VIRTUAL ISPRM 2021 Congress

The use of drugs to boost post-stroke motor recovery

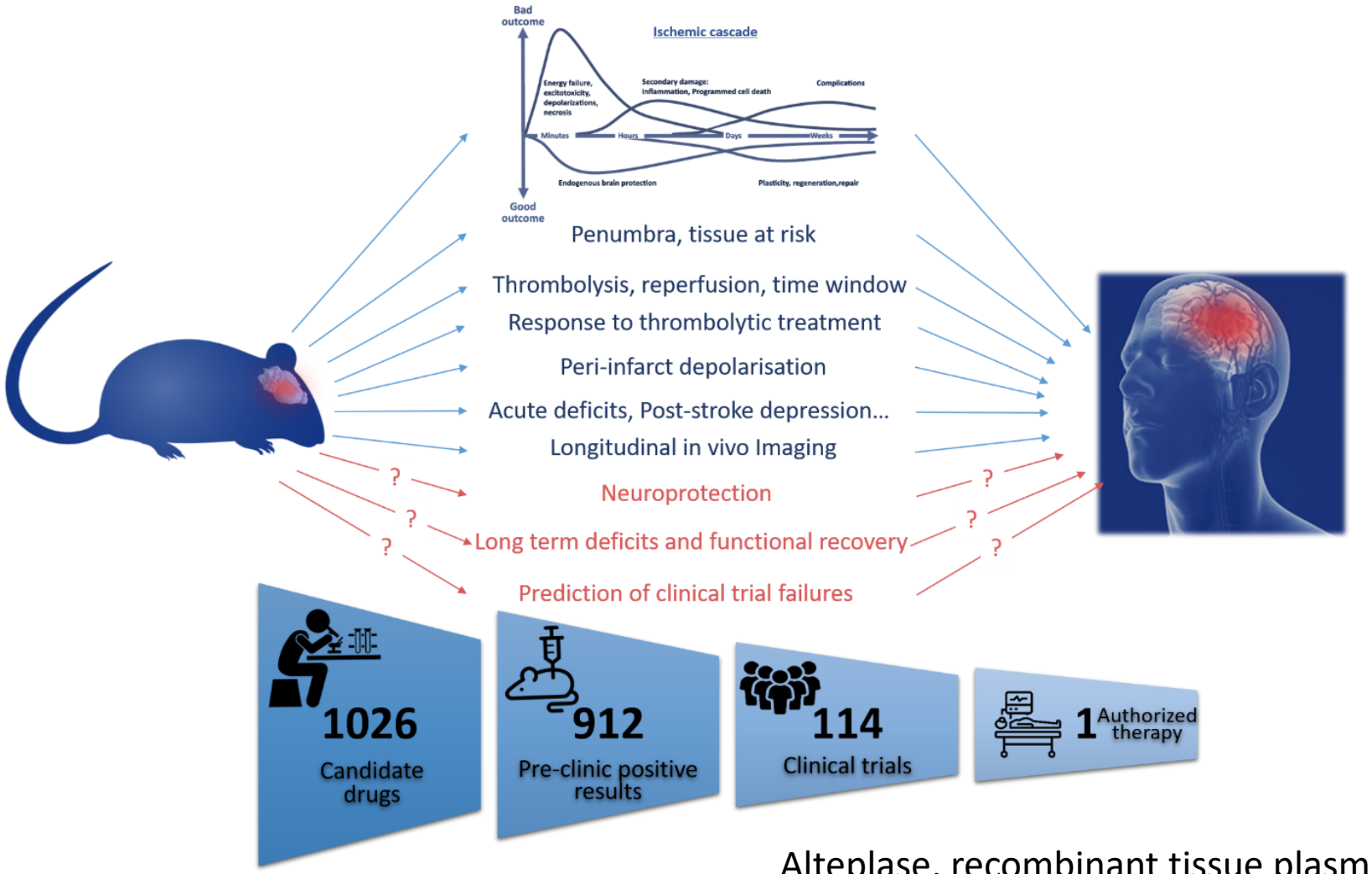
Isabelle LOUBINOUX
Toulouse

ToNIC, Toulouse NeuroImaging Center, Université de Toulouse

Inserm

ToNIC Toulouse NeuroImaging Center
UMR1214 iDream Team

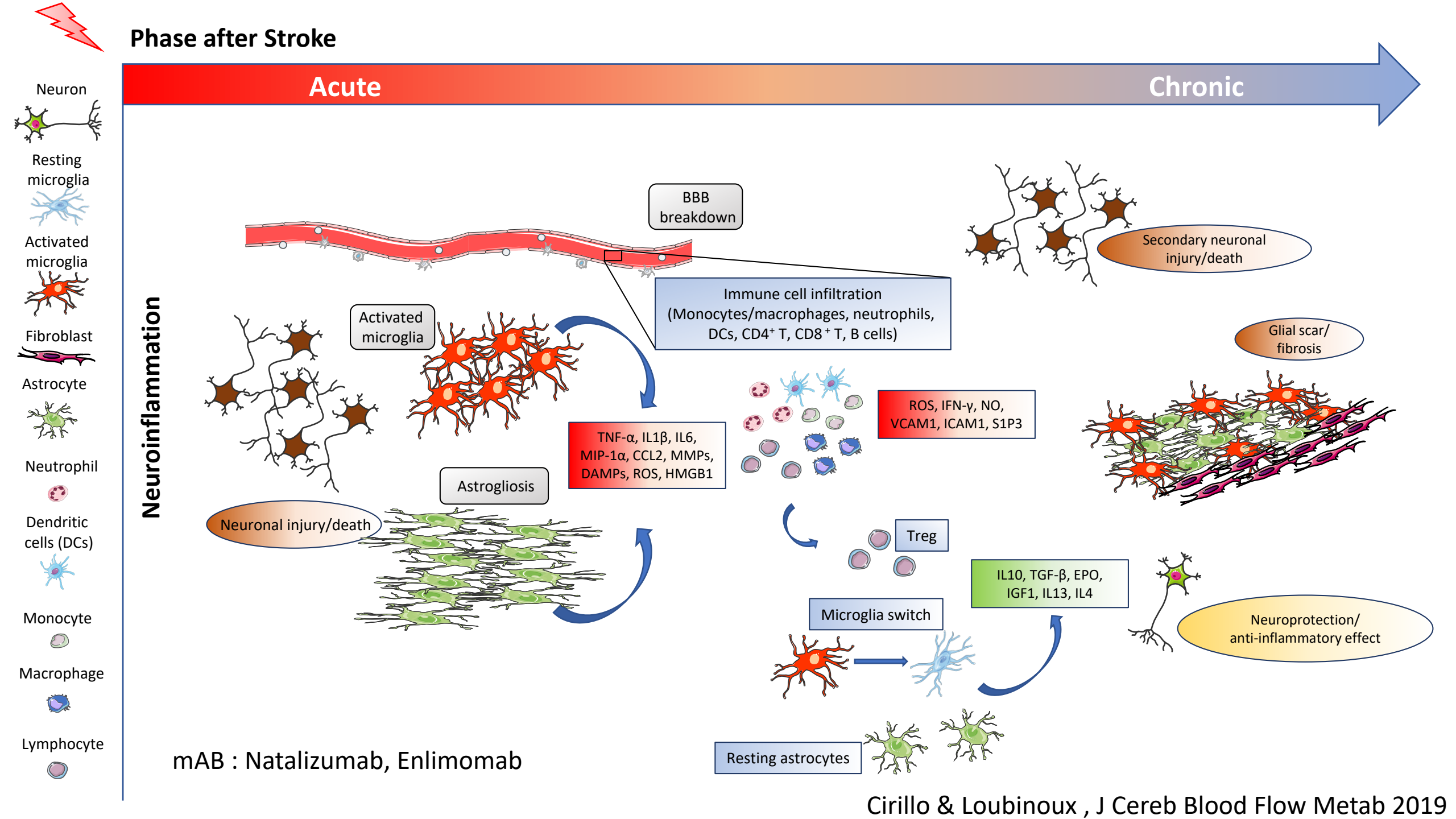
Drugs post-stroke



Alteplase, recombinant tissue plasminogen activator (rt-PA)

➥ Thrombolysis and recanalisation in the acute phase

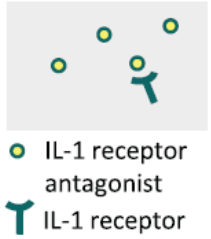
http://www.strokalliance.com



Cirillo & Loubinoux , J Cereb Blood Flow Metab 2019

Acute phase of stroke

Difficult to find a balanced strategy between the 'good' inflammation / 'bad' inflammation

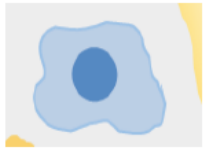


Therapeutic strategies targeting IL-1-induced inflammation

Recombinant human IL-1 receptor antagonist, rhIL1-Ra

Positive results in a Phase II clinical trial (intravenous administration) (Emsley et al., 2005)

Not beneficial in a Phase II clinical trial (subcutaneous administration) **(SCIL-STROKE)** (Smith et al., 2018)



Therapeutic strategies targeting microglial activation

Minocycline

Positive results in two Phase II clinical trials (Lampl et al., 2007; Padma Srivastava et al., 2012)

Phase IV clinical trial stopped for futility (**NeuMAST**) (Kohler et al., 2013)

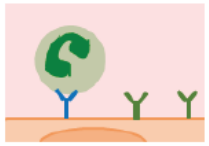
Therapeutic strategies targeting endothelial selectins

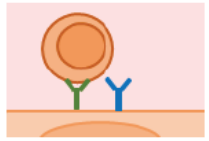
Enlimomab (mouse anti-ICAM-1)

Worse stroke outcome in a Phase III clinical trial (Enlimomab Acute Stroke Trial Investigators, 2001)

E-selectin tolerance

Results from Phase II clinical trial not disclosed (http://clinicaltrials.gov/show/NCT00012454)





Therapeutic strategies targeting leukocyte infiltration

UK-279, 276 (Recombinant neutrophil inhibitory factor, blocking its interaction with ICAM-1) **(ASTIN)**

Phase II clinical trial stopped for futility (Krams et al., 2003)

Hu23F2G (Humanized monoclonal antibody against neutrophil CD11/CD18, blocking its interaction with ICAM-1) **(HALT)**

Phase III clinical trial stopped for futility (results not disclosed) (del Zoppo, 2010)

Fingolimod (sphingosine-1-phosphate receptor on lymphocytes)

Positive results in two pilot studies (Fu et al., 2014; Zhu et al., 2015)

Natalizumab (humanized antibody against the VCAM-1 leukocyte ligand VLA-4) **(ACTION)**

Not beneficial in a Phase II clinical trial (Elkins et al., 2017)

Drieu et al., Ther Adv Neurol Dis 2018

Pharmacotherapy for the subacute phase : Where are we ?

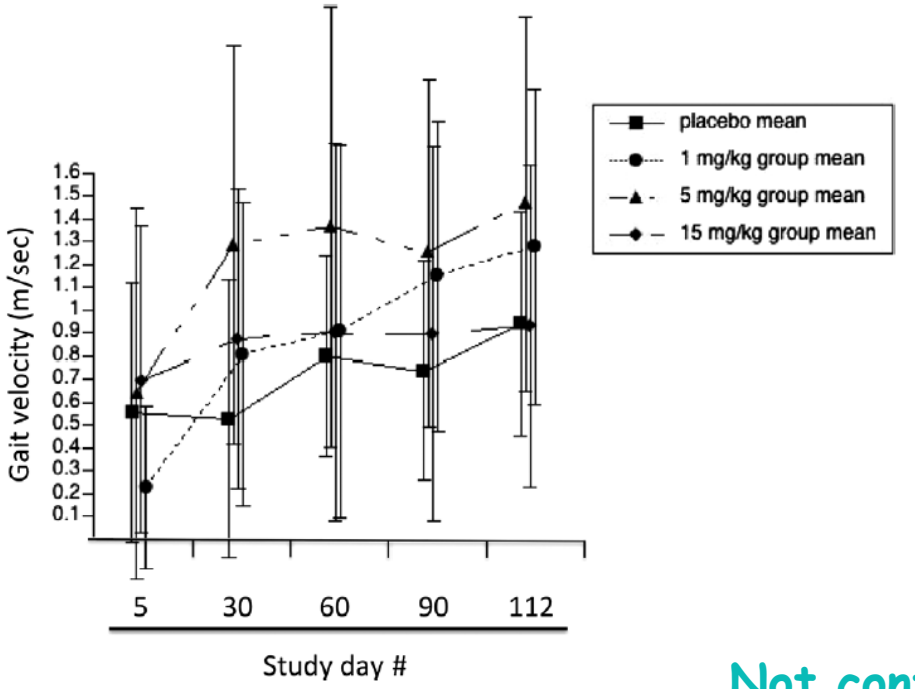
- Drugs for axon repair
- Neurotransmitters : SSRI, dopa, GABA antagonists
- Growth factors

1. Drugs for axon repair

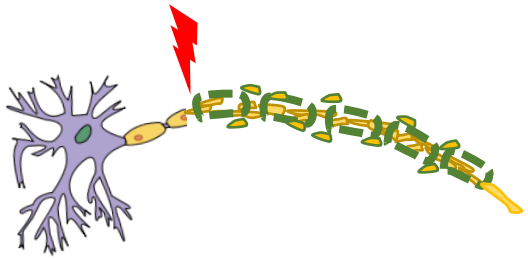
Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Repeat Doses of GSK249320 in Patients With Stroke

Steven C. Cramer, MD; Bams Abila, MD, PhD, FFPM; Nicola E. Scott, MSc; Monica Simeoni, PhD; Lori A. Enney; on behalf of the MAG111539 Study Investigators

Cramer et al., Stroke 2013



2 doses i.v. : 24h + 9 days after



Inhibitor of axonal growth

MAG: myelin-associated glycoprotein

⇨ GSK249320 : anti-MAG

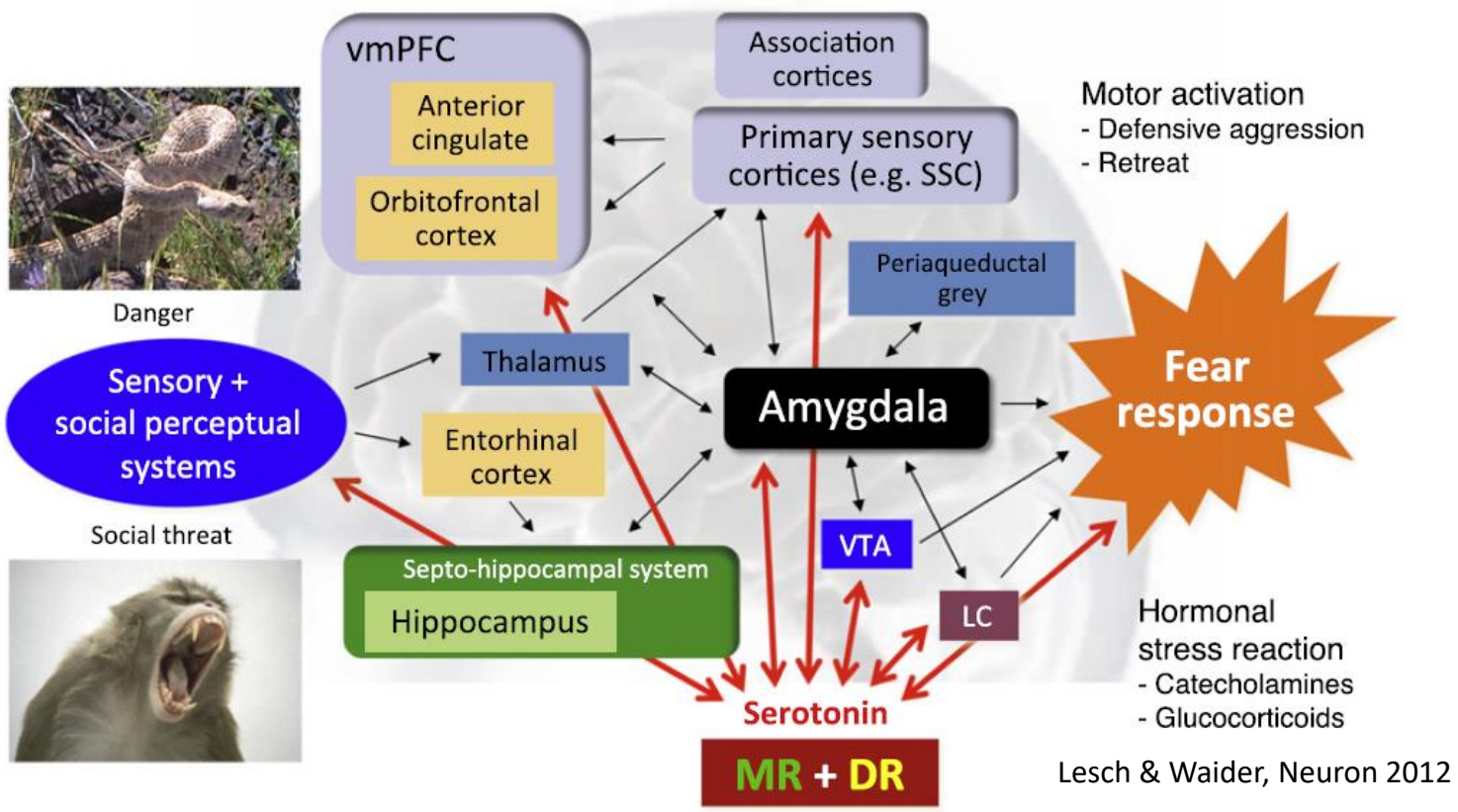
Not confirmed in a trial including 120 patients

Proof-of-Concept Randomized Trial of the Monoclonal Antibody GSK249320 Versus Placebo in Stroke Patients

2 i.v. doses : 24-72h + 5 days after

Cramer et al., Stroke 2017

Antidepressant and Motricity



Lesch & Waider, Neuron 2012

Good tolerance. Rare side effects.

Mechanisms of action for inhibitors of serotonin recapture

1. Anti-depressant impacts Motricity

- Hypothesis of a primary function of the serotoninergic system : **facilitates motricity** (Jacobs & Fornal, 1997)
- Respiratory function (Hilaire et al., Resp Phys Neuro 2010)
- Increased sensorimotor synapse strength (Bayley et al., 1999; 2000)

➢ Training stimulates the 5-HT system

⇨ Associate Rehabilitation + SSRI

Chollet et al., CURRENT NEUROLOGY AND NEUROSCIENCE REPORTS 2018

2. Anti-depressant : Anti-inflammatory

Anti-depressants

Inflammation

IL-1, TNF-α

IDO Indoleamine
2,3 dioxygenase enzyme

Tryptophane depletion

Neurotoxic metabolites

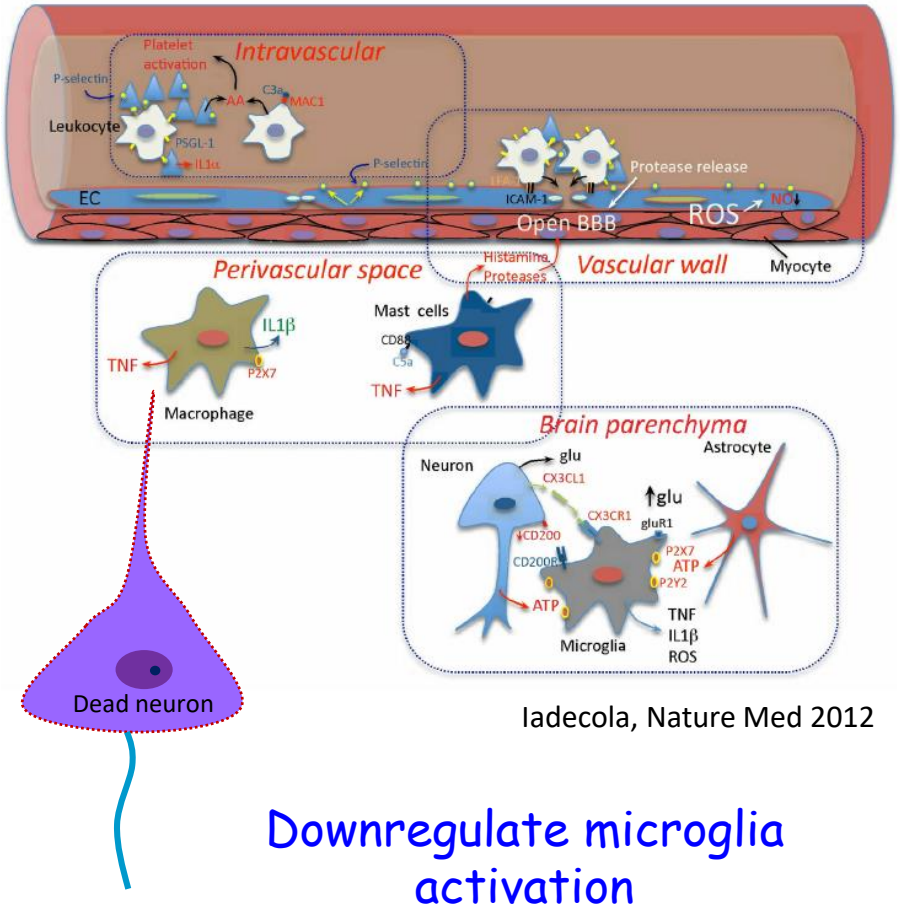
DEPRESSION

Eskeland et al., Acta Derm V 2017

Stroke

Limit neutrophil infiltration

Lim et al., J Neurosci Res 2009



Iadecola, Nature Med 2012

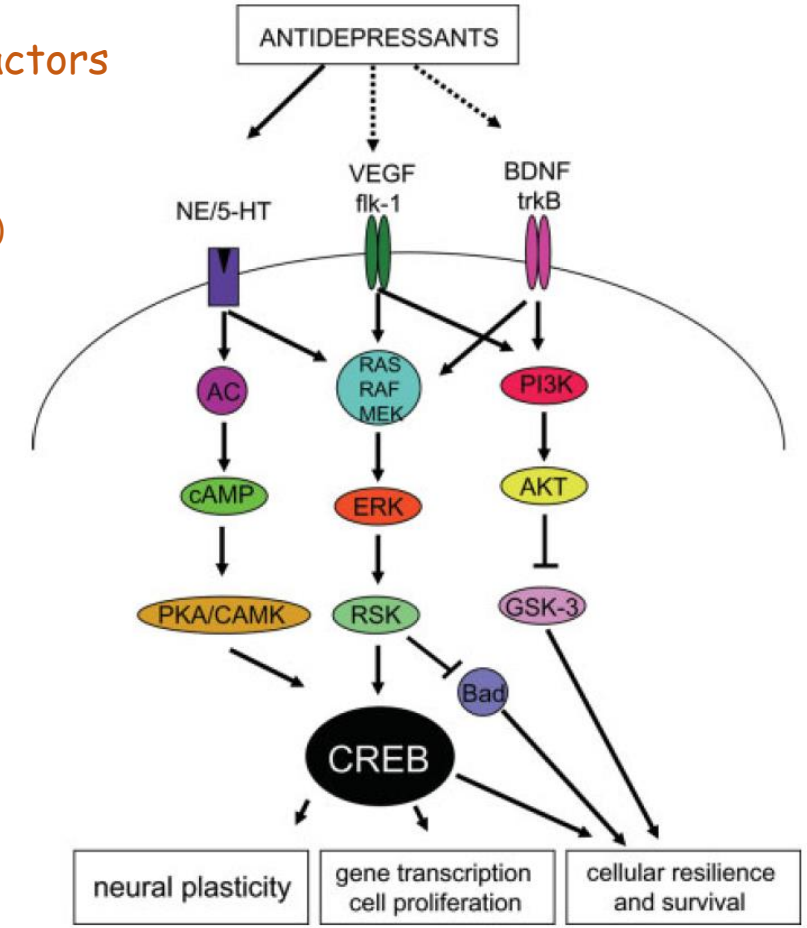
Downregulate microglia activation

3. Anti-depressant : neurogenesis

Up-regulation of growth factors

BDNF, FGF, VEGF

(Lee et al., Neuropharmacology 2011)



Warner-Schmidt,
Hippocampus 2006

Neurogenesis: increase stem cell survival and differentiation

(Li et al., Exp Neurol 2009;

Buga et al., Oncotarget 2016)

Improve declarative memory and ↗ hippocampal volume in PTSD

(Vermetten, 2003)

The functionality of Neurogenesis must be appreciated over minimum 1 year.

No trial has lasted long enough to assess regeneration of long-range tractus.

What modulate neurogenesis ?

Neurogenesis

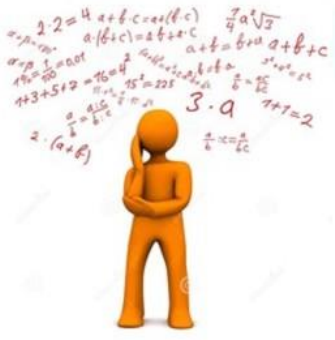
Enhanced by:	Reduced by:
• Exercise	• Distress
• Complex Environments	• Inactivity
• New Learning	• Boredom
• Nutrition	• Depression
• Low Stress	• Poor Nutrition
	• Age

Your Brain on Exercise

↑ Serotonin

↑ Neurogenesis

↑ Brain volume & cognitive function



↑ Creativity

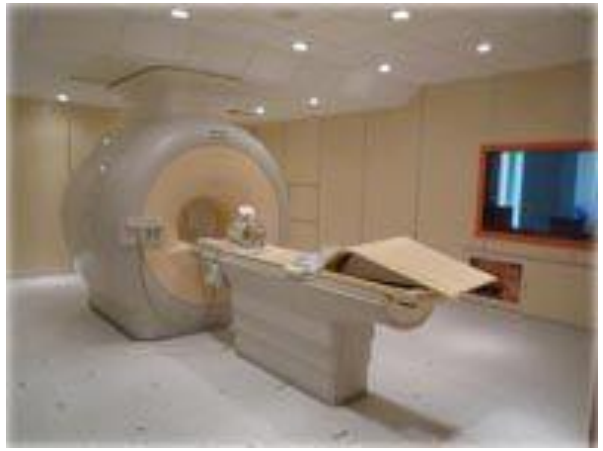
↑ Cannibinoids

= Runner's High

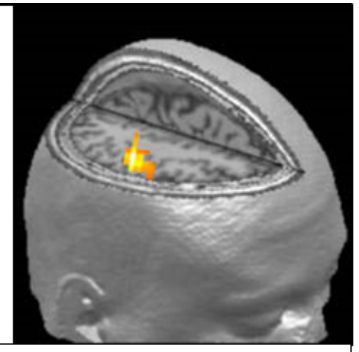
Run-Fit.com

Anti-depressant must be paired with rehabilitation

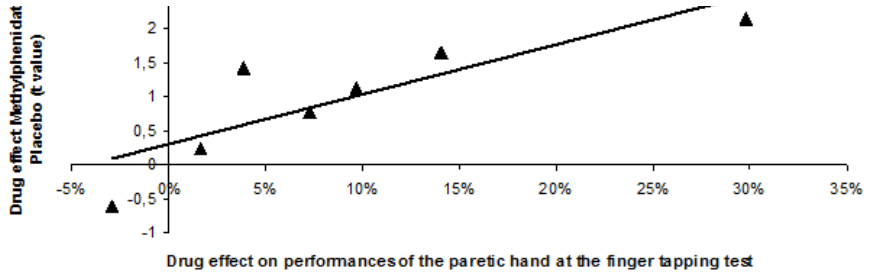
An anti-depressant improves post-stroke Motricity



Fluoxetine targets the ipsilesional primary motor cortex M1



Fluoxetine effect on activation size correlates with fluoxetine improvement on performance



Functional MRI : intermediary criteria of drug efficacy

Pariente et al. Annals Neurol 2001

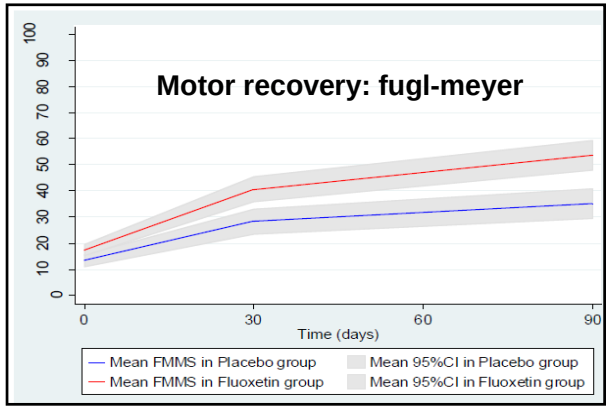
2. Selective Serotonin Reuptake Inhibitors

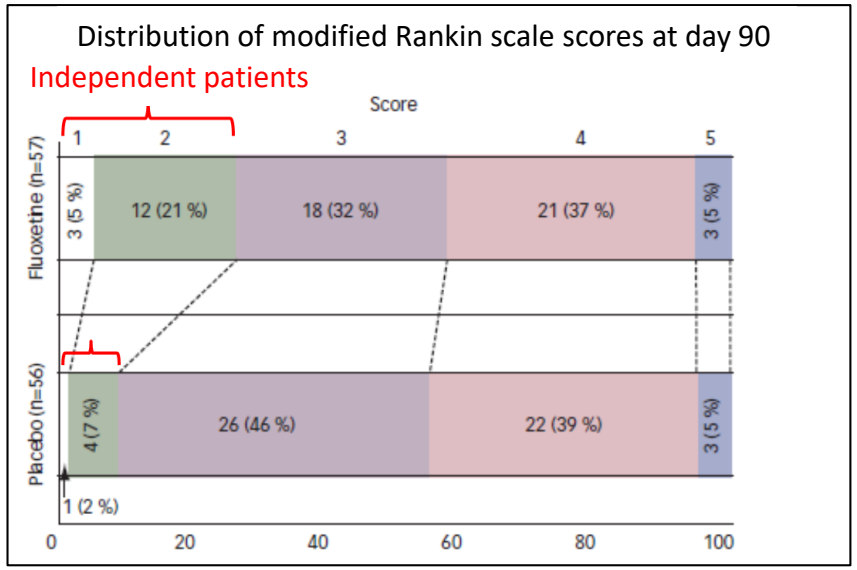
Clinical trial phase IIa : Fluoxetine 3 months/placebo

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

Lancet Neurol, 2011

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux





- Improvement of motor recovery
- Functional improvement: independence
- Patients severely impaired

A great hope. Results had to be confirmed in bigger clinical trials

2. Meta-analyses : Selective Serotonin Reuptake Inhibitors

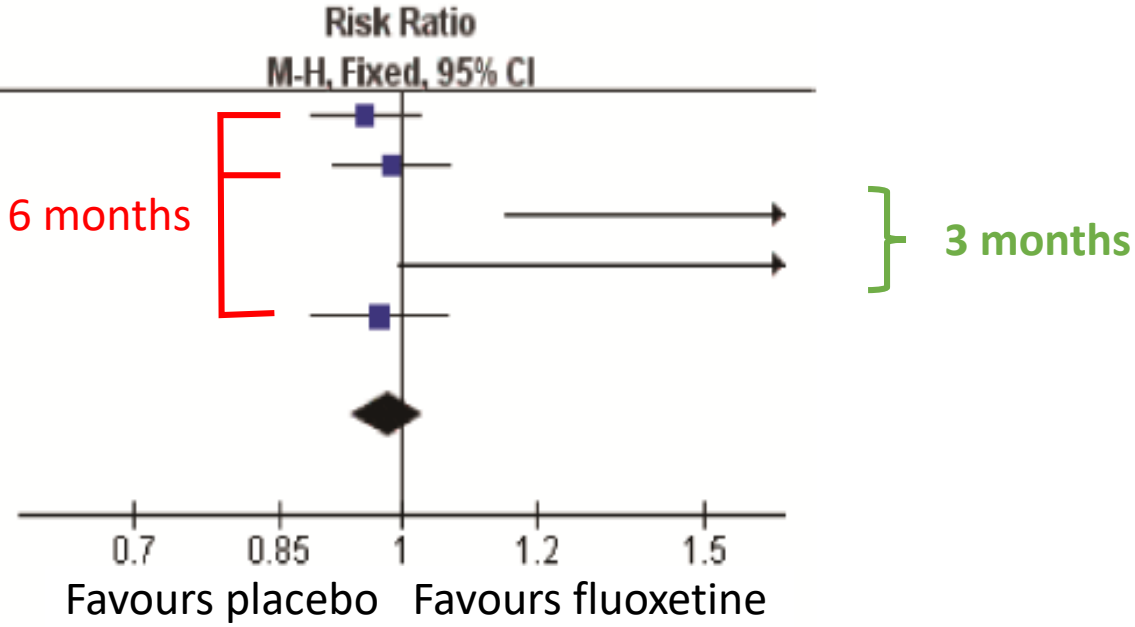
Fluoxetine : 6 month vs 3 month treatment

A. mRS (0-2)

Study or Subgroup	fluoxetine Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFINITY 2020	432	624	458	632	29.9%	0.96 [0.89, 1.03]
EFFECTS 2020	466	737	475	742	31.1%	0.99 [0.91, 1.07]
FLAME 2011	15	57	5	56	0.3%	2.95 [1.15, 7.56]
FMRICH 2020	8	14	3	16	0.2%	3.05 [1.00, 9.31]
FOCUS 2019	572	1553	588	1553	38.6%	0.97 [0.89, 1.07]
Total (95% CI)		**2985**		**2999**	**100.0%**	**0.98 [0.94, 1.03]**
Total events	1493		1529			

Heterogeneity: Chi² = 9.83, df = 4 (P = 0.04); I² = 59%

Test for overall effect: Z = 0.72 (P = 0.47)



6 month fluoxetine does not increase the pourcentage of independent patients

- What about a 3 month treatment ?
- Scale not sensitive

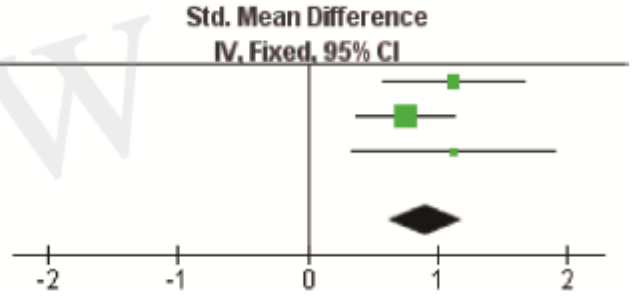
Liu et al., Frontiers Neurol 2021

2. Selective Serotonin Reuptake Inhibitors

B. FMMS

Study or Subgroup	fluoxetine Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Asadollahi 2018	32.34	22.77	30	9.76	16.33	30	28.2%	1.12 [0.58, 1.67]
FLAME 2011	36.4	21.3	57	21.9	16.7	56	57.9%	0.75 [0.37, 1.13]
FMRICH 2020	48	15.6	14	23	25.9	16	13.9%	1.12 [0.34, 1.90]
Total (95% CI)			**101**			102	100.0%	**0.91 [0.62, 1.20]**

Heterogeneity: Chi² = 1.53, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 6.12 (P < 0.00001)

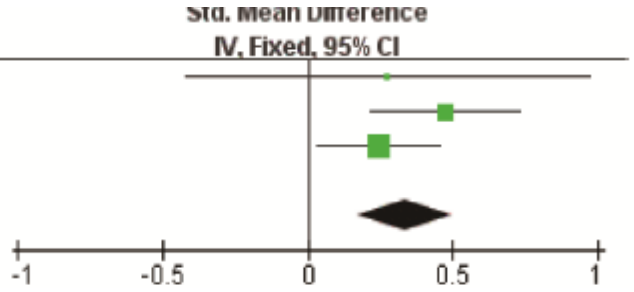


Favours placebo **Favours fluoxetine**

C. BI

Study or Subgroup	fluoxetine Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Dam 1996	23.5	12.2	16	19.1	18.27	16	5.2%	0.28 [-0.42, 0.97]
Guo 2016	31.68	17.18	177	22.67	22.01	90	38.2%	0.47 [0.22, 0.73]
He 2016	32.12	17.04	177	27.65	19.16	170	56.6%	0.25 [0.04, 0.46]
Total (95% CI)			**370**			276	100.0%	**0.34 [0.18, 0.49]**

Heterogeneity: Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)

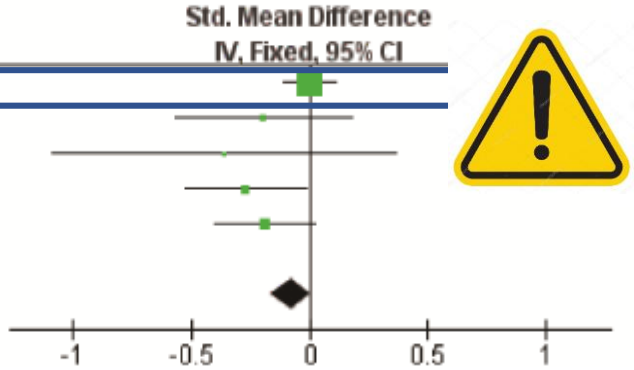


Favours placebo **Favours fluoxetine**

D. NIHSS

Study or Subgroup	fluoxetine Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
EFFECTS 2020	-2	2.56	678	-2	2.56	681	65.3%	0.00 [-0.11, 0.11]
FLAME 2011	-7	3.8	57	-6.2	4.35	55	5.4%	-0.19 [-0.57, 0.18]
FMRICH 2020	-3.5	3.23	14	-2	4.63	16	1.4%	-0.36 [-1.09, 0.36]
Guo 2016	-5.47	2.83	177	-4.66	3.22	90	11.4%	-0.27 [-0.53, -0.02]
He 2016	-5.54	2.84	177	-4.96	3.27	170	16.6%	-0.19 [-0.40, 0.02]
Total (95% CI)			**1103**			1012	100.0%	**-0.08 [-0.16, 0.01]**

Heterogeneity: Chi² = 6.34, df = 4 (P = 0.18); I² = 37%
Test for overall effect: Z = 1.78 (P = 0.08)



Favours fluoxetine Favours placebo

EFFECTS :
Neurological deficits at inclusion :
Median NIHSS score 3 (2–6)
Ceiling effect !

Liu et al., Frontiers Neurol 2021

2. Selective Serotonin Reuptake Inhibitors

< 3 months fluoxetine improves Barthel and Fugl-Meyer scores
in medium size trials

Time consuming scales (FMS) not compatible with large clinical trials

➥ Although highly recommended by recent guidelines (Kwakkel et al, Int J Stroke 2017).

Fluoxetine did not improve mRS scores but improved FMS and Barthel scores.

➥ This discrepancy could result from low sensitive scales and heterogeneities between trials : treatment duration, age of patients, delay of inclusion, and **severity of deficit**

➡ **Post-hoc analyses on most severe patients in large clinical trials (Affinity, Effects, Focus)**

Hyponatremia, fractures, and epilepsy : very unfrequent side effects (1.5%)

Fluoxetine is safe (do not prescribe in too old patients) / increased bone fracture risk

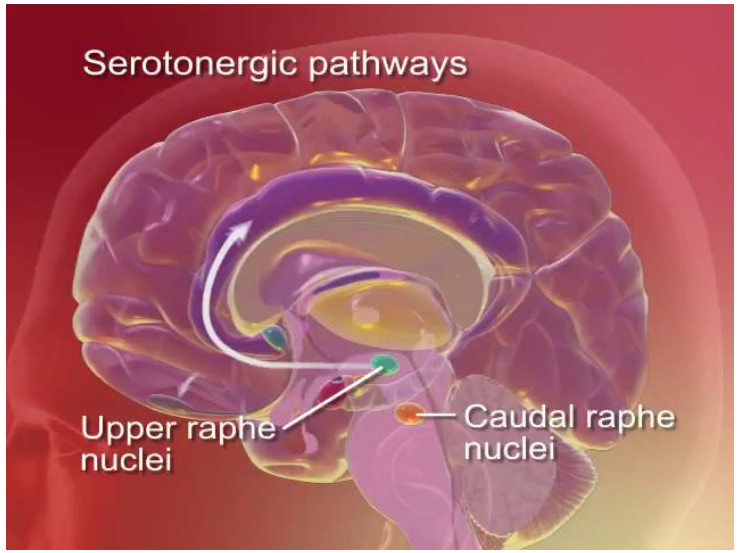
The use of fluoxetine for post-stroke motor recovery should be considered in view of the risk/benefit ratio.

Analysis 1.12. Comparison 1 SSRI versus control at end of treatment, by SSRI, Outcome 12 Disability (sensitivity analyses all studies regardless of RoB).

Study or subgroup	Control N	Control Mean(SD)	SSRI N	SSRI Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.12.1 Fluoxetine							
Chen 2001	19	79.3 (8.9)	18	71.6 (9.4)		0.66%	0.83[0.15,1.5]
Cheng 2003	25	-26.4 (14.2)	32	-29.1 (17.4)		1.09%	0.17[-0.35,0.69]
Dam 1996	16	61.9 (13)	16	54.1 (21.1)		0.61%	0.43[-0.27,1.14]
FOCUS Trial Collaboration 2018	1402	59.7 (31.2)	1397	60.2 (31.5)		54.76%	-0.02[-0.09,0.06]
He 2016	177	88.8 (14.7)	170	84.7 (18.9)		6.74%	0.24[0.03,0.45]
Kong 2007	37	60.4 (12.5)	36	52.3 (13.5)		1.36%	0.62[0.15,1.09]
Li 2008	58	40.8 (3.7)	28	38.4 (5.8)		1.43%	0.53[0.07,0.99]
Marquez Romero 2013	14	65 (21.4)	16	45 (73.2)		0.57%	0.35[-0.37,1.07]
Razazian 2014	75	15.7 (2.6)	75	14.3 (1.8)		2.79%	0.63[0.3,0.96]
Robinson 2000a	14	59.2 (11.6)	13	56.2 (7.7)		0.52%	0.29[-0.47,1.05]
Robinson 2000b	13	60.5 (10.8)	15	63.1 (8.2)		0.54%	-0.27[-1.01,0.48]
Wang 2003	51	75 (4.2)	47	61 (6.9)		1.07%	2.46[1.93,2.98]
Wiart 2000	16	87.4 (22.8)	15	88.7 (25.3)		0.61%	-0.05[-0.76,0.65]
Xu 2001	26	73 (4.4)	27	67 (4.1)		0.82%	1.39[0.79,2]
Zhao 2011	37	-27.6 (7.1)	34	-34.6 (5.2)		1.19%	1.11[0.6,1.61]
Subtotal ***	**1980**		**1939**			**74.77%**	**0.14[0.08,0.2]**
Heterogeneity: Tau²=0; Chi²=143.86, df=14(P<0.0001); I²=90.27%							
Test for overall effect: Z=4.3(P<0.0001)							
1.12.2 Sertraline							
Xie 2005	65	88.7 (7.9)	65	79.8 (4.5)		2.04%	1.38[0.99,1.76]
Subtotal ***	**65**		**65**			**2.04%**	**1.38[0.99,1.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.03(P<0.0001)							
1.12.3 Paroxetine							
Chen 2005b	40	65.8 (5.9)	38	51.8 (7.3)		0.97%	2.09[1.53,2.64]
Chen 2002	24	61 (12.2)	20	51.5 (10.3)		0.78%	0.82[0.2,1.44]
He 2005	27	84.3 (8.4)	27	78.3 (15)		1.02%	0.48[-0.06,1.02]
Xu 2006	28	-27.6 (4.8)	29	-32.8 (4.1)		0.95%	1.14[0.58,1.7]
Ye 2004	30	78.8 (14.2)	30	50.3 (13.4)		0.75%	2.04[1.41,2.67]
Subtotal ***	**149**		**144**			**4.48%**	**1.29[1.03,1.55]**
Heterogeneity: Tau²=0; Chi²=24.34, df=4(P<0.0001); I²=83.56%							
Test for overall effect: Z=9.76(P<0.0001)							
1.12.4 Citalopram							
Acler 2009	10	82 (28)	10	75 (25)		0.39%	0.25[-0.63,1.13]
Andersen 2013	319	1.5 (1.5)	323	1.3 (1.2)		12.53%	0.15[-0.01,0.3]
Gao 2016	85	71.5 (16.2)	86	72.3 (15.9)		3.34%	-0.05[-0.35,0.25]
Li 2006	50	64.4 (8.2)	49	59.2 (9)		1.85%	0.6[0.19,1]
Liu 2006	30	64.4 (12.1)	30	35.4 (9.1)		0.6%	2.67[1.97,3.38]
Subtotal ***	**494**		**498**			**18.71%**	**0.24[0.11,0.37]**
Heterogeneity: Tau²=0; Chi²=53.39, df=4(P<0.0001); I²=92.51%							
Test for overall effect: Z=3.71(P=0)							
Total ***	**2688**		**2646**			**100%**	**0.23[0.18,0.29]**
Heterogeneity: Tau²=0; Chi²=328.1, df=25(P<0.0001); I²=92.38%							
Test for overall effect: Z=8.39(P<0.0001)							
Test for subgroup differences: Chi²=106.51, df=1 (P<0.0001), I²=97.18%							

Favours control -2 -1 0 1 2 Favours SSRI

Favours placebo **Favours SSRI**



Human Anatomy Serotonin Pathways, Larry J.

SSRI improve disability in medium size trials
P < 0.0001

Legg et al., Cochrane Database Sys Review 2019

2. Neurotransmitters : Dopamine

Dopamine Augmented Rehabilitation in Stroke (DARS): a multicentre double-blind, randomised controlled trial of co-careldopa compared with placebo, in addition to routine NHS occupational and physical therapy, delivered early after stroke on functional recovery

Efficacy Mech Eval 2019

Gary A Ford,[1]* Bipin B Bhakta,[2]† Alastair Cozens,[3] Bonnie Cundill,[4] Suzanne Hartley,[4] Ivana Holloway,[4] David Meads,[5] John Pearn,[2] Sharon Ruddock,[4] Catherine M Sackley,[6] Eirini-Christina Saloniki,[5] Gillian Santorelli,[4] Marion F Walker[7] and Amanda J Farrin[4]

[1]Oxford University Hospitals NHS Foundation Trust, University of Oxford, Oxford, UK

Placebo 285 patients versus Co-careldopa 308 patients
Treated 8 weeks before rehabilitation session, 15 days post-stroke; Follow-up : 6 mois, 12 mois

No effect of co-careldopa for Rivermaed Mobility Index, Barthel index , ability to walk independently, Nottingham Extended Activities of Daily Living, ABILHAND Manual Ability Measured, modified Rankin Scale, Montreal Cognitive Assessment scores, General health Questionnaire, pain, fatigue.

Dopamine + rehabilitation is not clinically effective in improving walking, physical functioning, mood or cognition post-stroke.

2. Neurotransmitters : GABA antagonist

Safety and efficacy of $GABA_A$ α5 antagonist S44819 in patients with ischaemic stroke: a multicentre, double-blind, randomised, placebo-controlled trial

*Hugues Chabriat, Claudio L Bassetti, Ute Marx, Marie-Laure Audoli-Inthavong, Aurore Sors, Estelle Lambert, Marine Wattez, Dirk M Hermann, on behalf of the RESTORE BRAIN study investigators**

The Lancet Neurol 2019

GABAa antagonist : reduced post-ischemic inhibition of perilesional cortex

585 patients; 3 groups : 150 mg S44819, 300 mg S44819, placebo twice daily

At day 90, no effect of S44819 for mRS, NIHSS, Barthel index, Montreal Cognitive Assessment (MoCA) scores, time for part A and B of Trail Making Test

GABA antagonist S44819 is not clinically effective in improving function, motricity or cognition

Pharmacotherapy : where are we ?

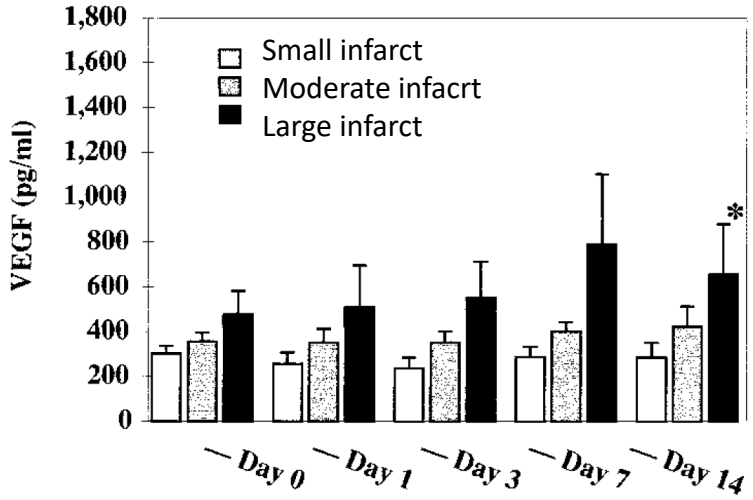
- Drug for axon repair
  - Anti-MAG : Anti-Myelin Associated Glycoprot (Cramer, Stroke 2017) inefficient
- Serotoninergic drugs
  - 3 month treatment efficacious ?

- Growth factors
  - Hematopoïetic: G-CSF, granulocyte Colony-Stimulating Factor, n=548, no effect (Cochrane 2013)
  - Fibroblast: bFGF, basic Fibroblast Growth Factor, n=286, toxic, STOP (Bogousslavsky, Cerebrovascular Dis 2002)
  - Neurotrophic: Brain-Derived Neurotrophic Factor, toxic
  - Neuronal Growth Factor : intranasal NGF for TBI (Chiaretti Brain Injury 2017), dementia (De Bellis, J Alzheimer 2018)

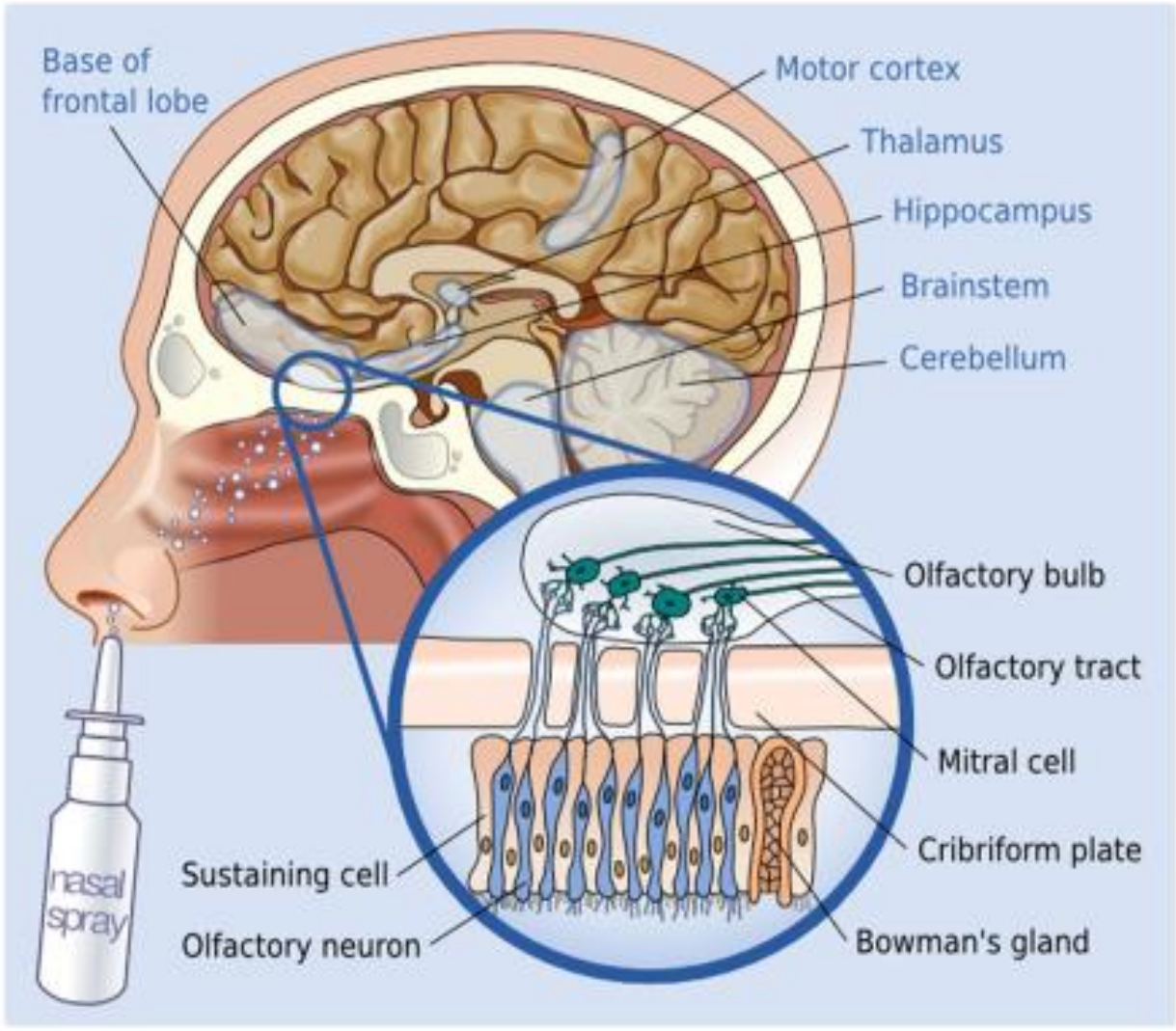
Intranasal pathway to deliver molecules to the Central Nervous System

- Rapid delivery : few minutes in *Macaca fascicularis* brain *(Sosa et al., Rev Salud Anim 2007)*

Stroke patients : growth factor production



- Increased growth factor production during the first month post-stroke *(Slevin et al., 2000)*



Transport along olfactory and trigeminal neurons results in increased delivery in particular brain areas

Lioutas et al. Intranasal insulin and IGF-1 as neuroprotectants in acute ischemic stroke. Trans Stroke Res 2015

NGF = Nerve Growth Factor

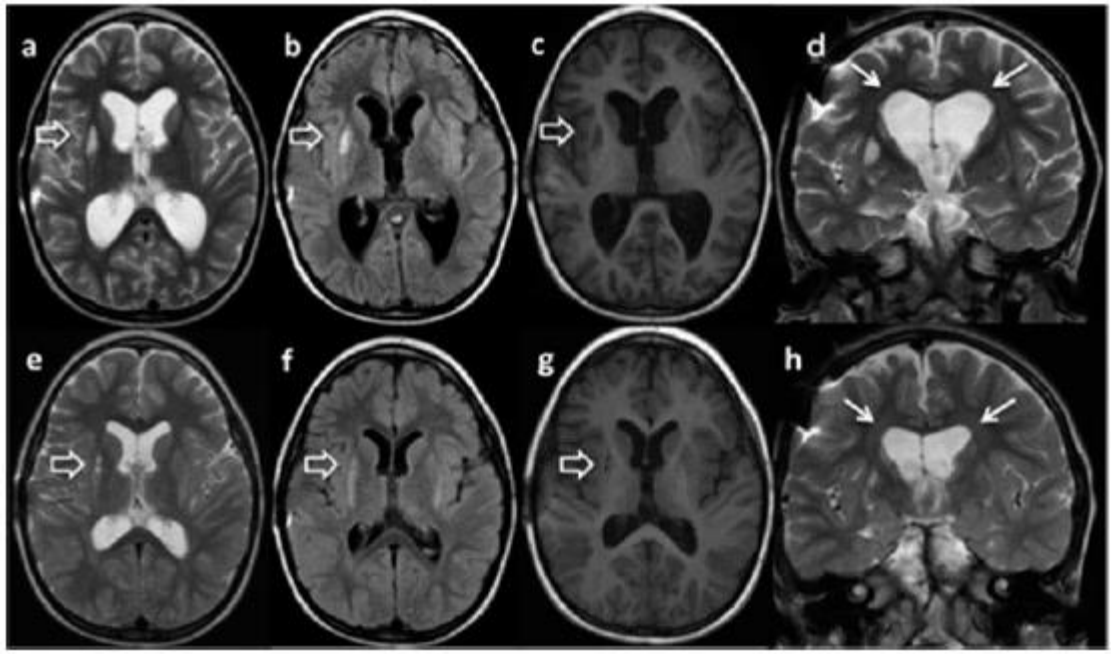
Case report
Intranasal Nerve Growth Factor administration improves cerebral functions in a child with severe traumatic brain injury and persistent unresponsive wakefulness syndrome

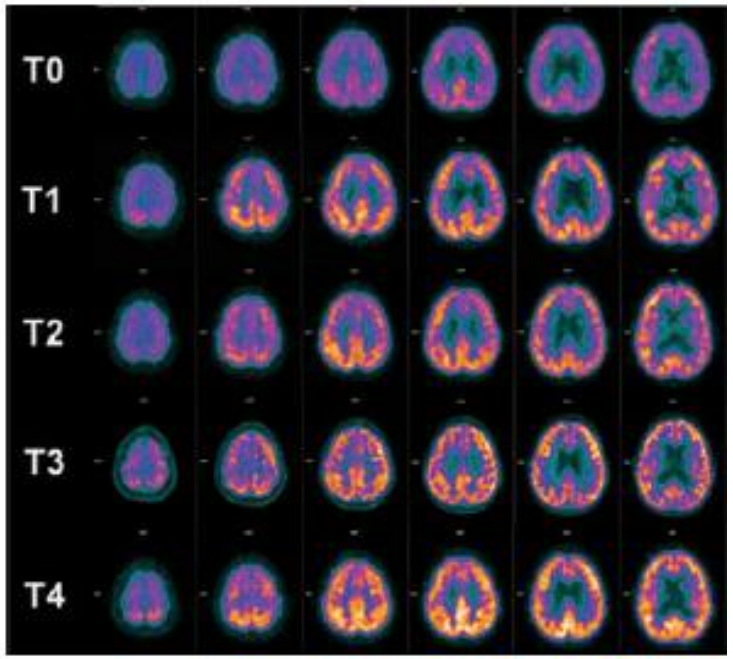
6 month post-trauma. Treatment duration : 10 days/month during 4 months, high dose

➡ No side effects.
➡ Improvements in voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions.

Before

4 months after



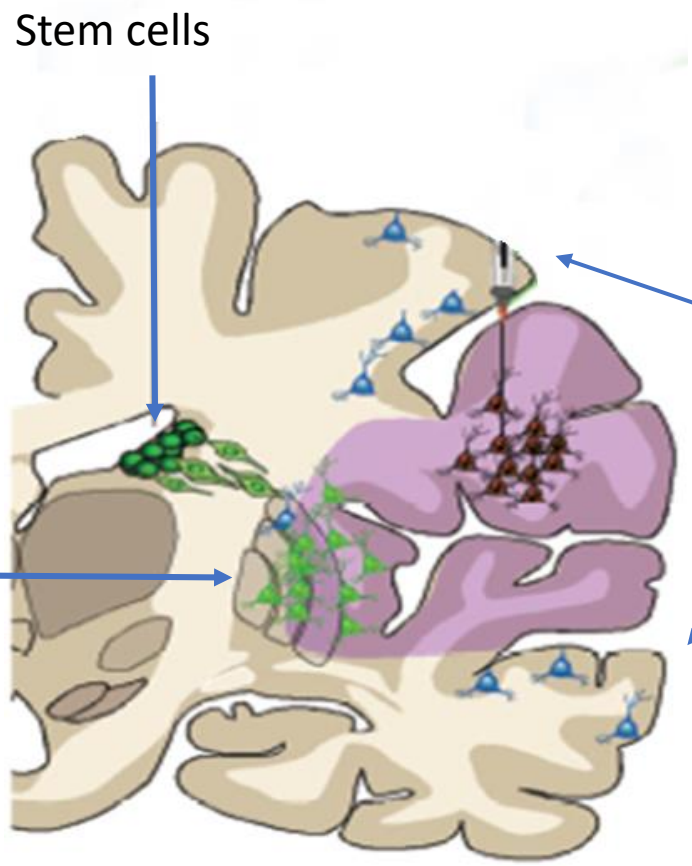


Metabolism improvement

PET ^{18F}-FDG

Chiaretti et al., Brain Injury 2017

Adult neurogenesis : long maturation

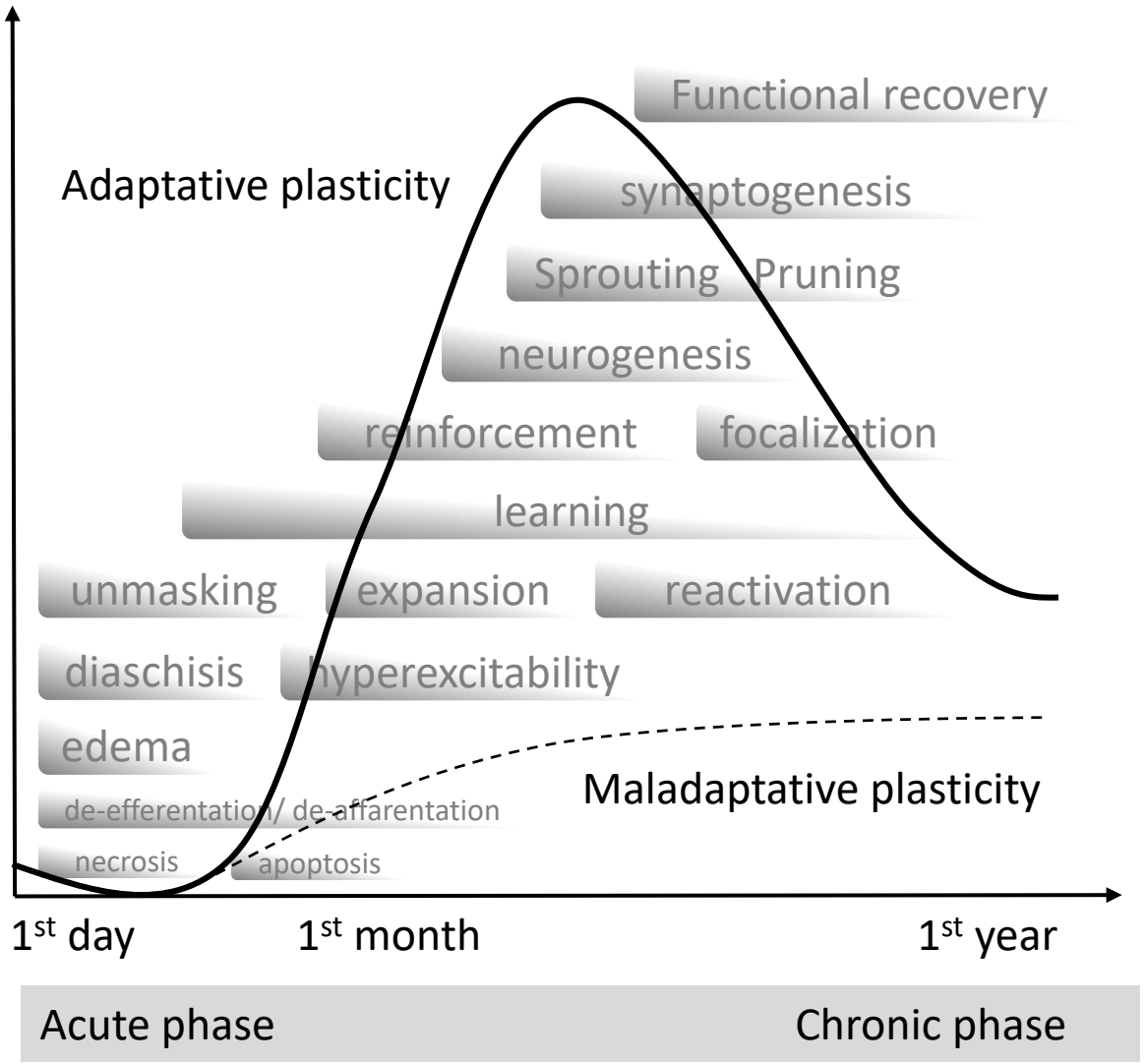


0.2% neurons are replaced at **5 weeks** in rodents (Magavi et al, Nature, 2000; Arvidsson et al, Nature Medecine, 2002)

19 % of reconstructed tissues at **3.5 months** (Davoust et al., Stem Cell Res & Ther 2017)

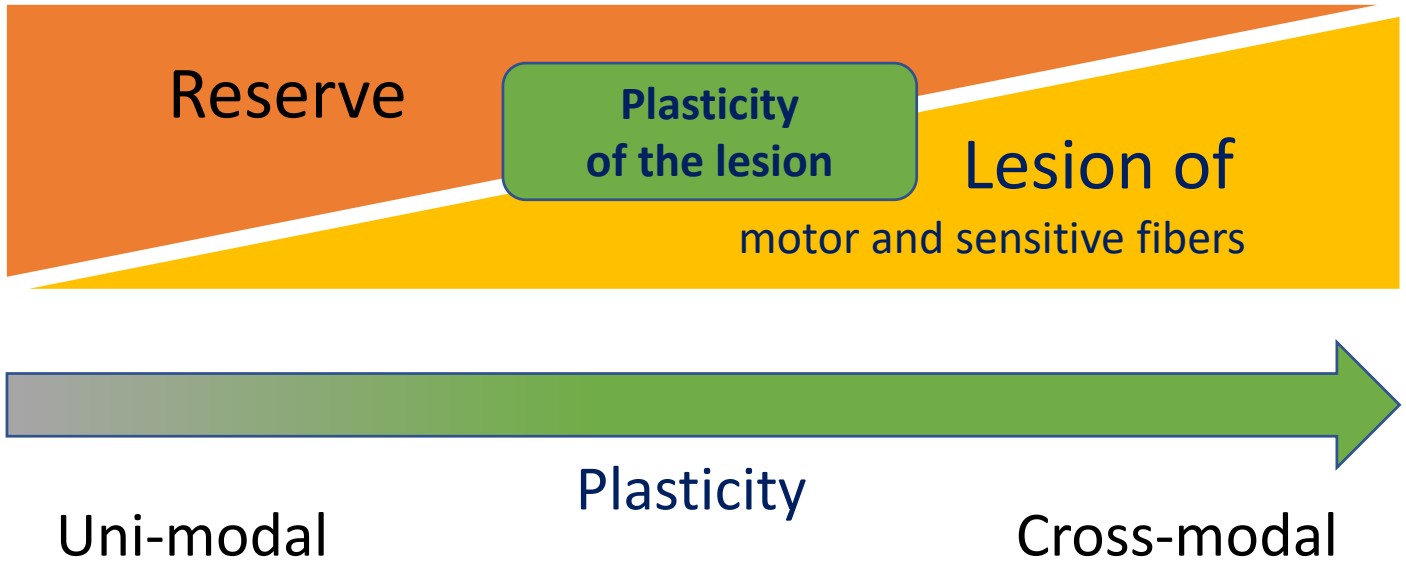
NGF : Stimulation of neurogenesis is safe in patients with acute brain lesions (Chiaretti, Brain Injury 2017)

Plasticity mechanisms post-stroke



Cirillo, Loubinoux, JCBFM 2019

SENSORIMOTOR RECOVERY AFTER STROKE



DRUGS

↗ **Adaptative plasticity**

↘ **Maladaptative plasticity**

Adverse events

- ✓ Epilepsia
- ✓ Pain
- ✓ Synkinesis
- ✓ Spasticity
- ✓ Learned non-used

Graft of stem cells in perilesional tissue is safe in stroke patients and holds great promise

(Kalladka et al., Lancet 2016; Steinberg et al., Stroke 2016; Muir et al., J Neurol Neurosurg Psy 2020)