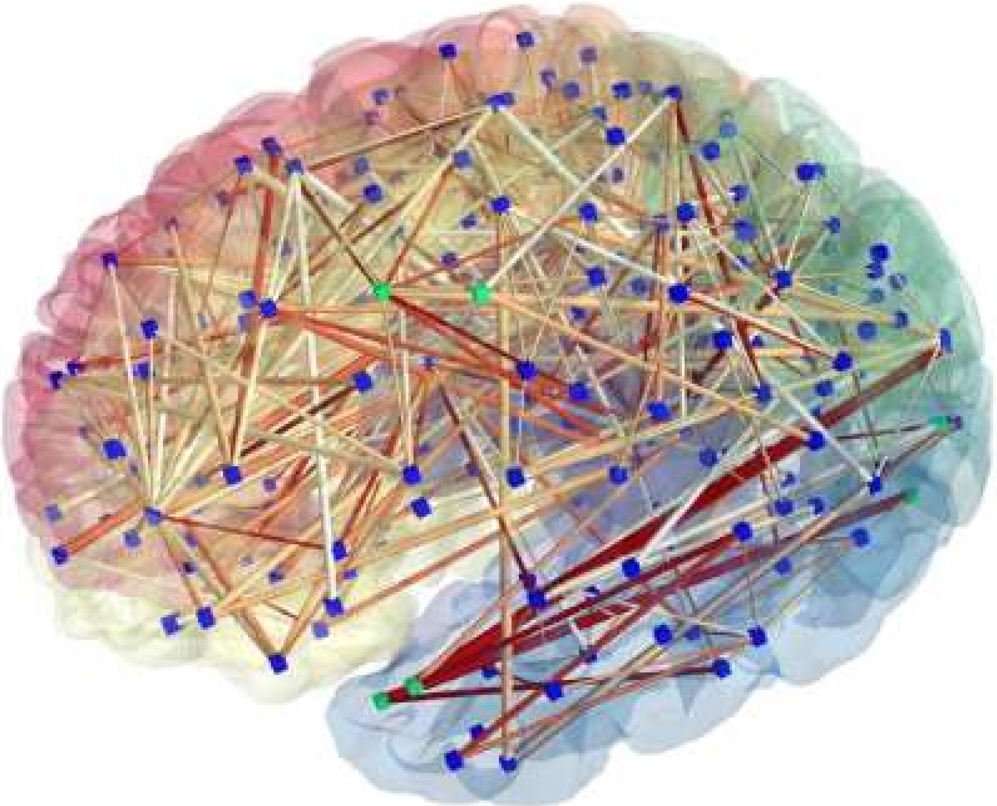
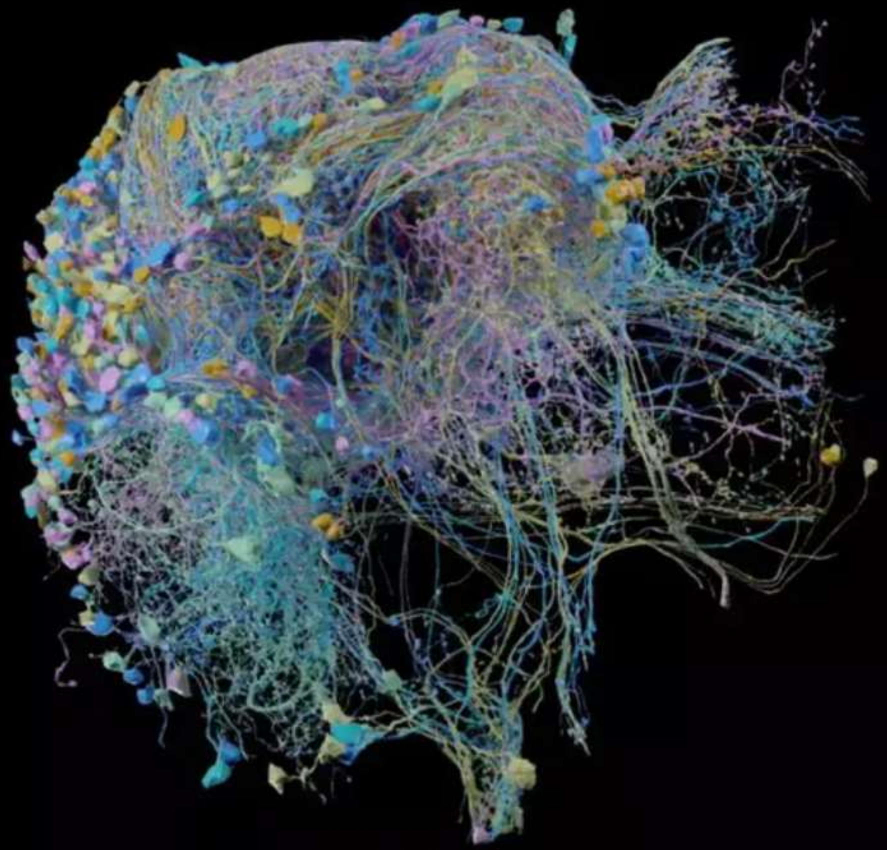


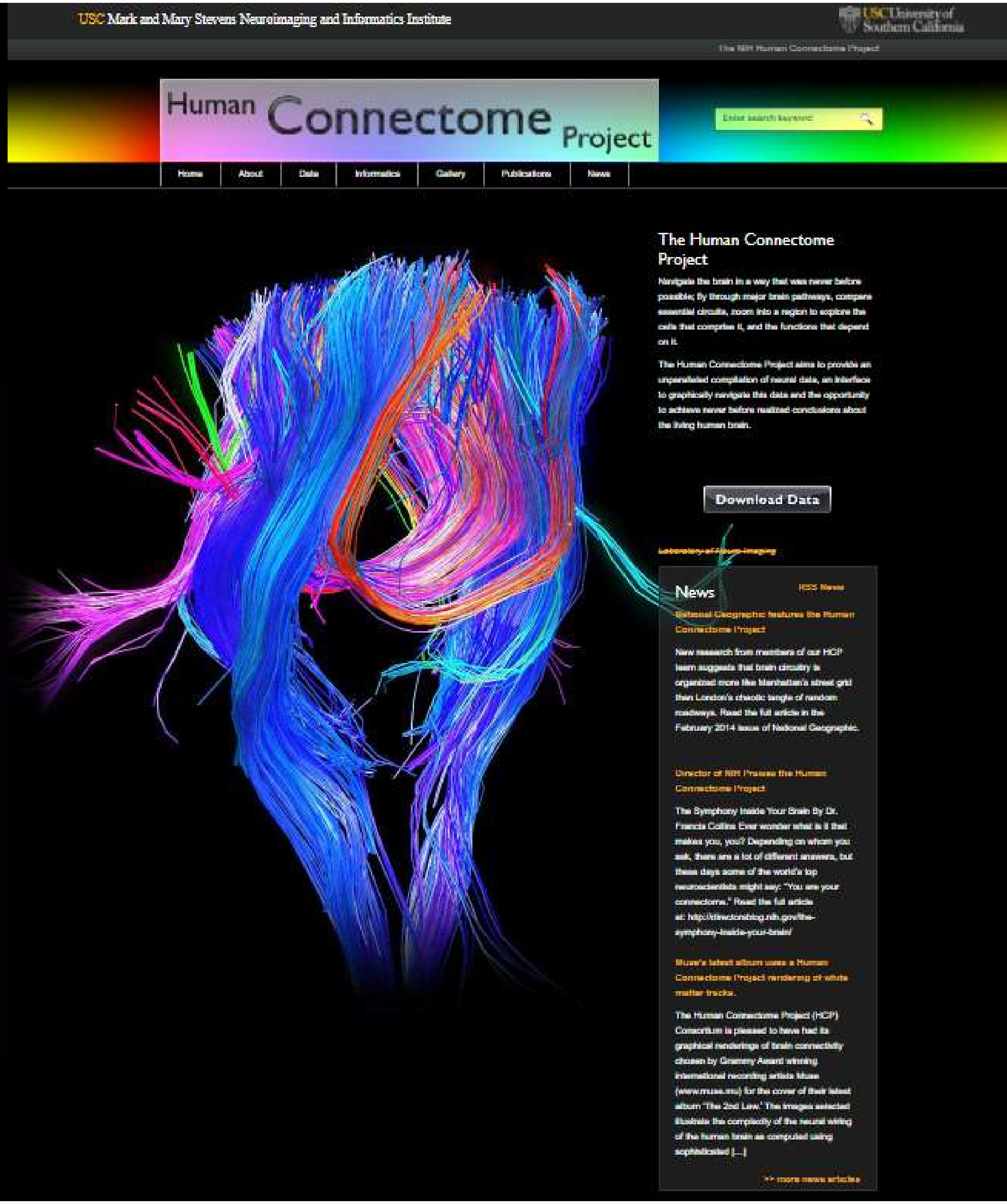
Table 1 Names and abbreviations of the brain regions considered in the human connectome from Hagmann et al. (2008) (in alphabetical order)

Abbreviation	*Brain region*
BSTS	Bank of the superior temporal sulcus
CAC	Caudal anterior cingulate cortex
CMF	Caudal middle frontal cortex
CUN	Cuneus
ENT	Entorhinal cortex
FP	Frontal pole
FUS	Fusiform gyrus
IP	Inferior parietal cortex
ISTC	Isthmus of the cingulate cortex
IT	Inferior temporal cortex
LING	Lingual gyrus
LOCC	Lateral occipital cortex
LOF	Lateral orbitofrontal cortex
MOF	Medial orbitofrontal cortex
MT	Middle temporal cortex
PARC	Paracentral lobule
PARH	Parahippocampal cortex
PC	Posterior cingulate cortex
PCAL	Pericalcarine cortex
PCUN	Precuneus
POPE	Pars opercularis
PORB	Pars orbitalis
PREC	Precentral gyrus
PSTC	Postcentral gyrus
PTRI	Pars triangularis
RAC	Rostral anterior cingulate cortex
RMF	Rostral middle frontal cortex
SF	Superior frontal cortex
SMAR	Supramarginal gyrus
SP	Superior parietal cortex
ST	Superior temporal cortex
TP	Temporal pole
TT	Transverse temporal cortex

Taken from Deco, G., Ponce-Alvarez, A., Mantini, D., Romani, G.L., Hagmann, P., & Corbetta, M. (2013). Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *Journal of Neuroscience, 33*, 11239–11252.

Connettoma

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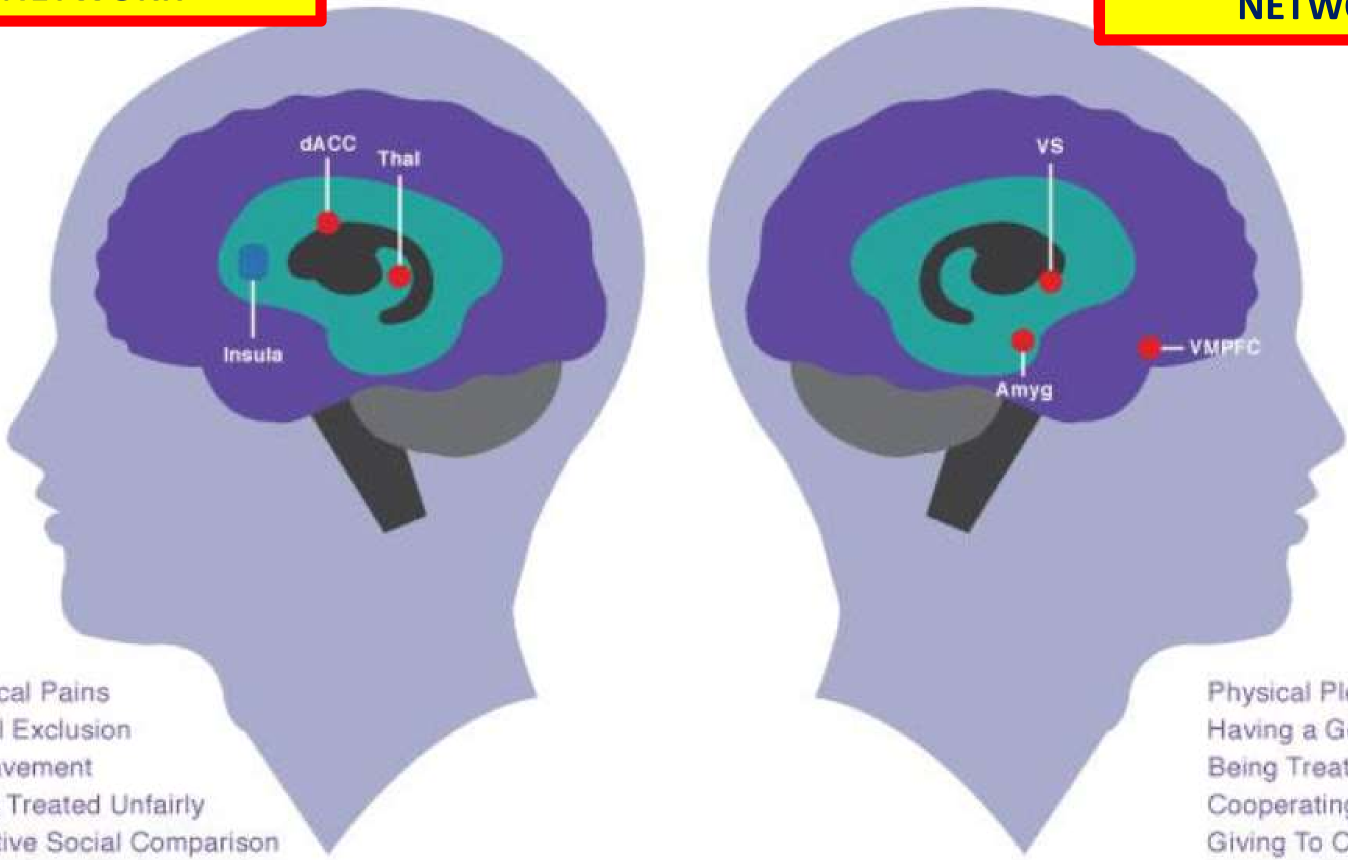
PAIN NETWORK

Pain and Pleasure

REWARD NETWORK



Physical Pains
Social Exclusion
Bereavement
Being Treated Unfairly
Negative Social Comparison

Physical Pleasures
Having a Good Reputation
Being Treated Fairly
Cooperating
Giving To Charity

Pain Network

dACC = Dorsal Anterior Cingulate Cortex

Thal = Thalmus

INS = Insula

Reward Network

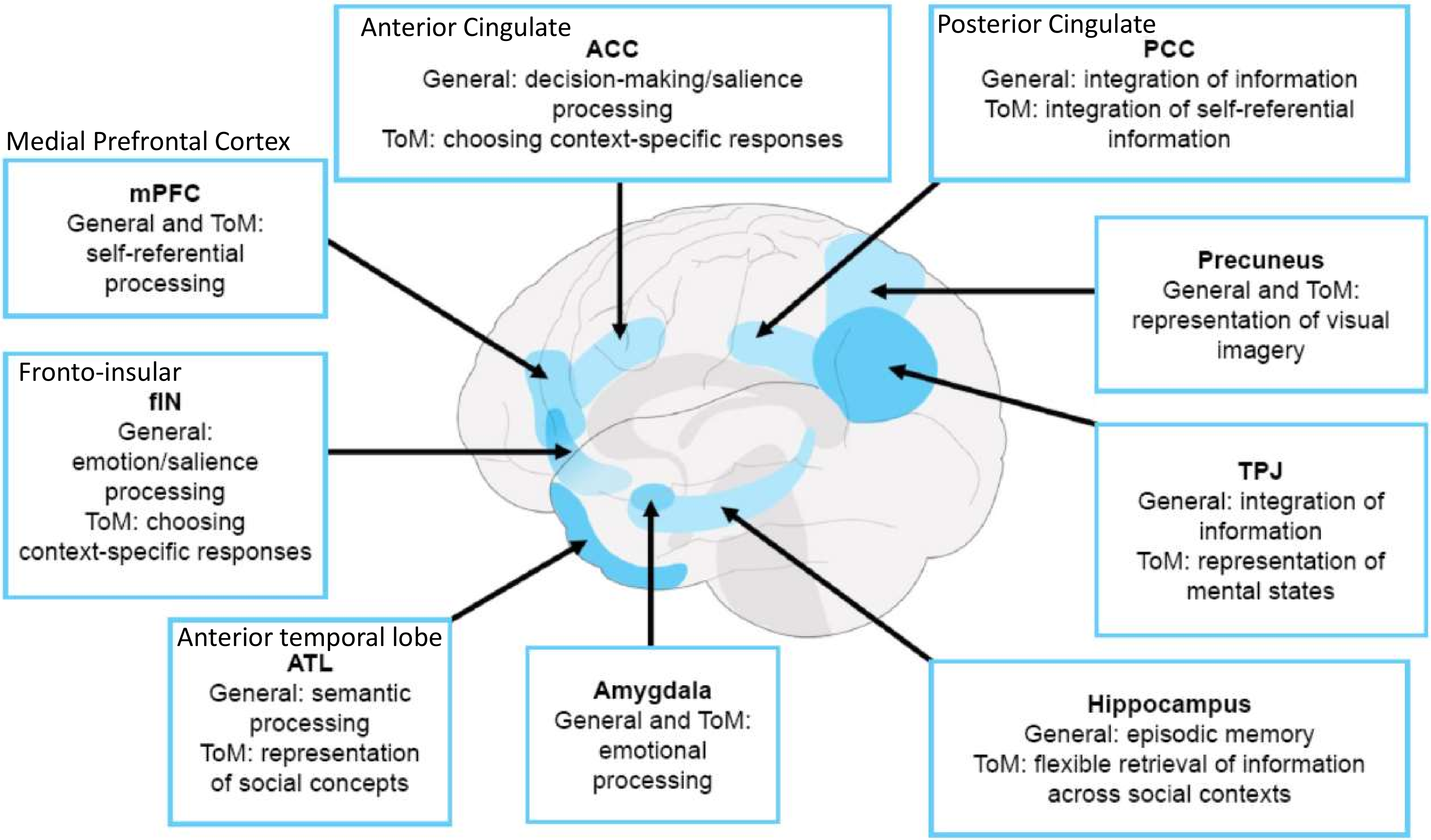
VS = Ventral Striatum

Amyg = Amygdala

VMPFC = Ventromedial Prefrontal Cortex

Theory of mind (ToM)

- La **teoria della mente** (D. Premack e G. Woodruff 1978)
- **Capacità di attribuire stati mentali a sé stessi e agli altri ed è fondamentale in ogni interazione sociale**
- **Stati mentali sono considerati emozioni, cognizioni/conoscenze, desideri, intenzioni, credenze-,**
- **Aspetto fondamentale è la capacità di comprendere che gli altri hanno stati mentali diversi dai proprie potere quindi analizzare, comprendere e giudicare il comportamento degli altri.**
- **La teoria della mente è una teoria nel senso che la presenza della mente propria e altrui può essere inferita soltanto attraverso l'introspezione, e attraverso la congettura che gli altri, avendo atteggiamenti e comportamenti simili ai nostri, abbiano anche stati mentali propri.**
- **In questo senso, ogni individuo possiede una propria teoria della mente, e alcune condizioni come l'autismo e la schizofrenia sono state interpretate come un deficit specifico di questa abilità.**



Anterior Cingulate
ACC
General: decision-making/salience processing
ToM: choosing context-specific responses
Posterior Cingulate
PCC
General: integration of information
ToM: integration of self-referential information
Medial Prefrontal Cortex
mPFC
General and ToM: self-referential processing
Precuneus
General and ToM: representation of visual imagery
Fronto-insular
fIN
General: emotion/salience processing
ToM: choosing context-specific responses
TPJ
General: integration of information
ToM: representation of mental states
Anterior temporal lobe
ATL
General: semantic processing
ToM: representation of social concepts
Amygdala
General and ToM: emotional processing
Hippocampus
General: episodic memory
ToM: flexible retrieval of information across social contexts

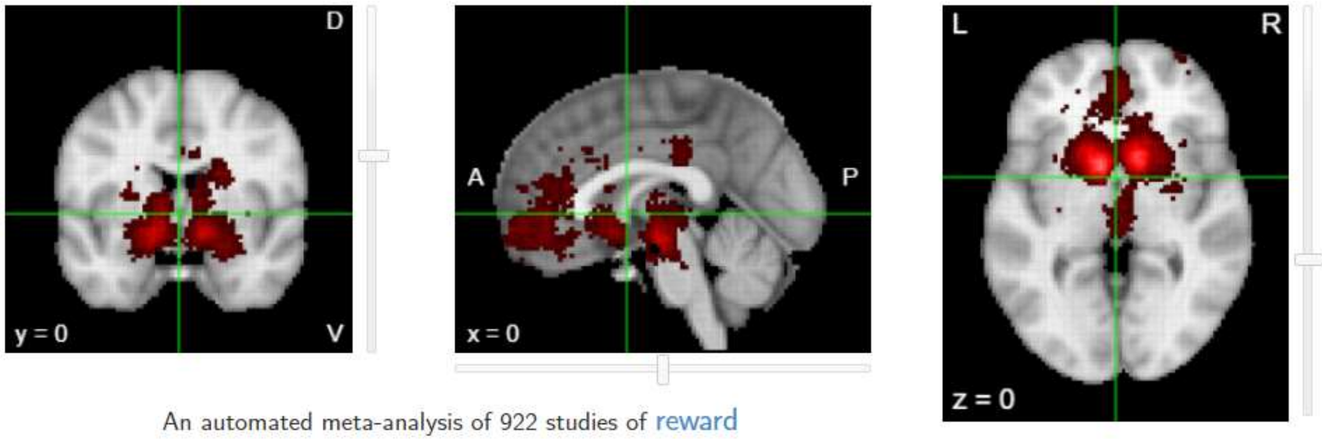
Aggiornamento su studi e dati desunti da fMRI

Neurosynth.org Home **Meta-analyses** Studies Locations Genes Decoder Code FAQs

neurosynth.org

Neurosynth is a platform for large-scale, automated synthesis of functional magnetic resonance imaging (fMRI) data.

It takes thousands of published articles reporting the results of fMRI studies, chews on them for a bit, and then spits out images that look like this:



An automated meta-analysis of 922 studies of reward

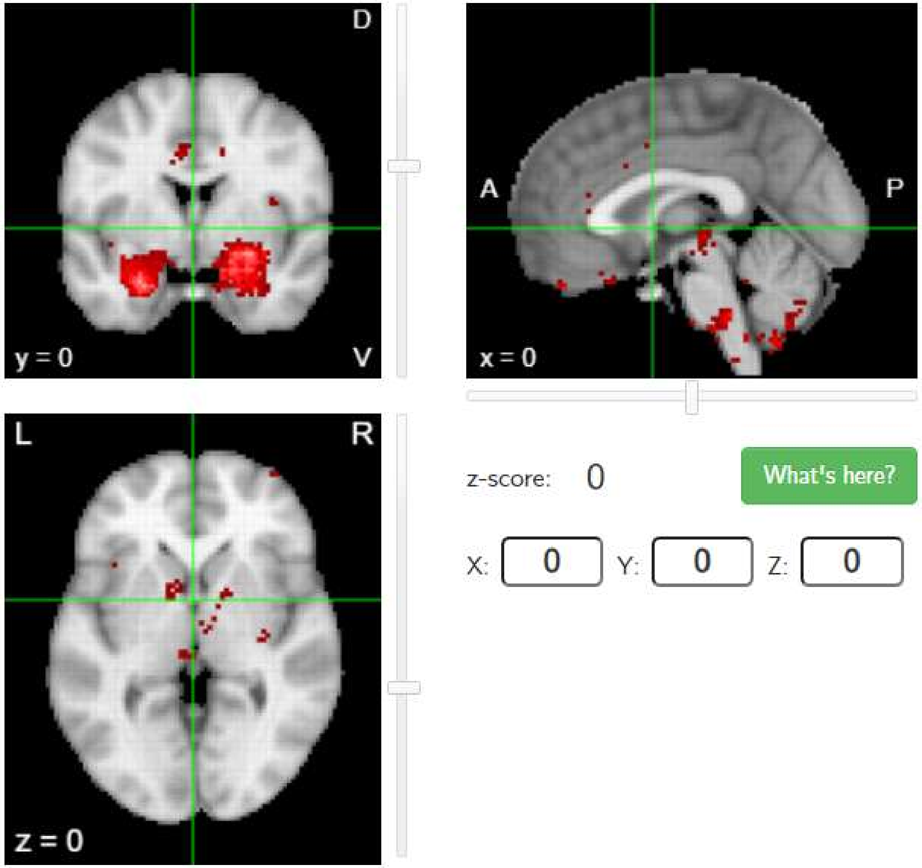
Metanalisi automatizzata di 922 studi sul ''rinforzo''

conditioning

An automated meta-analysis of 160 studies

Search for another term:

Maps | Studies | FAQs



z-score: 0

What's here?

X: 0 Y: 0 Z: 0

Layers

- conditioning: association test
- conditioning: uniformity test
- anatomical

Color palette: red

Positive/Negative: positive

☑ Crosshairs
☐ Pan/zoom
☑ Labels

Thresholds: 0 0

Opacity: 1

Maps Studies FAQs

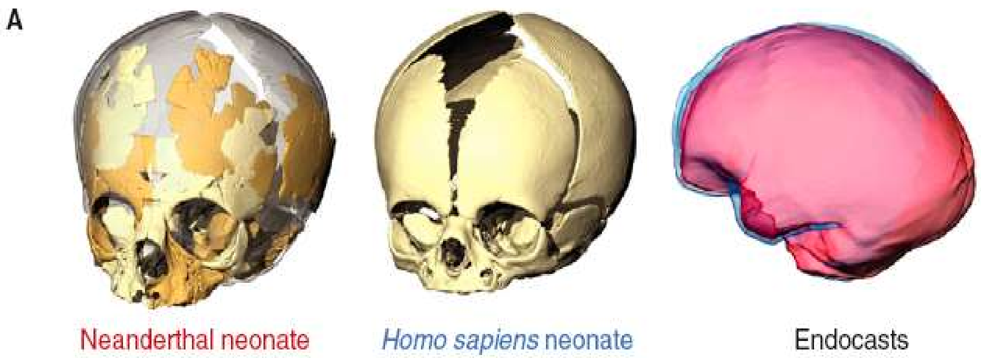
Studies associated with conditioning

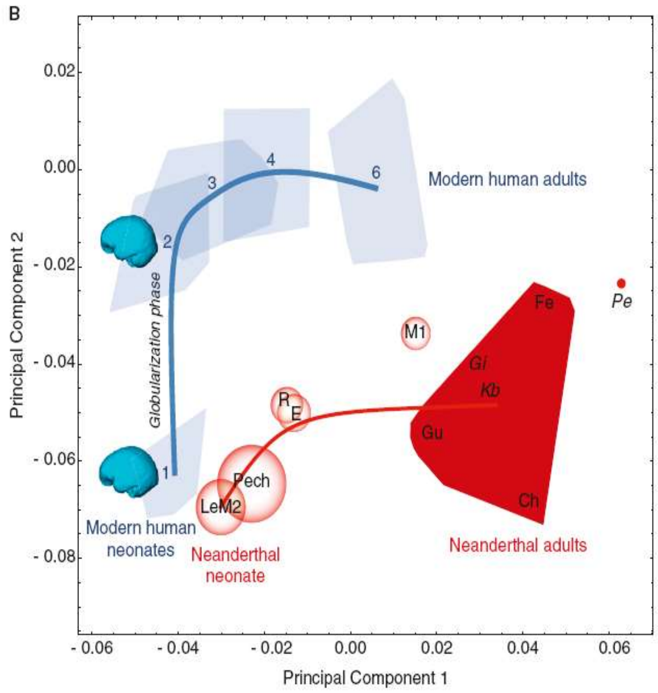
Show 10 entries

Search:

Title	Authors	Journal	Loading
Altered reward learning and hippocampal connectivity following psychosocial stress.	Kruse O, Tapia Leon I, Stalder T, Stark R, Klucken T	NeuroImage	0.72
Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging.	Buchel C, Dolan RJ, Armony JL, Friston KJ	The Journal of neuroscience : the official journal of the Society for Neuroscience	0.703
Contextual fear conditioning in humans: cortical-hippocampal and amygdala contributions.	Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C	The Journal of neuroscience : the official journal of the Society for Neuroscience	0.642
Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning.	Marschner A, Kalisch R, Vervliet B, Vansteenwegen D, Buchel C	The Journal of neuroscience : the official journal of the Society for Neuroscience	0.634
The scent of salience--is there olfactory-trigeminal conditioning in humans?	Moessnang C, Pauly K, Kellermann T, Kramer J, Finkelmeyer A, Hummel T, Siegel SJ, Schneider F, Habel U	NeuroImage	0.575
Human fear conditioning and extinction in neuroimaging: a systematic review.	Sehlmeyer C, Schoning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, Konrad C	PloS one	0.511
Impact of COMT Val158Met-polymorphism on appetitive conditioning and amygdala/prefrontal effective connectivity.	Klucken T, Kruse O, Wehrum-Osinsky S, Hennig J, Schweckendiek J, Stark R	Human brain mapping	0.497
Cerebellar activation during leg withdrawal reflex conditioning: an fMRI study.	Dimitrova A, Kolb FP, Elles HG, Maschke M, Gerwig M, Gizewski E, Timmann D	Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology	0.479
Time course of amygdala activation during aversive conditioning depends on attention.	Straube T, Weiss T, Mentzel HJ, Miltner WH	NeuroImage	0.471
Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy.	Critchley HD, Mathias CJ, Dolan RJ	Neuron	0.467

Brain development during evolution



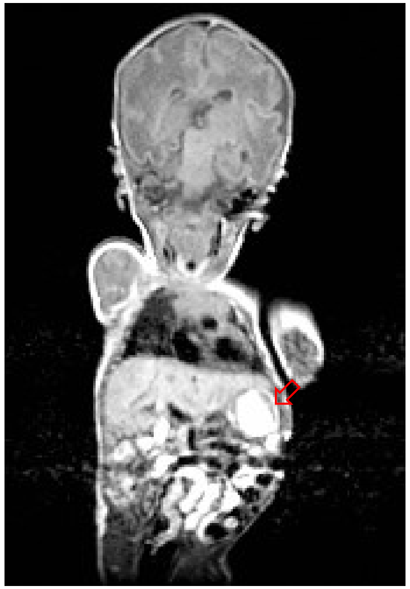


Neandertal and modern human brains grow differently:
❖humans brain growth postnatal is globular, neandertal postnatal growth was not
❖The shape changes of the frontal and parietal bone in the human are driven by the increase in brain volume

Environment and stimuli shape the brain through evolution
the pathway from genetic variation to individual differences in personality may be mediated via variation in regional brain structure

Brain development after birth differs between Neanderthals and modern humans Philipp Gunz, Simon Neubauer, Bruno Maureille, and Jean-Jacques Hublin ,Current Biology 2010 Vol 20 No 21

Magnetic Resonance technique:
Non-invasive method to study brain development & injury



MRI Baby

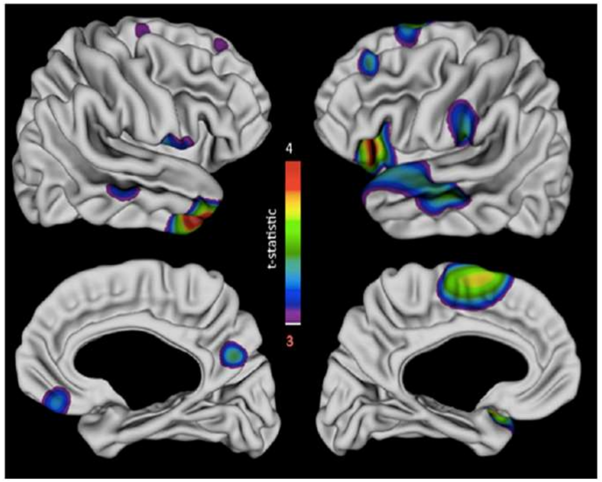
Early growth and brain maturation <u>into adolescence in term newborns</u>

Monozygotic twin study (term birth):
subtle variations of the in utero environment, with mild birth weight (BW) variation are accompanied by
① differences in postnatal intelligence quotient (IQ)
② alterations of brain anatomy

Greater BW within the **normal range** confers a sustained and generalized increase in brain volume, which in the cortical sheet, is specifically driven by altered **surface area**

Measure	Effect of BW t	Effect of BW P	Estimated change with 500-g BW increase: Absolute	Estimated change with 500-g BW increase: Relative
IQ	2.3	0.02	2.0 points	0.13 SD
VIQ	0.9	0.4	0.9 points	0.06 SD
PIQ	2.5	0.02	2.3 points	0.15 SD
Total brain volume	9.2	<0.0005	27 cm^3	2%, 0.25 SD
GMV	5.7	<0.0005	19 cm^3	2.1%, 0.27 SD
WMV	3.7	0.0002	10 cm^3	1.9%, 0.17 SD
Total cortical volume	5.8	<0.0005	16 cm^3	2.3%, 0.27 SD
Mean cortical thickness	2.3	0.02	0.025 mm	0.6%, 0.15 SD
Total surface area	8.3	<0.0005	35.7 cm^2	1.8%, 0.3 SD

Main effect of BW is shown for cognitive [IQ, VIQ, PIQ (Full Scale, Verbal and Performance Intelligence Quotient respectively)] and global anatomical outcomes.



Raznahan A et al. PNAS 2012 vol 109/28 11366-11371


Nato pretermine

Il nato pretermine

Pretermine è il nato prima di 37 settimane complete di gestazione, sono circa il 10% dei nati in Italia

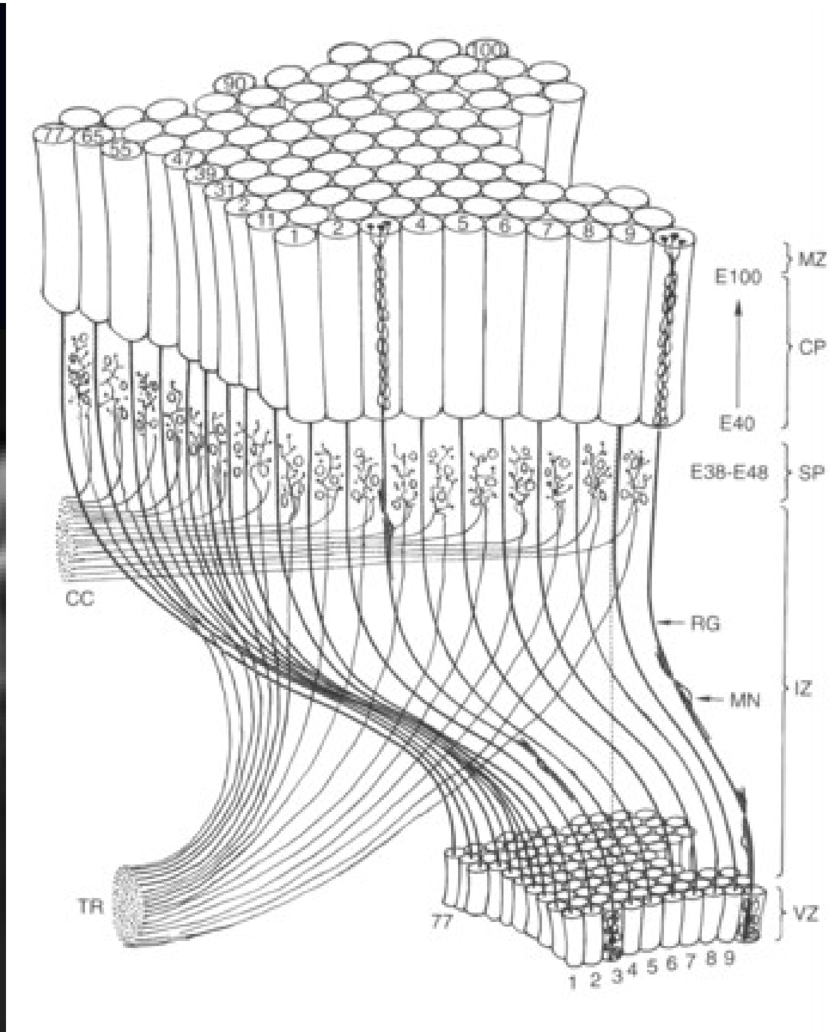
Limite di sopravvivenza dalla 23 settimana di gestazione completata, con un peso medio di 400 grammi

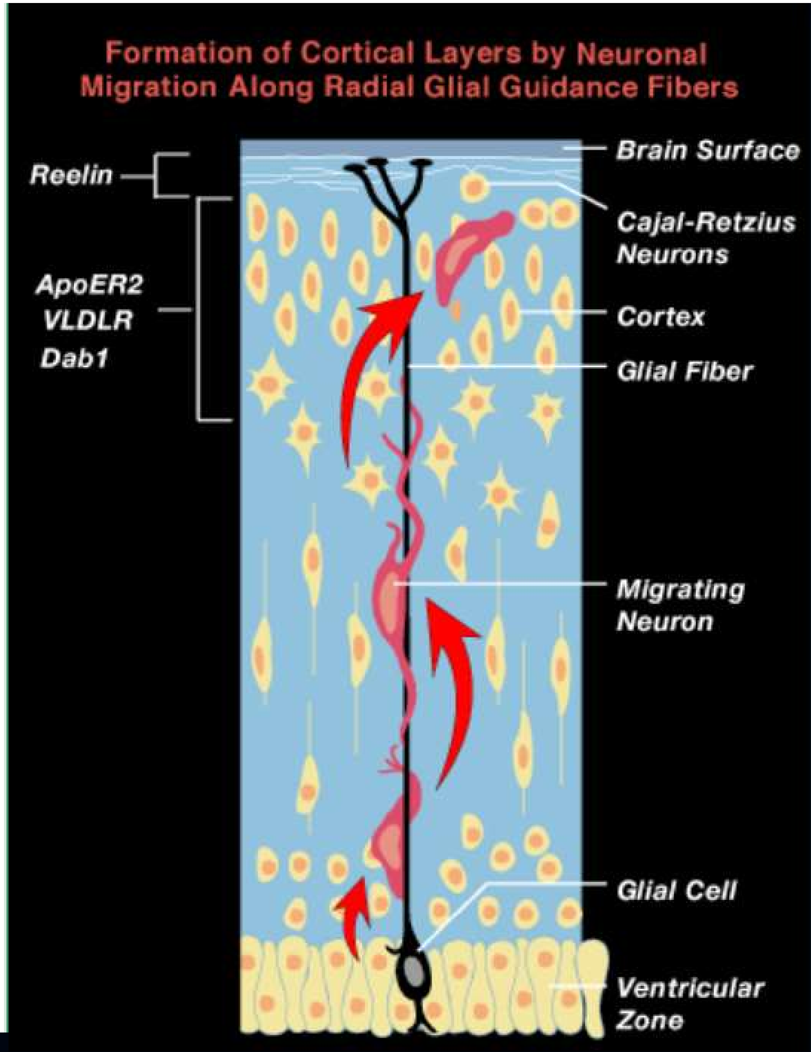
Rischio maggiore se nati prima delle 32 settimane e sotto i 1500 grammi

Se gemelli rischio aumentato in specifiche classi di soggetti

Categoria a rischio di sviluppo di patologia non solo metabolica e neurologica, ma disturbi psico-comportamentali ed emotivo-relazionali (autismo, ADHD, DOP, DOC, Disabilità intellettiva, deficit sensoriali, disturbi apprendimento, patologia psichiatrica anche a lungo termine)

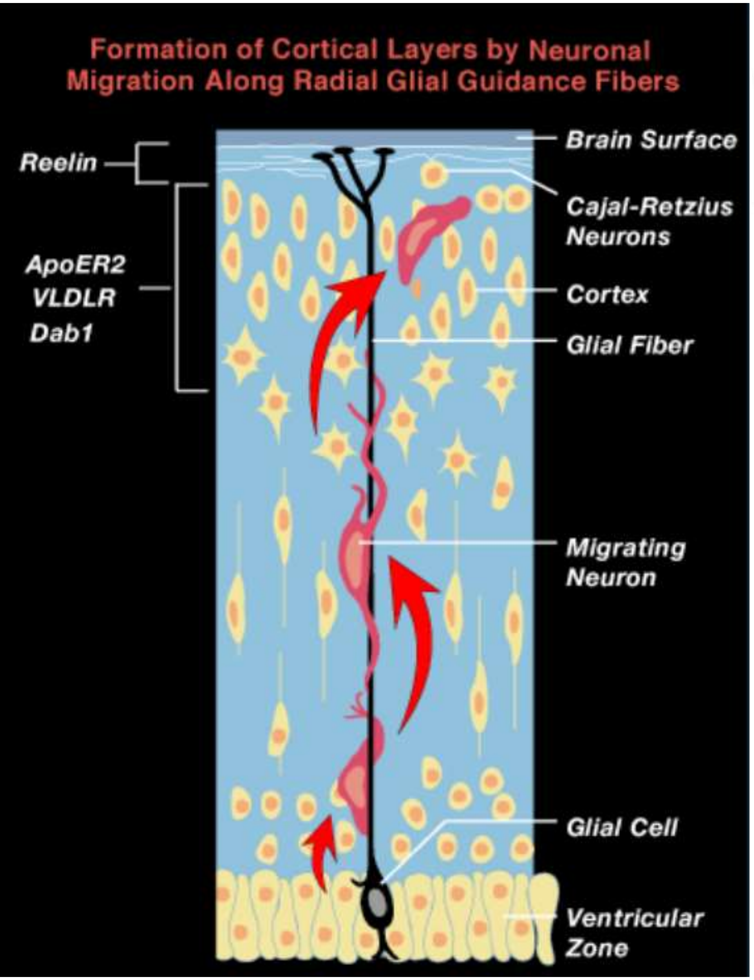
Correlazione dei rapporti tra microcolonne neuroblasti zona germinativa e organizzazione della corteccia → network neuronali

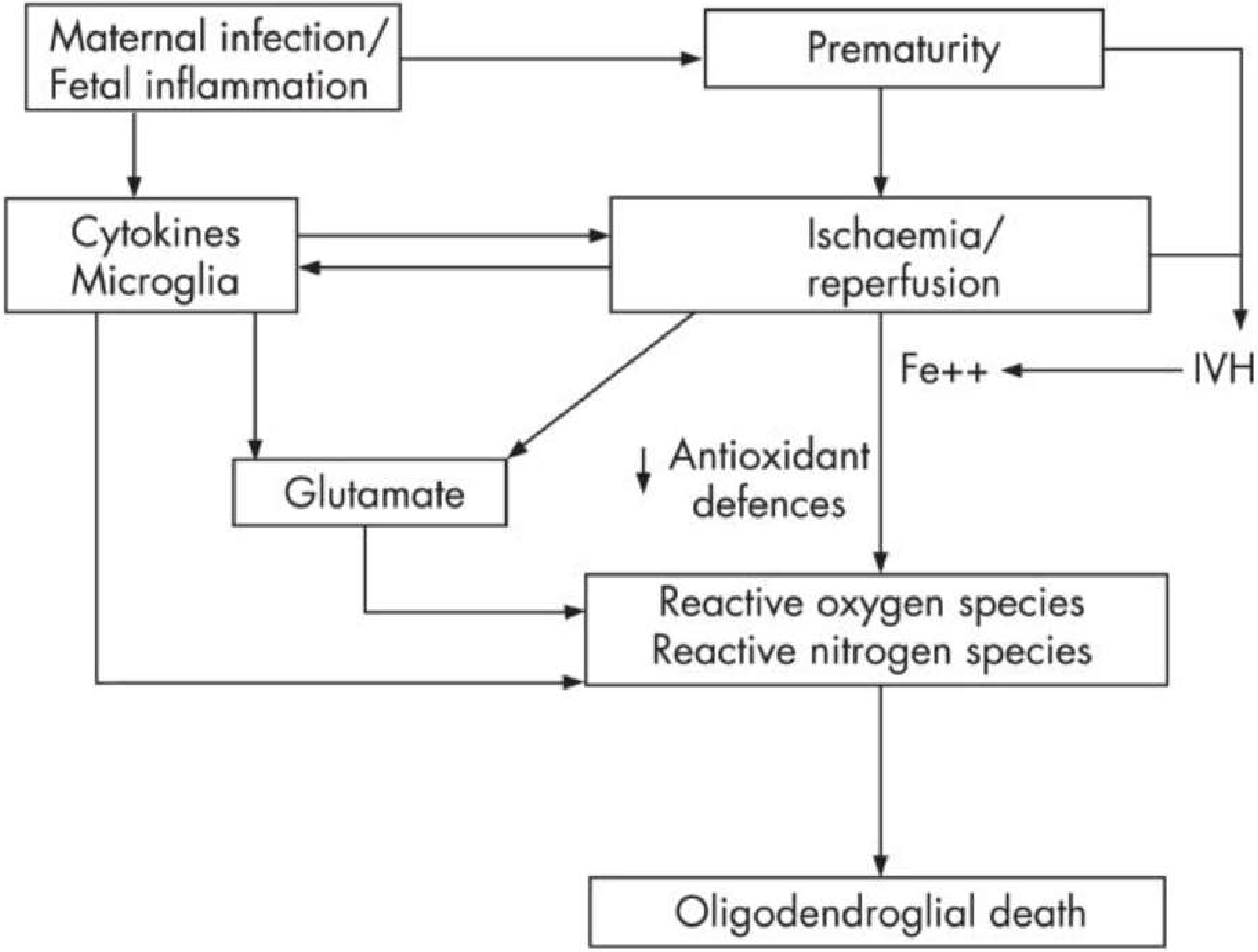




Zona germinativa / ventricular zone
Neuroblasti e cellule della glia

Pretermine e insulto alle cellule della oligodendroglia→ guida migrazione neuronale

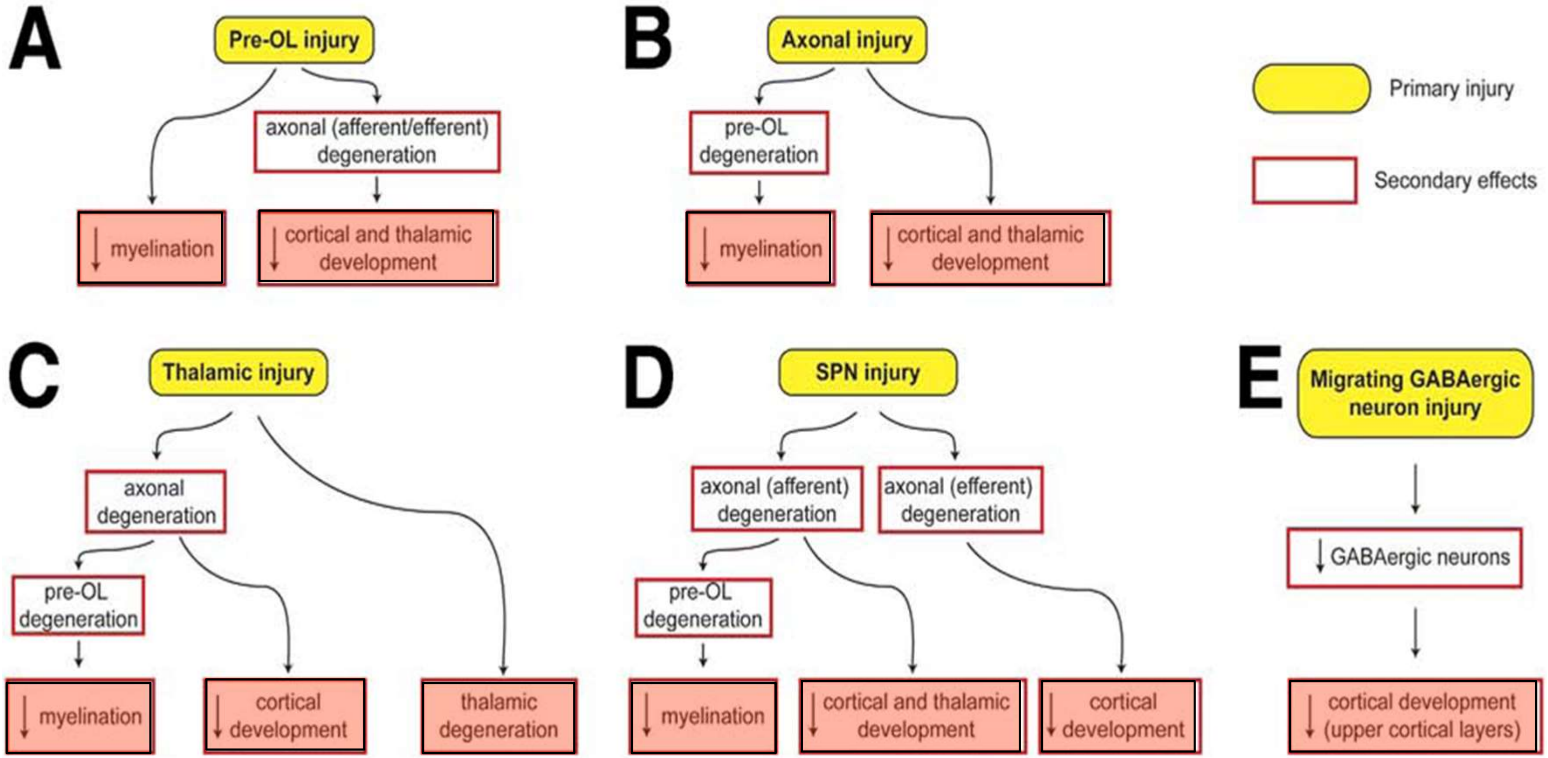




Sequence of injury events leading to altered brain development

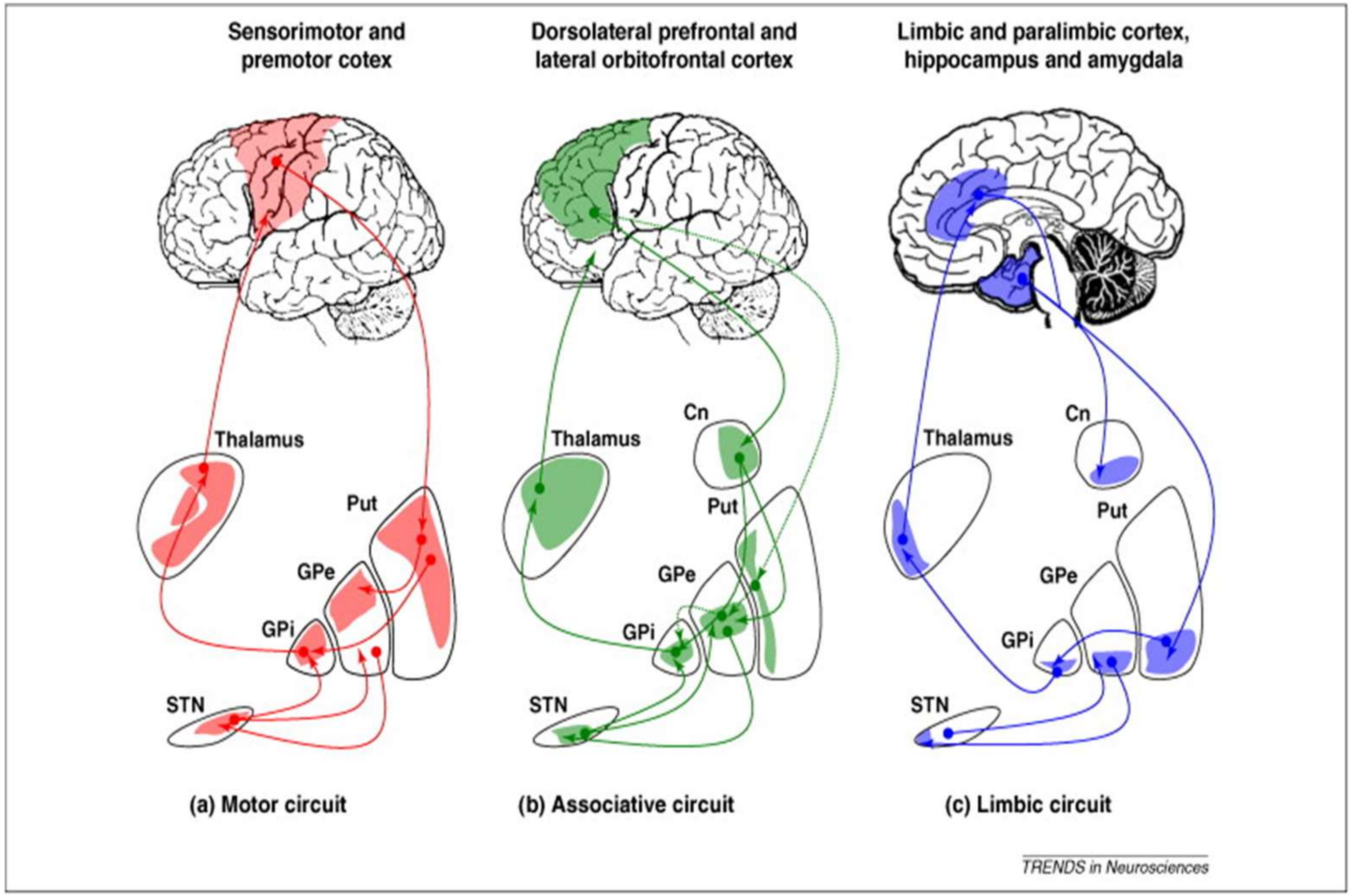
Pre-OL
Glia non mielinizzata

SPN
Neuroni del subplate

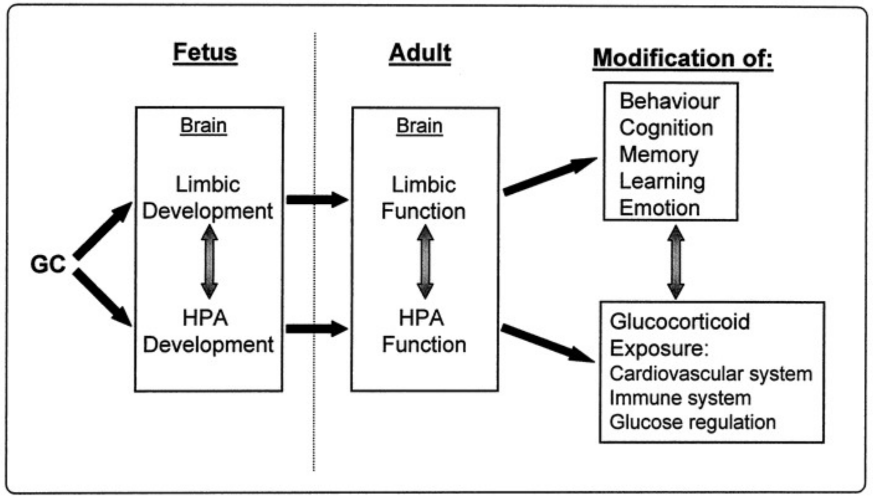


Volpe, J. J. (2009). The Lancet Neurology 8(1): 110-124; Sem Ped Neurol 16: 167-178

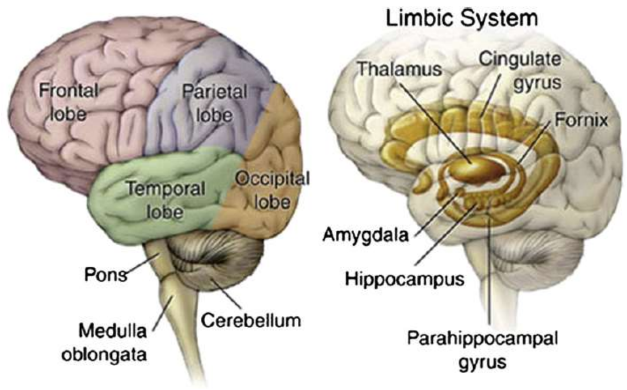
Cortico-basal ganglia thalamo cortical circuits altered in 6 year old preterm children



Developmental consequences of perinatal stress



The knowledge that neonatal emotional experience and associated learning processes are critical in the maturation of prefronto-limbic circuits emphasizes the great importance of preterm and neonatal care



Regions of the limbic system, such as the hippocampus, amygdala, nucleus accumbens, PFC and OFC, and cingulate gyrus, play distinct roles in cognitive and emotional development and are affected by early stress/separation

Matthews SG Pediatr Res 2000;47:291-300
Braun K J Perinatol 2011

Structural brain connectivity in school age preterm infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition

Whole brain connectom differences in children born extremely preterm (sotto 28 seg) vs moderately preterm

- Structural connectivity (SC) was modeled by characterizing the efficacy of connections as the average fractional anisotropy (FA) and as the inverse of the apparent diffusion coefficient along the fiber bundles connecting 83 different cerebral regions.

EP vs. control	FA-weighted analysis	ADC-weighted analysis
	p-value / effect size	*p-value / effect size*
Whole brain SC	$3.71 \cdot 10^{-7(*)}$ / 4.95	0.37159058 / 0.33
Right intrahemispheric SC	$2.87 \cdot 10^{-5(*)}$ / 4.02	0.81567628 / −0.90
Left intrahemispheric SC	$1.67 \cdot 10^{-5(*)}$ / 4.14	0.19646567 / 0.85
Interhemispheric SC	$9.64 \cdot 10^{-5(*)}$ / 3.72	$0.03459978^{(*)}$ / 1.82

ADC based structural connectivity, as an indicator of WM maturation and myelination was reduced in interhemispheric WM pathways in EP children compared to controls, FA based SC is reduced also in intrahemispheric connectivity

Decreased fractional anisotropy-weighted SC (FAw-SC)

Fischi E et al Cerb cortex 2014

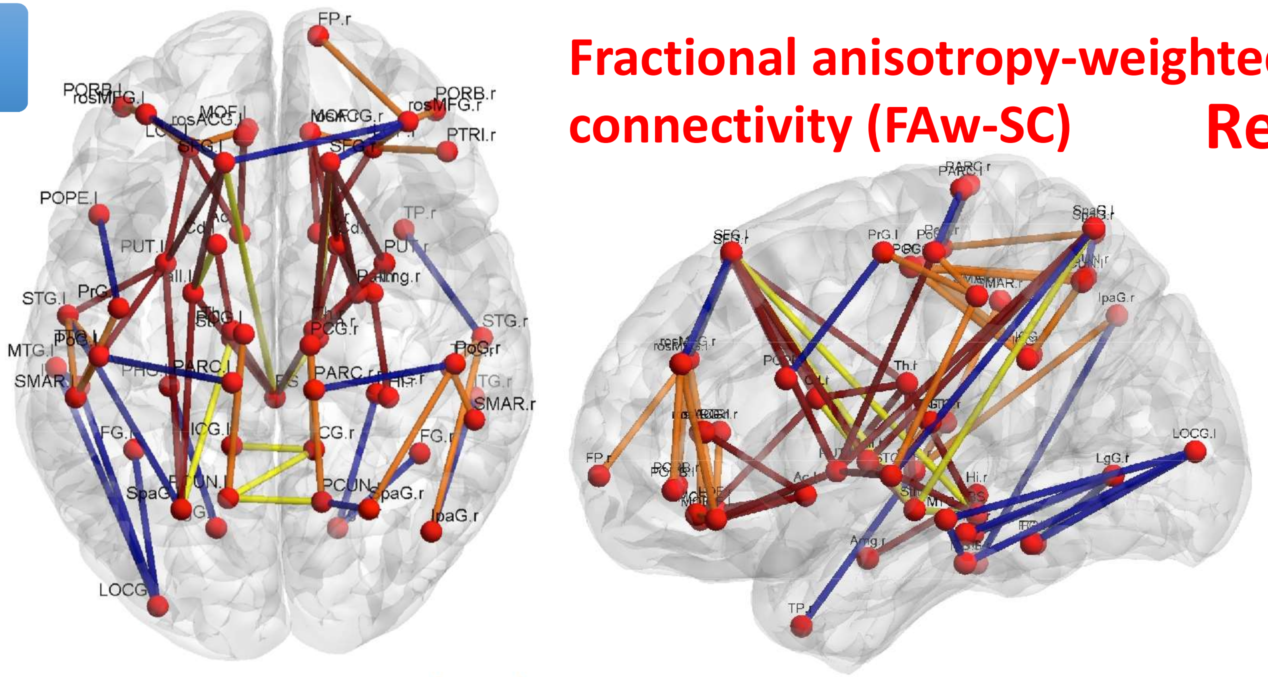
Fractional anisotropy-weighted Structural connectivity (FAw-SC) Results (EP)

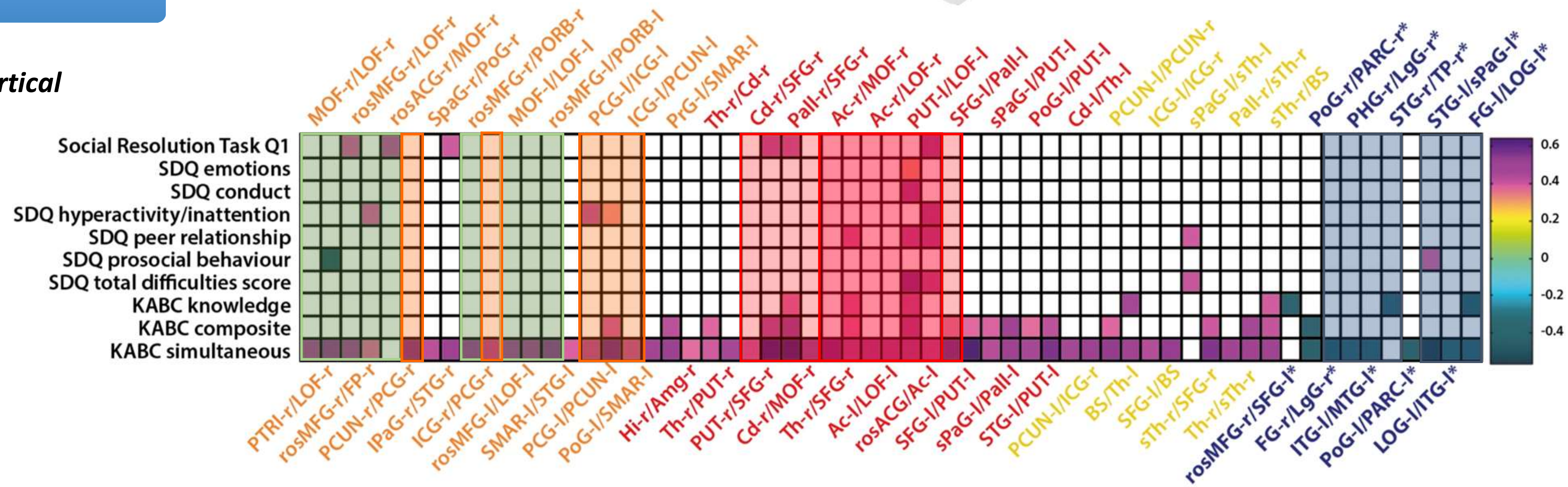
FAwSC EP<Controls

- **C**ortico **B**asal ganglia **T**halamo **C**ortical **L**oop
- Short Cortico-cortical
- **B**rain **S**tem **S**ub**th**alamic Commisural

FAwSC EP>Controls

- ***Short Cortico-cortical***



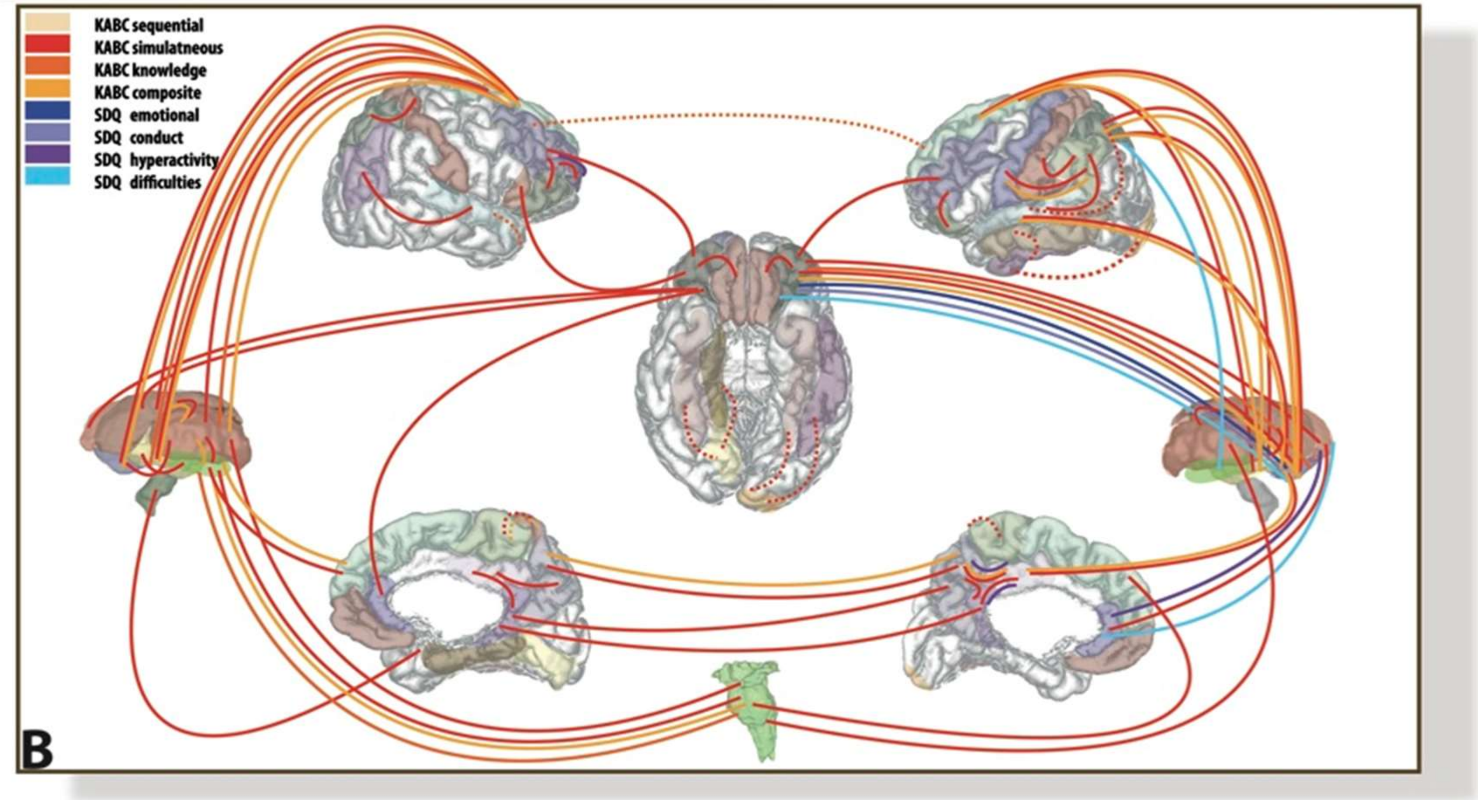


Gomez E.F., Vasung L., et al 2014. Structural brain connectivity in school age preterm infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition, ***Cerebral Cortex****, in press,* ***doi:10.1093/cercor/bhu073***

Structural brain connectivity <u>in school age preterm</u> infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition

Results (EP)

Cognitive skills



Schematic drawing of altered connections in EP subjects whose FAw-SC strength correlates with socio-cognitive outcome.

Dotted lines: negative correlation. Continuous lines: positive correlation.

GOMEZ E.F., VASUNG L., et al 2014. Structural brain connectivity in school age preterm infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition, **Cerebral Cortex**, **doi:10.1093/cercor/bhu073**

Fractional anisotropy-weighted Structural connectivity (FAw-SC)

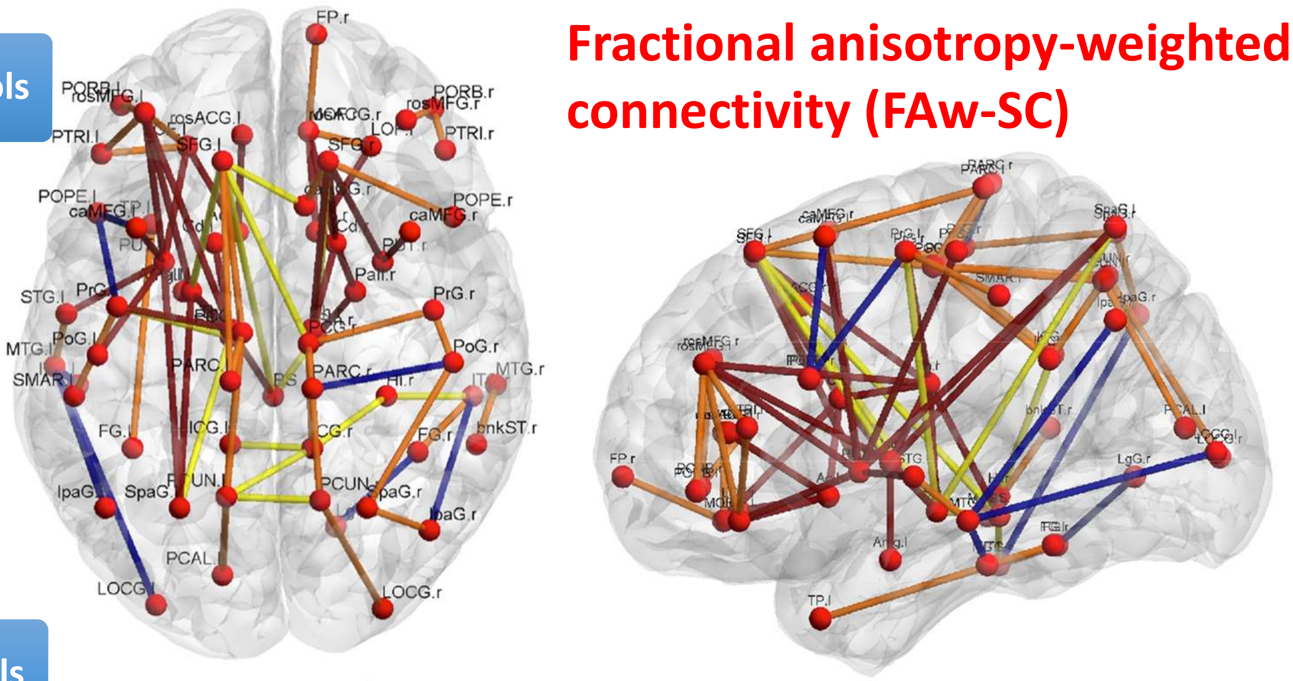
Results (IUGR) < 10° percentile

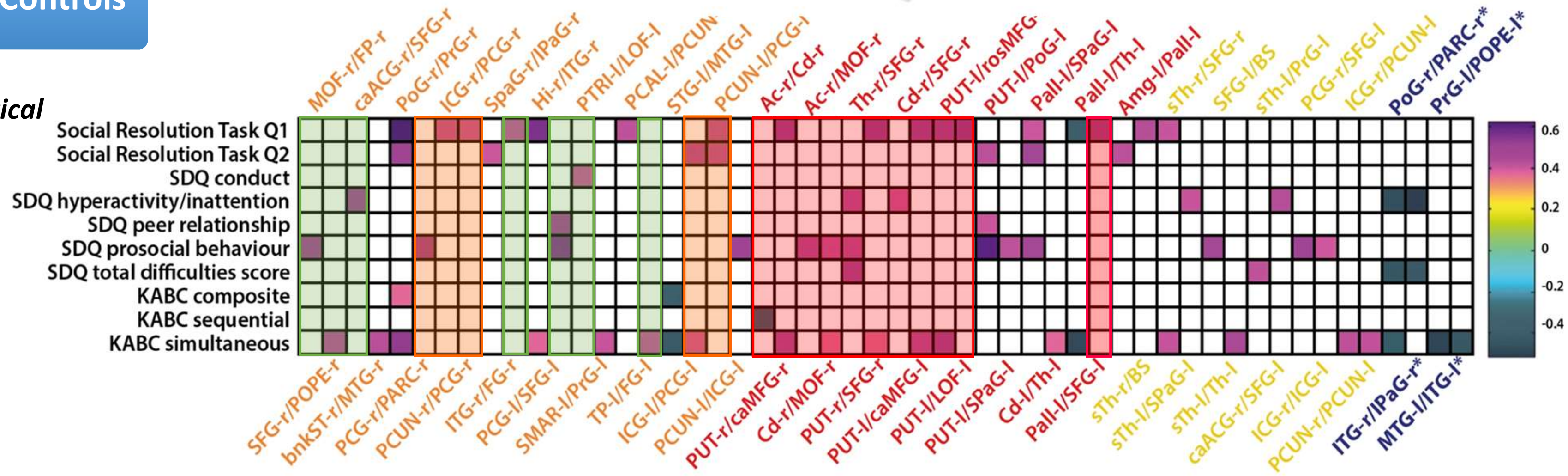
FAwSC IUGR<Controls

- **C**ortico **B**asal ganglia **T**halamo **C**ortical **L**oop
- Short Cortico-cortical
- **B**rain **S**tem **S**ub**th**alamic
- Commisural

FAwSC IUGR>Controls

- ***Short Cortico-cortical***

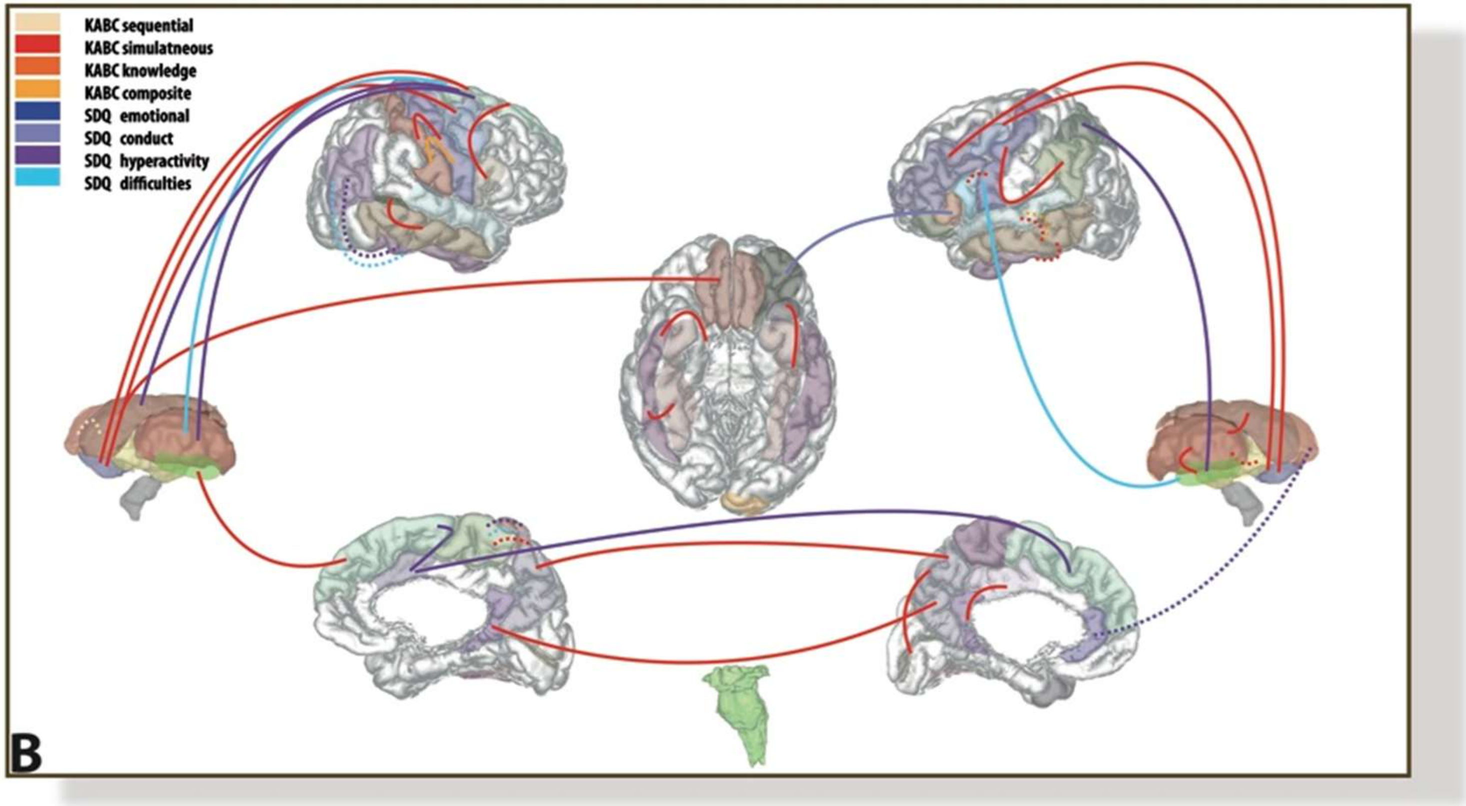




GOMEZ E.F., VASUNG L., et al 2014. Structural brain connectivity in school age preterm infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition, **Cerebral Cortex**, in press, **doi:10.1093/cercor/bhu073**

Results (IUGR)

Cognitive skills



Schematic drawing of altered connections in IUGR subjects whose FAw-SC strength correlates with socio-cognitive outcome.

Dotted lines: negative correlation. Continuous lines: positive correlation.

GOMEZ E.F., VASUNG L., et al 2014. *Structural brain connectivity in school age preterm infants provides evidence for impaired networks relevant for higher-order cognitive skills and social cognition*, ***Cerebral Cortex***, *in press*, ***doi:10.1093/cercor/bhu073***

| NATURE | VOL 518 | 5 FEBRUARY 2015

THE BRAIN, INTERRUPTED

Babies are increasingly surviving premature birth — but researchers are only beginning to understand the lasting consequences for their mental development.

BY ALISON ABBOTT

Alison Abbott *is* Nature*'s senior European correspondent.*