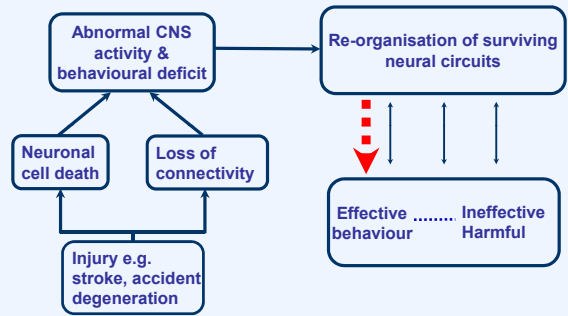


Can the brain be repaired after injury? Rebuilding neural circuits using the olivocerebellar path as a model

Rachel Sherrard

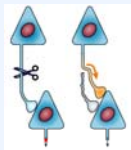


Central Nervous System (CNS) Injury



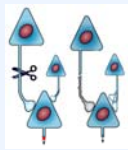
Innate Reorganisation Post Injury

1. Axonal regeneration



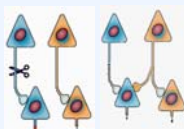
- Optimal
- Cell-specific
- Does not happen

2. Terminal sprouting



- Terminal sprouting
- Heterologous
- ? functional benefit

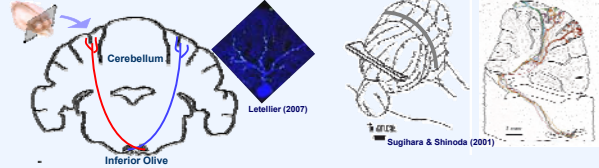
3. Collateral reinnervation



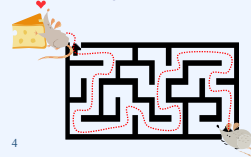
- Long-distance growth
- Homologous
- Mainly developing CNS

Model: Rat Olivocerebellar System

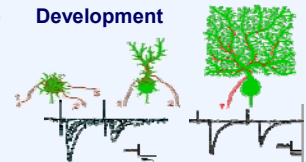
Structure



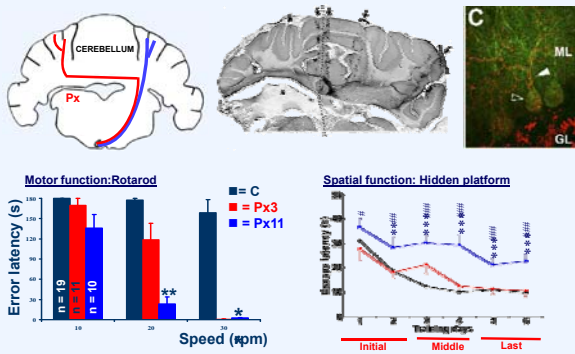
Function (motor & navigation)



Development

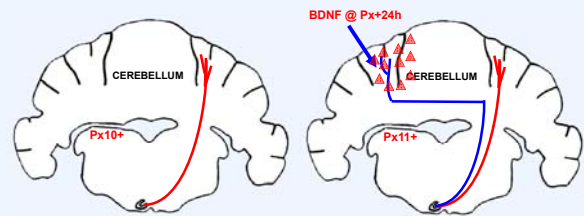


Olivocerebellar reinnervation



5

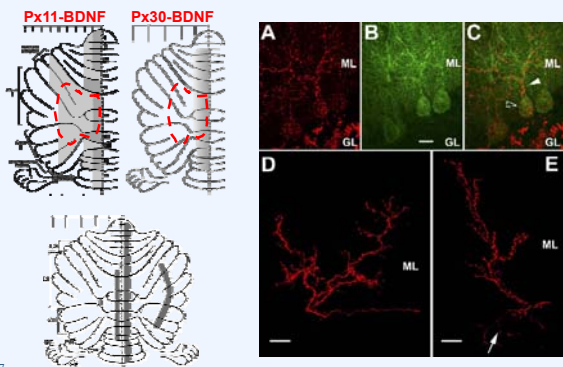
But.... Can we recreate it?



- Replicate developmental status
 - ↓ inhibitory environment
 - ↑ growth promotion
- Px > P10 + GF (BDNF, NT3 & IGF-1) @ +24hrs

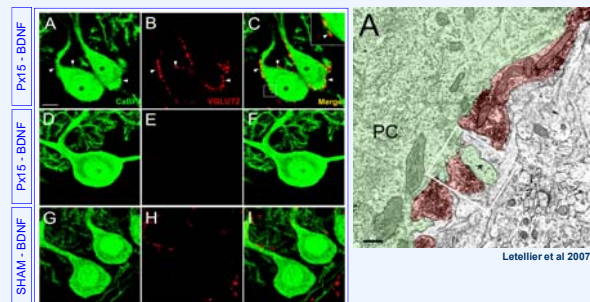
6

Growth factor induced reinnervation



7

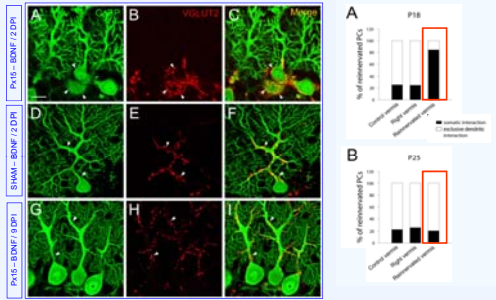
Reinnervating axon-target interactions



Reinnervating CFs recapitulate perisomatic spine induction

8

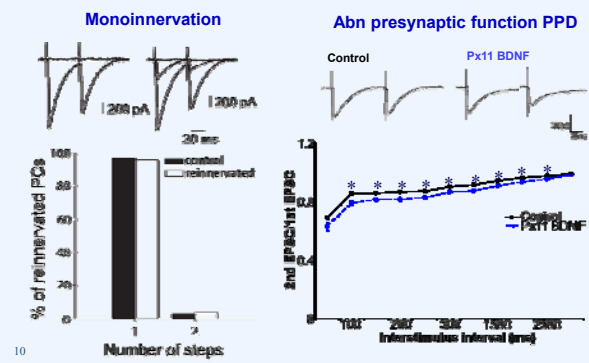
Reinnervating axon-target interactions



Somato-dendritic translocation recapitulates normal development

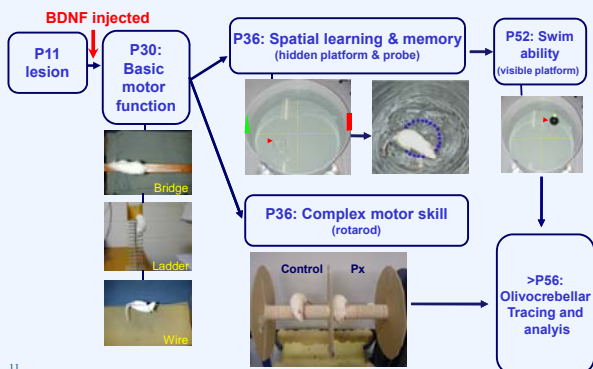
9

Reinnervating synaptic function



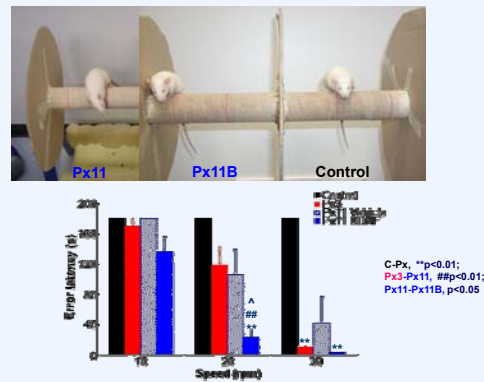
10

BDNF-induced reinnervation: function



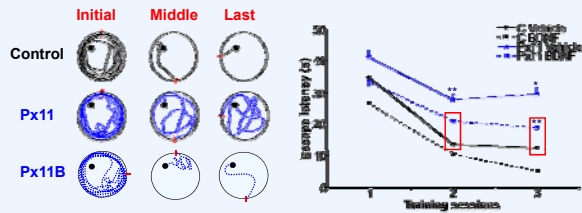
11

BDNF-induced reinnervation: Behaviour



12

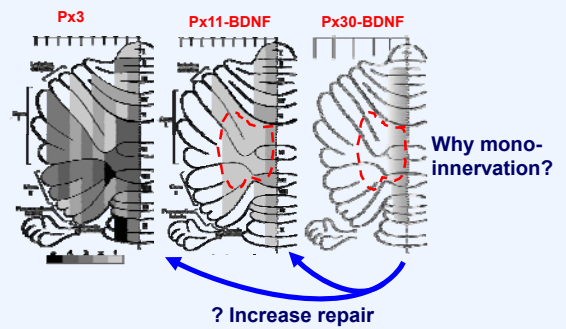
BDNF-induced reinnervation: Behaviour



Visible platform test: all groups orientate and swim to platform
 Motor **AND** spatial improvement
 Behaviour correlates with reinnervation

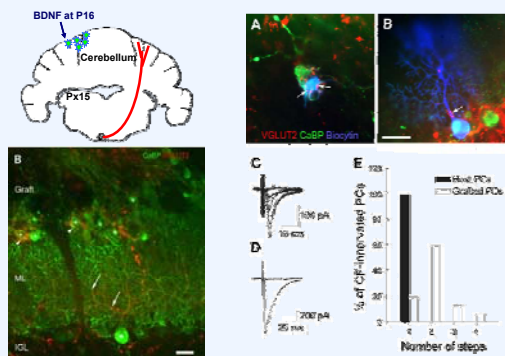
13

Questions.....



14

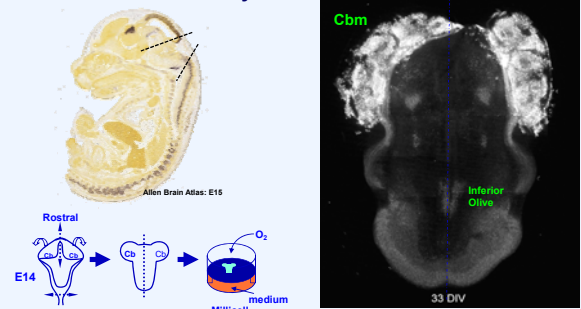
Mono-innervation: target maturation



15

Mono-innervation: axon maturation

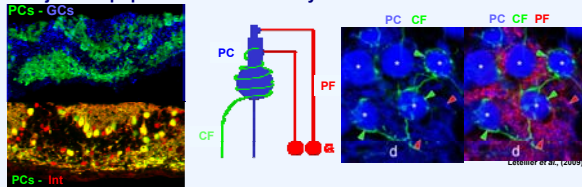
In vitro olivocerebellar system



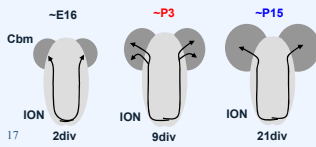
16

In vitro: a genuine model

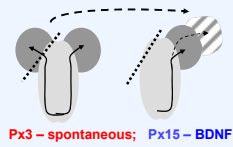
1. Major cell populations and circuitry



2. Main developmental stages

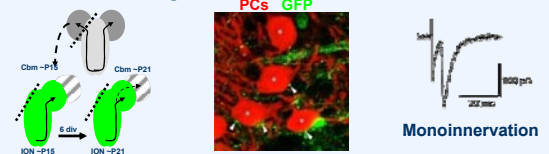


3. Reinnervation in vitro

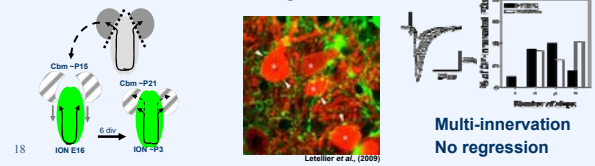


Mono-innervation: axon maturation

Mature axon & target



Immature axon, mature target

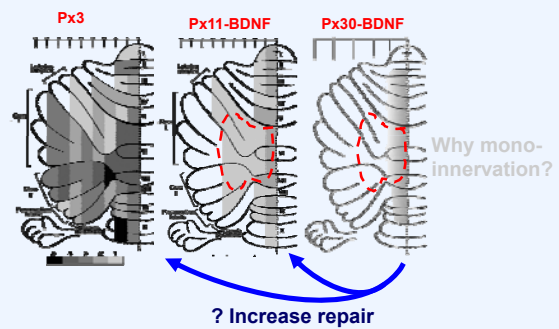


Effect of Maturation on Repair

Axon	Target	Innervation	Outcome
Immature			
Mature			

19

Questions.....



20

Increasing reinnervation

- **Focussed: homotypic for fine skills**

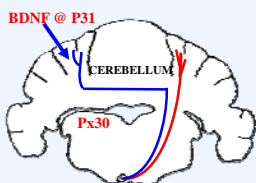
- **Problems**

- Altered gene expression: NB “off”
 - Unfocussed growth

- **Rehabilitation**

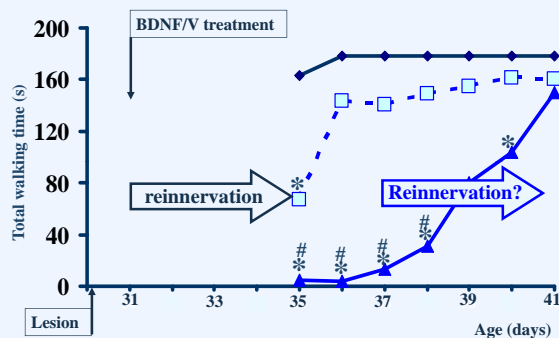
- **Lesion & treatment:**

- Px30 + BDNF/vehicle @ 24hrs
 - Motor activity from +5 days
 - Rotarod: 30min/day x28 days



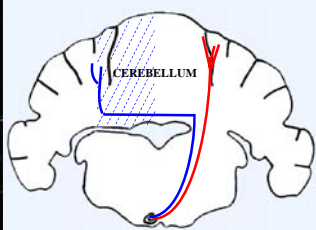
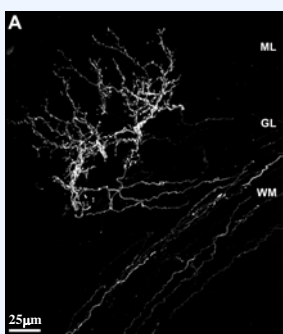
21

Exercise/training induces reinnervation



22

Reinnervation after exercise



23

Need more than training....

- **Training problems**

- Compliance
 - Skills do not transfer

- **Complex activity**

- motivation

- **Psychomotor stimulus**

- Enriched environment
 - Virtual reality

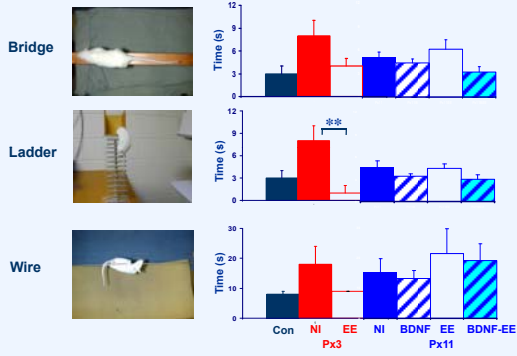
- **Lesion + EE**

- Behaviour
 - Anatomy

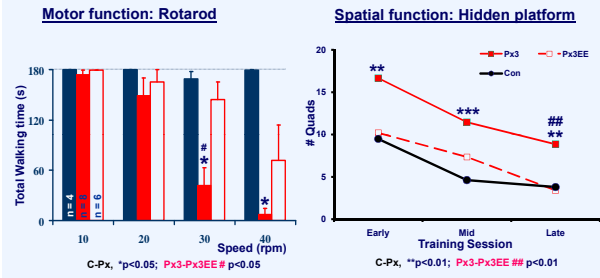


24

Basic motor function: minor effect of EE

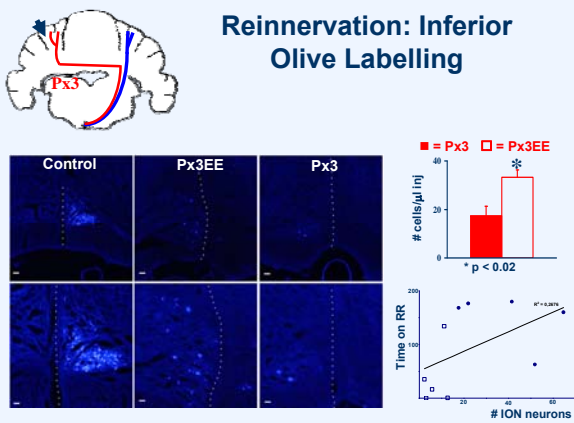


Environment Enrichment Improves Function



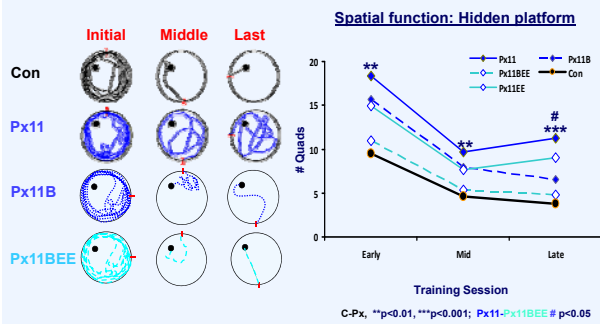
26

Reinnervation: Inferior Olive Labelling



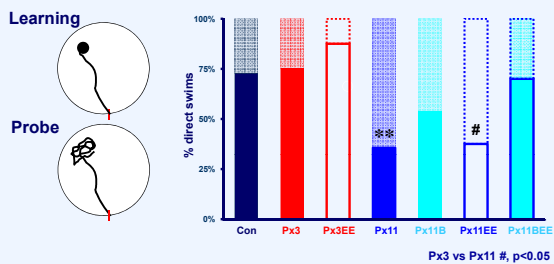
27

Enrichment & BDNF: additive effect



28

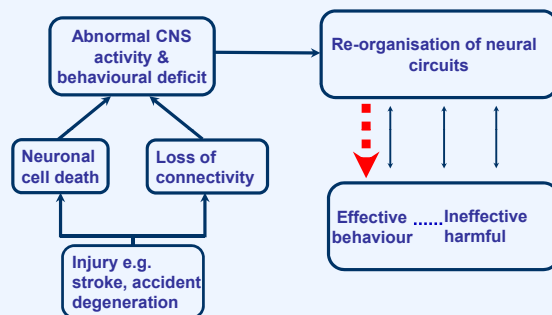
Spatial learning: memory



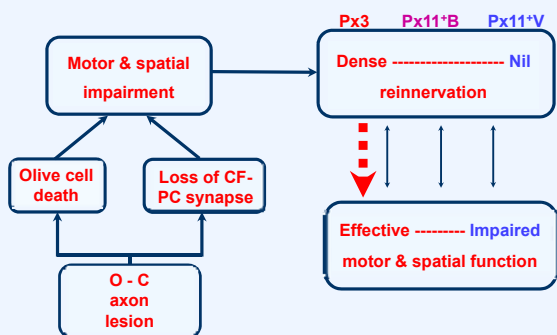
Visible platform test:
 • all groups orientate and swim to platform

29

Central Nervous System (CNS) Injury



Central Nervous System (CNS) Injury



Can the brain be repaired after injury?

Skilled function improvement

Homotypic reconnection

Complex rehabilitation

- ↑ circuit repair
- long-distance collaterals

But..... care

- young and old do not interact normally



Thank you!

Kirsty Dixon
Sally Speare
Melina Willson
Catriona McEInea
Mathieu Letellier

Jean Mariani, NPA
Ann Lohof, NPA
Adrian Bower, UNDA

Amgen Inc



Ramaciotti Foundation



33