Brain Reconstruction: the next biomedical breakthrough, or a biological impossibility?

Jack Price
Centre for the Cellular Basis of Behaviour
Institute of Psychiatry, KCL.
1. Brain Repair with stem cells

2. The Impossibility of Brain Reconstruction?

3. A way forward?
Brain Repair: the unmet medical need

- Stroke
- Traumatic Brain Injury
- Alzheimer’s disease
- Parkinson’s disease
- Batten’s disease
- Cerebral palsy
Stroke

- **150,000** Britons per year
- Third most common cause of death in the USA & Europe
- Most common cause of severe disability
- A major area of unmet medical need.
Brain Reconstruction: the fantasy?

When Will We Be Able to Build Brains Like Ours?
Sooner than you think -- and the race has lately caused a 'catfight'

By Terry Sejnowski | Tuesday, April 27, 2010 | 47 comments

"It is not impossible to build a human brain and we can do it in 10 years."

Henry Markham
Human Enhancement

• Positive

“...These same powers that can repair and replace diseased or damaged tissue may, in a healthy individual, augment normal functioning. That is why regenerative medicine may never be simply or merely therapeutic, but is likely always to have an enhancing dimension.”

Harris (2007)
Human Enhancement

- Negative

“…there is at least a theoretical prospect that these cells will alter the recipients’ cognition, mood, and behaviour—brain functions that are central to our concept of the self (especially to our personality, character, and agency).”

“ That early human trials of CBIs for neurological conditions must monitor subjects for changes in cognition, mood, and behaviour.”

Duggan et al (2009) AM J BIOETHICS
Approaches to Brain Reconstruction

- Endogenous neurogenesis
- Stem cell transplantation
- Stem cells ‘plus’
Sites of adult neurogenesis

- Human
- Rat

**Hippocampus**
**Sub-ependymal zone**
A stem cell transplantation strategy

Neural Stem Cells....
Neural Stem Cells...

- Conditional immortalisation
- Expansion
- Retention of multipotentiality
- Differentiation

4OH-Tamoxifen +

Stroke

CTX0E03

Sticky Tape

Mike Modo
Paul Stroemer.
World's first stem cell trial for stroke patients

Doctors have injected stem cells into the brain of a British stroke patient in the world's first trial of its kind.

By Stephen Adams, Medical Correspondent 2:23PM GMT 16 Nov 2010

The elderly man was injected with roughly two million neural stem cells at Southern General Hospital in Glasgow. They hope the stem cells will help the man recover from his stroke, by transforming themselves into mature neurons and also stimulating the brain to harness its own regenerative powers.

His progress will be monitored over the next two years.

The method controversially uses neural stem cells, which are those taken from the nascent brain of a discus foetus.

Stem cells injected into the brain of a stroke patient in world first

Researchers hope the brain stem cells will stimulate the growth of new neurons and reduce inflammation caused by the stroke.

Ian Sample, science correspondent guardian.co.uk, Tuesday 16 November 2010 13:03 GMT

The stem cells will release chemicals that may help heal brain damage resulting from the stroke. Photograph: Bbs United/Getty Images
Problem:
The cells work…

...but not the way we anticipated
phMRI of D2-agonist bromocriptine

Control
Lesion
Transplant

BOLD—blood oxygen level dependant phMRI

Toby Roberts
Mike Modo
Steve Williams
More young neurons in following a stroke and graft.

Zahra Hassani
Sandrine Thuret
Paul Stroemer
The Good News
…we have a novel potential therapy…

The Bad News
…it is NOT brain reconstruction

(except in a narrow sense)
How close are we to true Brain Reconstruction?

...not very.

Problems:

• Conceptual: how to build brain tissue?
• Regulatory: how to generate a therapeutic?
Technical/Conceptual issues

1. We don’t know how to build brain tissue

This is not development, and the brain has no blastema

- Cell fate
- Building circuits
- Embryonic parameters
- Ephemeral factors
- Emergent properties
Technical/Conceptual issues

2. How to build a brain reconstruction device?

- A fully constructed device?
- A self-assembly system?
Regulatory Issues

How would you test safety and efficacy of such a device?

• The device would have to integrate into intact brain without causing neuropathic pain, seizures, dystonia, or tissue rejection

• The device would mimic and enhance human brain function, yet deliver efficacy in an animal model

Consider
• The Stanfield experiment
• Human cortical connectivity
The ‘Stem Cell Plus’ strategy

Poly(lactic-co-glycolic acid)

Engineering Scaffold Particles
The ‘stem cell plus’ strategy
A way forward? pluripotent stem cells
Shinya Yamanaka
Induced pluripotent cells (iPSCs) from human hair

The four ‘Yamanaka Factors’

Keratinocytes

Hair sample

iPS Colonies

Neural stem cells

Neurons

Induced pluripotent cells (iPSCs) from human hair
Corticogenesis
Corticogenesis

...or more like