Cours du 12 décembre 2011
Fig. 1. Location of barrier sites in the CNS. Barriers are present at three main sites: (1) the brain endothelium forming the blood–brain barrier (BBB), (2) the arachnoid epithelium forming the middle layer of the meninges, and (3) the choroid plexus epithelium which secretes cerebrospinal fluid (CSF). In each site, the physical barrier is caused by tight junctions that reduce the permeability of the paracellular (intercellular cleft) pathway. In circumventricular organs (CVO), containing neurons specialized for neurosecretion and/or chemosensitivity, the endothelium is leaky. This allows tissue-blood exchange, but as those sites are separated from the rest of the brain by an external glial barrier, and from CSF by a barrier at the ependyma, CVOs do not form a leak across the BBB. (Based on Segal and Zlokovic, 1990), modified by A. Reichel (with permission).

Fig. 2. Cell types associated with the brain endothelium forming the blood–brain barrier. Pericytes are enclosed within the endothelial basal lamina and form the closest associations with endothelium. The end-feet of astrocytic glial cells are apposed to the outer surface of the basal lamina. In the perivascular space are found microglia, the synaptic terminals and boutons of nerve fibres, and (in arterioles), smooth muscle cells. In the larger vessels, cells of the meninges form a perivascular cuff or sheath projecting down from the brain surface, and demarcating the Virchow–Robin space (not shown). Agents can influence endothelial function by ligand-receptor interaction, from the blood or the brain side. Some receptors are coupled to elevation of intracellular [Ca^{2+}]. The heavy arrows indicate the ability of the endothelium to release agents to the blood or brain side following receptor activation, as part of their ‘effector’ function.

News from the brain: the GPR124 orphan receptor directs brain-specific angiogenesis
Phase 1
Activation du glucose
2 ATP
2 ADP
Glucose → Fructose-1,6-diphosphate

Légende:
● = Atome de carbone
P_i = Phosphate inorganique

Phase 2
Scission du glucose
Dihydroxyacétone phosphate ↔ Glycéraldéhyde phosphate
4 ADP
2 NAD^+
2 Acide pyruvique

Phase 3
Oxydation du glucose et formation d'ATP
4 ATP
2 NADH + H^+
2 acide lactique

Vers le cycle de Krebs (voie aérobie)

Glycolyse
Glycose

2 ADP + 2 P_i
2 ATP

2 NAD^+
2 NADH
2 Acide lactique

CH_3

O

C=O

H-C-OH

+2 H^+

2 Acide pyruvique

Narahro → Pyruvate → Lactate → Lactate
Fragile balance: RNA editing tunes the synapse

Bassil G


Figure 1 Regulation of A-to-I RNA editing by FMRP in Drosophila. (a) The data of Bhogal et al.\textsuperscript{2}, together with other studies, suggest a model in which ADAR and FMRP cooperate in the nucleus to regulate ADAR activity, possibly on double-stranded RNA targets comprising exonic and intronic sequences. (b) In wild-type neurons (left), the amount of RNA editing is tightly controlled or fine-tuned by FMRP, whereas RNA editing is imbalanced and dysregulated in fragile X syndrome (right), as a result of a loss of control at the fulcrum.
Reprogramming in amphibian limb regeneration: A model for study of genetic and epigenetic control of organ regeneration

Nayuta Yakushiji, Hitoshi Yokoyama, Koji Tamura

Astrocyte–neuron lactate transport is required for long-term memory formation


Cell
2011 vol. 144 (5) pp. 8...

Day 1: Training

Mice usually go into the dark compartment because they prefer dark environment. Once entered, however, a foot-shock is delivered through the grid floor.

Day 2: Memory test

Normal mice never go into the dark compartment again.

CaMKIIα(K42R) mice easily go into the dark compartment.
Figure 1. DAB and Isofagomine Disrupt Long-Term Memory

Acquisition (Acq) and retention are expressed as mean latency ± SEM (in seconds, sec). Latency scores, n and detailed statistic are reported in Table S1. See also Figure S1. 

(A) Hippocampal injections of DAB 15 min before IA training had no effect on short-term memory tested at 1 hr after training (n = 7/group). 

(B and C) Hippocampal injections of DAB 15 min before (B) n = 11/group) or immediately after training (C) n = 7-9/group) disrupted long-term memory at 24 hr (Test 1). The disruption persisted 7 days after training (Test 2), and memory did not recover after a reminder shock (Test 3). DAB-injected rats had normal retention after retraining (Test 4).

(D) Hippocampal injections of DAB 24 hr after IA training did not affect long-term memory (n = 8/group).

(E) Hippocampal injections of isofagomine 15 min before training disrupted long-term memory (n = 8-9/group). *p < 0.05.
Figure 2. L-Lactate Rescues the DAB-Induced Memory Impairment

Lactate concentration, latency scores, n and detailed statistic are reported in Table S2.

(A) Dorsal hippocampal extracellular lactate in freely moving rats infused with either vehicle or DAB. Baseline was collected for 20 min before training (0 min, 1) and continued for 50 min. Training resulted in a significant increase in lactate levels compared to baseline (*p < 0.05) that was completely blocked by DAB (#p < 0.05). Data are expressed as % of baseline ± SEM (mean of the first 2 samples set 100%). See also Figure S2.

(B–D) Acquisition (Acq) and retention are expressed as mean latency ± SEM (in seconds, sec).

(B and C) Hippocampal injection of DAB or vehicle in combination with 10 nmol DAB, n = 7/group), 100 nmol L-lactate (C, n = 12/group) or vehicle were performed 15 min before training and memory was tested at 24 hr. 100 nmol but not 10 nmol of L-lactate rescued the memory impairment by DAB (Test 1). The effect persisted at 7 days after training (Test 2).

(D) Hippocampal injections of D-lactate 15 min before training disrupted long-term memory (n = 7–8/group). *p < 0.05.
Figure 3. DAB Impairs In Vivo Hippocampal LTP and the Impairment Is Rescued by L-Lactate

(A) Average Field EPSP data recorded for 120 min posttetanus shows that DAB injection (bar) before high frequency stimulation (arrow) blocks LTP (p < 0.05 versus controls at 120 min, n = 4/group). LTP is abolished in animals receiving an intraperitoneal injection of the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (3mg/kg) 30 min prior to tetanus (open triangles). Inset: Representative EPSP traces were recorded before and 120 min after (indicated by arrows) LTP induction. Left panel, control; right panel, in the presence of DAB.

(B and C) No effect on the relationship between stimulus strength and the size of the postsynaptic response (input-output relationship, B, n = 4/group, p > 0.05) or paired-pulse facilitation (PPF, C, n = 4/group, p > 0.05).

(D) DAB injected 30 min after high frequency stimulation did not affect synaptic potentiation (n = 4/group).

(E) L-lactate reversed the blocking effect of DAB on LTP (n = 4/group).

All data are expressed as mean values ± SEM.
(D–G) Memory acquisition (acq) and retention are expressed as mean latency ± SEM (in seconds, sec).
(D) Hippocampal injections of MCT1-ODN 1 hr before training did not affect short-term memory (n = 7/group).
(E) Hippocampal injection of MCT1-ODN disrupted long-term memory. MCT1- or SC1-ODN were injected 1 hr before training and rats were tested 24 hr after training (Test 1) and 6 days later (Test 2). The memory disruption persisted at Test 2, and memory did not recover following a reminder shock (Test 3). MCT1-ODN amnesic rats showed normal retention after retraining (Test 4) (n = 10–11/group).
(F) L-lactate but not glucose rescued the memory impairment induced by blocking MCT1 expression (n = 7–13/group). MCT1- or SC1-ODN were injected 1 hr before training. L-lactate, glucose or vehicle (PBS) were injected 15 min before training. Rats were tested 24 hr after training (Test 1) and 6 days later (Test 2).
(B–D) Acquisition (acq) and retention are expressed as mean latency ± SEM (in seconds, sec).
(B) Hippocampal injections of MCT2-ODN 1 hr before training did not affect short-term memory tested 1 hr later (n = 8/group).
(C) Hippocampal injections of MCT2-ODN disrupted long-term memory. MCT2- or SC2-ODN were injected 1 hr before training. Rats were tested 24 hr after training (Test 1) and 6 days later (Test 2). The memory disruption persisted at Test 2, and memory did not recover following a reminder foot shock (Test 3). The amnesic rats that received the MCT2-ODN showed normal retention after retraining (Test 4) (n = 8/group).
(D) Neither L-lactate nor glucose rescued the memory impairment induced by MCT2 disruption (n = 6–8/group). MCT2- or SC2-ODN were injected 1 hr before training. L-lactate, glucose or vehicle (PBS) were injected 15 min before training. Rats were tested 24 hr after training (Test 1) and 6 days later (Test 2). *p < 0.05.
Figure 7. Training-Induced Increase of Arc, pCREB, and Pcofilin Are Completely Blocked by DAB and Significantly Rescued by L-Lactate

Mean %, n, and detailed statistic are reported in Table S6.

(A–F) Examples (A) and densitometric western blot analysis of Arc (B), pCREB (C), CREB (D), pcofilin (E), and coflin (F) performed on dorsal hippocampal extracts from trained and untrained rats injected 15 min before training with vehicle, DAB + vehicle or DAB + L-lactate and euthanized 30 min (for Arc) or 20 hr (for all other markers) after training. See also Figure S3.

Arc (B), pCREB (C), and pcofilin (E) expression were significantly increased after training. This increase was completely blocked by DAB and rescued by L-lactate. There is no change in expression of CREB (D) and coflin (F) across samples (n = 4–7/group).

Data are expressed as mean percentage ± SEM of untrained, vehicle-injected control (100%) mean values. All proteins values were normalized to those of actin. *p < 0.05.
Cellular scaling rules for primate brains

Proc Natl Acad Sci USA
2007 vol. 104 (9) pp. 3562–7


Table 1. Comparative cellular composition of the brain of the tree shrew and six primate species

<table>
<thead>
<tr>
<th>Species</th>
<th>Body mass, g</th>
<th>Brain mass, g</th>
<th>Total neurons, $\times 10^6$</th>
<th>Total nonneurons, $\times 10^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tree shrew</td>
<td>172.5 ± 3.5</td>
<td>2.752 ± 0.011</td>
<td>261.40</td>
<td>199.65</td>
</tr>
<tr>
<td>Marmoset</td>
<td>361.0 ± 1.4</td>
<td>7.780 ± 0.654</td>
<td>635.80 ± 115.73</td>
<td>590.74 ± 70.81</td>
</tr>
<tr>
<td>Galago</td>
<td>946.7 ± 102.6</td>
<td>10.150 ± 0.060</td>
<td>936.00 ± 115.36</td>
<td>666.59 ± 63.50</td>
</tr>
<tr>
<td>Owl monkey</td>
<td>925.0 ± 35.4</td>
<td>15.730</td>
<td>1,468.41</td>
<td>1,195.13</td>
</tr>
<tr>
<td>Squirrel monkey</td>
<td>n.a.</td>
<td>30.216</td>
<td>3,246.43</td>
<td>2,075.03</td>
</tr>
<tr>
<td>Capuchin monkey</td>
<td>3,340.0</td>
<td>52.208</td>
<td>3,690.52</td>
<td>3,297.74</td>
</tr>
<tr>
<td>Macaque monkey</td>
<td>3,900.0</td>
<td>87.346</td>
<td>6,376.16</td>
<td>7,162.90</td>
</tr>
<tr>
<td>Variation, macaque/marmoset</td>
<td>10.8×</td>
<td>11.2×</td>
<td>10.0×</td>
<td>12.1×</td>
</tr>
</tbody>
</table>

Species ordered by increasing brain size. Values are mean ± SD. n.a., not available.
Table 1. Brain weights and glia–neuron ratios for layer II/III of prefrontal area 9L (species mean)

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>Brain weight, g</th>
<th>Glia–neuron ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Homo sapiens</em></td>
<td>6</td>
<td>1,373.3</td>
<td>1.65</td>
</tr>
<tr>
<td><em>Pan troglodytes</em></td>
<td>6</td>
<td>336.2</td>
<td>1.20</td>
</tr>
<tr>
<td><em>Gorilla gorilla</em></td>
<td>2</td>
<td>509.2</td>
<td>1.21</td>
</tr>
<tr>
<td><em>Pongo pygmaeus</em></td>
<td>2</td>
<td>342.7</td>
<td>0.98</td>
</tr>
<tr>
<td><em>Hylobates muelleri</em></td>
<td>1</td>
<td>101.8</td>
<td>1.22</td>
</tr>
<tr>
<td><em>Papio anubis</em></td>
<td>2</td>
<td>155.8</td>
<td>0.97</td>
</tr>
<tr>
<td><em>Mandrillus sphinx</em></td>
<td>1</td>
<td>159.2</td>
<td>1.02</td>
</tr>
<tr>
<td><em>Macaca maura</em></td>
<td>6</td>
<td>92.6</td>
<td>0.84</td>
</tr>
<tr>
<td><em>Erythrocebus patas</em></td>
<td>2</td>
<td>102.3</td>
<td>1.09</td>
</tr>
<tr>
<td><em>Cercopithecus kandti</em></td>
<td>1</td>
<td>71.6</td>
<td>1.15</td>
</tr>
<tr>
<td><em>Colobus angolensis</em></td>
<td>1</td>
<td>74.4</td>
<td>1.20</td>
</tr>
<tr>
<td><em>Trachypithecus francoisi</em></td>
<td>1</td>
<td>91.2</td>
<td>1.14</td>
</tr>
<tr>
<td><em>Alouatta caraya</em></td>
<td>1</td>
<td>55.8</td>
<td>1.12</td>
</tr>
<tr>
<td><em>Saimiri boliviensis</em></td>
<td>1</td>
<td>24.1</td>
<td>0.51</td>
</tr>
<tr>
<td><em>Aotus trivirgatus</em></td>
<td>1</td>
<td>13.2</td>
<td>0.63</td>
</tr>
<tr>
<td><em>Saguinus oedipus</em></td>
<td>1</td>
<td>10.0</td>
<td>0.46</td>
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<tr>
<td><em>Leontopithecus rosalia</em></td>
<td>2</td>
<td>12.2</td>
<td>0.60</td>
</tr>
<tr>
<td><em>Pithecia pithecia</em></td>
<td>1</td>
<td>30.0</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Evolution of increased glia–neuron ratios in the human frontal cortex


Table 2. Glia–neuron ratios in layer II/III of different areas in frontal cortex

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>Area 4</th>
<th>Area 9L</th>
<th>Area 32</th>
<th>Area 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homo sapiens</td>
<td>6</td>
<td>2.19 (0.06)</td>
<td>1.65 (0.09)</td>
<td>1.63 (0.09)</td>
<td>1.55 (0.18)</td>
</tr>
<tr>
<td>Pan troglodytes</td>
<td>6</td>
<td>1.54 (0.05)</td>
<td>1.20 (0.06)</td>
<td>0.91 (0.09)</td>
<td>1.24 (0.13)</td>
</tr>
<tr>
<td>Macaca maura</td>
<td>6</td>
<td>1.29 (0.09)</td>
<td>0.84 (0.03)</td>
<td>0.68 (0.05)</td>
<td>0.95 (0.06)</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard error).

![Graph showing glia–neuron ratios in different areas of the frontal cortex](image)
Evolution of the neocortex: a perspective from developmental biology

Rakic P
CRITICAL PERIOD AND MATURATION OF LOCAL GABAERGIC CIRCUITS

Critical period

Postnatal days

P12-14 Eye opening

plasticity

P8  P18  P28  >P50

GAD67 decrease
GAD67 increase

Pre-CP
Immature
Non plastic

CP
Mature
Plastic

Adult
Consolidated
Non plastic
Reversing Neurodevelopmental Disorders in Adults

Dan Ehninger,¹ Weidong Li,¹ Kevin Fox,² Michael P. Stryker,³ and Alcino J. Silva¹,*

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²Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF10 3US, UK
³Department of Physiology, W.M. Keck Foundation Center for Integrative Neuroscience, University of California, San Francisco, San Francisco, CA 94143-0444, USA
*Correspondence: silva@ucla.edu
DOI 10.1016/j.neuron.2006.12.007
**Figure 1** | Neurodevelopmental model of schizophrenia. a, Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing through the first two post-natal decades. The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the progressive reduction of grey-matter volume observed with longitudinal neuroimaging. Beneath this observed overall reduction, local changes are far more complex. Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis. b, The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.
Blue diamond: Nduf family
Red triangles: Atp5 family
Green dots: Cox6 family
A novel (ancient?) signaling mechanism
Central visual pathway and critical period for binocular vision
Otx2 expression in PV cells parallels critical period

Sugiyama et al. *Cell* 2008
Otx2 expression, as PV maturation, is activity-dependent

Sugiyama et al. Cell 2008
AN OTX2 MOTIF IS NECESSARY FOR ITS BINDING TO CORTICAL CELLS

(a) Otx2 motif and domains
(b) Peptide constructs
(c) VC expression with AP-NtHD
(d) VC expression with AP-NtHD + Otx2
(e) VC expression with AP-Nt(AA)HD
(f) VC expression with AP-HD
(g) VC expression with AP-NtHD
(h) VC expression with AP-Nt(AA)HD
(i) VC expression with AP-NtHD + RK-peptide
(j) VC expression with AP-NtHD + AA-peptide
(k) WFA expression with vehicle
(l) WFA expression with vehicle + ChABC
(m) AP-NtHD expression
(n) AP-NtHD expression
RK-PEPTIDE INFUSION IMPAIRS ENDOGENOUS Otx2 TRANSFER INTO V1

Beurdeley, Spatazza et al., in revision
RK-PEPTIDE REOPENS PLASTICITY IN THE ADULT

> P 60

D0  D2  D6  D7

Normal adult mouse visual acuity :
≈ 0.45 – 0.6

Beurdeley, Spatazza et al., in revision
RECOVERY FROM AMBLYOPIA

Recording site

Contra eye  Ipsi eye

Visual acuity (cyc/deg)

RK only  RK+recovery (7-21d)

Recording

Infusion

LTMD

P19  P33  P60  P67  P74-95
Otx2 is expressed in the choroid plexus where it can be specifically recombined

Spatazza et al. in preparation
Sacrifice 14 days after a single CRE-Tat injection.

RECOMBINING OTX2 IN THE CHOROID PLEXUS REDUCES ITS CORTICAL CONTENT AND REDUCES PV CELL MATURATION MARKERS

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>CRE-Tat</th>
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<tbody>
<tr>
<td><img src="image1.jpg" alt="a" /></td>
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<tr>
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<td><img src="image6.jpg" alt="f" /></td>
<td><img src="image6.jpg" alt="f" /></td>
</tr>
</tbody>
</table>

Sacrifice 14 days after a single CRE-Tat injection.
RECOMBINING OTX2 IN THE ADULT PLEXUS REOPENS PLASTICITY

Ottx2<sup>flox/flox</sup> mice > P60

CRE-Tat or vehicle injection

Recording site

Contra eye

Lpsi eye

A

CRE-MD

Cre+MD

VEP amplitude (μV)

0.1

0.32

0.51

(cyc/deg)

D0

D14

D18

STMD