Cours du 10 octobre 2011
**A**
Graded expression in embryonic neocortex

**B**
Predicted / observed shifts in markers of area identities

**C**
Organization of neocortex

- **wildtype**
- **Emx2 -/-**
- **Sey/Sey**
- **Emx1 -/-**
1 extra emx2 copy

1 emx2 copy missing
Elimination de Otx2 dans le domaine En1

Otx2 regulates the extent, identity and fate of neuronal progenitor domains in the ventral midbrain


Development 2004 vol. 131 (9) pp. 2037–48

TN Trochlear    OM Oculomotor
Altered dopaminergic innervation and amphetamine response in adult Otx2 conditional mutant mice


Mol Cell Neurosci
2006 vol. 31 (2) pp. 293-302

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**Diagram:**
- **Cortex cerebri**
- **PUT**
- **GPi**
- **GPe**
- **STN**
- **SN**
- **THA**

**Legend:**
- **GPe** — Globus pallidus externus
- **GPi** — Globus pallidus internus
- **SN** — Substantia nigra
- **STN** — Nucleus subthalamicus
- **THA** — Thalamus

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**Graphs:**
- **A**
  - En1<sup>cre+/+</sup> Amph
  - En1<sup>cre+/+</sup> Saline
  - En1<sup>cre+/+</sup>; Otx2<sup>fox/fox</sup> Amph
  - En1<sup>cre+/+</sup>; Otx2<sup>fox/fox</sup> Saline

- **B**
  - En1<sup>cre+/+</sup> Amph
  - En1<sup>cre+/+</sup> Saline

**Sector Crossings (5 min):**
- **Time (min):** 0, 5, 10, 15, 20, 25, 30
- **Sector Crossings:**
  - **Saline:**
  - **Amph:**

**Sector Crossings (30 min):**
- **Saline:**
- **Amph:**

**Significance:**
- **#**
- ****
- ****
- ****
Location and Size of Dopaminergic and Serotonergic Cell Populations Are Controlled by the Position of the Midbrain–Hindbrain Organizer

Claude Broccoli,1,2 Daniela M. Vogl Weberhorn,1,2 Massimo Signore,2 Inge Stöhr,1 Matthias Oesterheld,1 Yania Broccoli,1 Dario Acampora,2 Antonio Simeone,2 and Wolfgang Wurst1

The Journal of Neuroscience, April 13, 2016 • 36(15):3100–3110 • www.jneurosci.org
CRITICAL ROLE OF THE EMBRYONIC MID–HINDBRAIN ORGANIZER IN THE BEHAVIORAL RESPONSE TO AMPHETAMINE AND METHYLPHENIDATE
Table 1 | Boundaries in the developing vertebrate brain

<table>
<thead>
<tr>
<th>Regional interface</th>
<th>Cell lineage restriction</th>
<th>Signalling function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior neural border (ANB)</td>
<td>?</td>
<td>+ (anti-WNT, FGFs)</td>
</tr>
<tr>
<td>Pallial–subpallial boundary (PSB)</td>
<td>+ (Ventricular zone only)</td>
<td>None detected</td>
</tr>
<tr>
<td>Telencephalon–diencephalon</td>
<td>–</td>
<td>None detected</td>
</tr>
<tr>
<td>Zona limitans intrathalamica (ZLI)</td>
<td>+ (Two boundaries with lineage restriction anteriorly and posteriorly; does not extend into roof plate)</td>
<td>+ (SHH, WNTs?, FGFs?)</td>
</tr>
<tr>
<td>Thalamus–pretectum</td>
<td>–</td>
<td>None detected</td>
</tr>
<tr>
<td>Diencephalic–midbrain boundary (DMB)</td>
<td>+</td>
<td>None detected</td>
</tr>
<tr>
<td>Midbrain–hindbrain boundary (MHB)</td>
<td>+ (Might be leaky; possibly two boundaries dorsally)</td>
<td>+ (FGFs, WNT1)</td>
</tr>
<tr>
<td>Rhombomeres</td>
<td>+ (Except floor plate; ventricular zone only)</td>
<td>+ (WNT1, WNT3A?, WNT8B?, WNT10B?)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>–</td>
<td>Anteroposterior: –</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorsoventral: +</td>
</tr>
</tbody>
</table>

FGF, fibroblast growth factor; SHH, sonic hedgehog.
The development of the thalamic motor learning area is regulated by Fgf8 expression.
A Wnt1-regulated genetic network controls the identity and fate of midbrain-dopaminergic progenitors in vivo


Development
2006 vol. 133 (1) pp. 89–98

Genetic networks controlling the development of midbrain dopaminergic neurons

Prakash N, Wurst W

The Journal of Physiology
2006 vol. 575 (Pt 2) pp. 403–10
En1 and Wnt signaling in midbrain dopaminergic neuronal development

Alves Dos Santos MT, Smidt M

Neural Dev
2011 vol. 6 pp. 23

Figure 1 Spatial and temporal developmental stages leading to mesodiencephalic dopaminergic neurogenesis. (A) Sagittal and coronal
En1 and Wnt signaling in midbrain dopaminergic neuronal development

Alves Dos Santos MT, Smidt M

Figure 2 The impact of the engrailed genes in the development of the central nervous system and the mesodiencephalic dopaminergic system (A) Engrailed proteins are key players in diverse processes during embryonic development of the central nervous system (CNS), including patterning, axonal guidance and neuron specification. (B) Engrailed proteins are essential in mesodiencephalic dopaminergic (mdDA) neuron development from an early stage, where they are involved in morphogenesis and mdDA neurogenesis, and in the adult, where they play a role in mdDA neuron maintenance. E, embryonic day.

Figure 3 Canonical Wnt signaling mechanism. (1) Wnts bind to

Figure 4 Wnt signaling during the central nervous system and mesodiencephalic dopaminergic neuron development (A) Wnt signaling
Spatial Analysis of Expression Patterns Predicts Genetic Interactions at the Mid-Hindbrain Boundary

Dominik M. Wittmann, Florian Blöchl, Dietrich Trumbach, Wolfgang Wurst, Nilima Prakash, Fabian J. Theis

PLoS Computational Biology | Volume 5 | Issue 11 | e1000569

[Image of a diagram showing expression patterns and genetic interactions]
Otx2 expression is restricted to dopaminergic neurons of the ventral tegmental area in the adult brain.
Engrailed genes are cell-autonomously required to prevent apoptosis in mesencephalic dopaminergic neurons


Fig. 1. Loss of midbrain dopaminergic neurons in engrailed double mutant embryo by apoptosis. (A) E12 whole-mount preparation of isolated neural tube. TH-positive neurons are located in the mesencephalic flexure (arrow) of wild-type (A) and mutant (A') embryo. The TH domain in the mutant is smaller than the wild type and there are no axons heading in rostral direction. (B) Midsagittal sections of E14 embryos. In the wild type (B) TH+/DA neurons have continued to differentiate and start to form the SNC and VTA (arrow). In the mutant embryos (B'), no TH-positive cells are detectable in the ventral midbrain. Additionally, the anlage for the cerebellum (Cb), inferior colliculus (IC) and superior colliculus (SC) are absent. (C-E) Transverse sections of E12 En1+/tlz;En2−/− ventral
Progressive loss of dopaminergic neurons in the ventral midbrain of adult mice heterozygote for Engrailed1

Sonnier L, Le Pen C, Hartmann A, Bizot JC, Trovero F, Krebs MO, Prochiantz A

J Neurosci
2007 vol. 27 (5) pp. 1063-71
The transcription factor orthodenticle homeobox 2 influences axonal projections and vulnerability of midbrain dopaminergic neurons


Brain
2010 vol. 133 (Pt 7) pp. 202...

Otx2 controls neuron subtype identity in ventral tegmental area and antagonizes vulnerability to MPTP

Di Salvio M, Di Giovannantonio LG, Acampora D, Prosperi R, Omodei D, Prakash N, Wurst W, Simeone A

Nature Neuroscience
2010 vol. 13 (12) pp. 1481–8

Altered dopaminergic innervation and amphetamine response in adult Otx2 conditional mutant mice

Progressive loss of dopaminergic neurons in the ventral midbrain of adult mice heterozygote for Engrailed1

Sonnier L, Le Pen C, Hartmann A, Bizot JC, Trovero F, Krebs MO, Prochiantz A

J Neurosci
2007 vol. 27 (5) pp. 1063-71
Mitochondria in Neuroplasticity and Neurological Disorders

Mark P. Mattson,¹,* Marc Gleichmann,¹ and Aiwu Cheng¹
Otx2 controls neuron subtype identity in ventral tegmental area and antagonizes vulnerability to MPTP

Di Salvo M, Di Giovannantonio LG, Acampora D, Prosperi R, Omodei D, Prakash N, Wurst W, Simone A


Engrailed protects mouse midbrain dopaminergic neurons against mitochondrial complex I insults


Figure 1  A dopaminergic nerve terminal, before and after Engrailed treatment. Left, normally, MPTP and rotenone produce selective dopaminergic degeneration by binding to mitochondrial complex I and generating reactive oxygen species and inhibiting respiration. 6-Hydroxydopamine (6-OHDA) and α-synuclein may also exert their toxicities, in part, by targeting mitochondria. Right, after treatment with Engrailed, the homeobox protein enters dopaminergic neurons and binds the mRNA translational machinery, where it enhances the synthesis of the Ndufs1 subunit of complex I. Under these conditions, nigrostriatal neurons become resistant to the classical complex I inhibitors (MPTP and rotenone), as well as to 6-OHDA and α-synuclein. In addition, upregulation of Ndufs1 is also responsible, by an unknown mechanism, for elevating dopamine. Solid arrows indicate known toxic effects of rotenone and MPTP on complex I; dashed arrows indicate potential direct or indirect effects of 6-OHDA and α-synuclein on complex I.
Model-based gene selection shows engrailed 1 is associated with antipsychotic response

Webb BT, Sullivan PF, Skelly T, van den Oord EJ

Haplotype analysis of the engrailed-2 gene in young-onset Parkinson's disease

Rissling I, Strauch K, Höft C, Oertel WH, Möller JC

Association of transcription factor polymorphisms PITX3 and EN1 with Parkinson's disease


Autism-associated haplotype affects the regulation of the homeobox gene, ENGRAILED 2


Intrinsic single nucleotide polymorphisms of engrailed homeobox 2 modulate the disease vulnerability of autism in a Han Chinese population

Haplotype analysis of the engrailed-2 gene in young-onset Parkinson's disease

Rissling I, Strauch K, Höft C, Oertel WH, Möller JC

Department of Neurology, Philipps University, Marburg, Germany.