WFNR
World Federation for NeuroRehabilitation

Special interest group (SIG)
Neuropharmacology and neurorehabiltiation

Neuropharmacological aspects of neurorehabilitation

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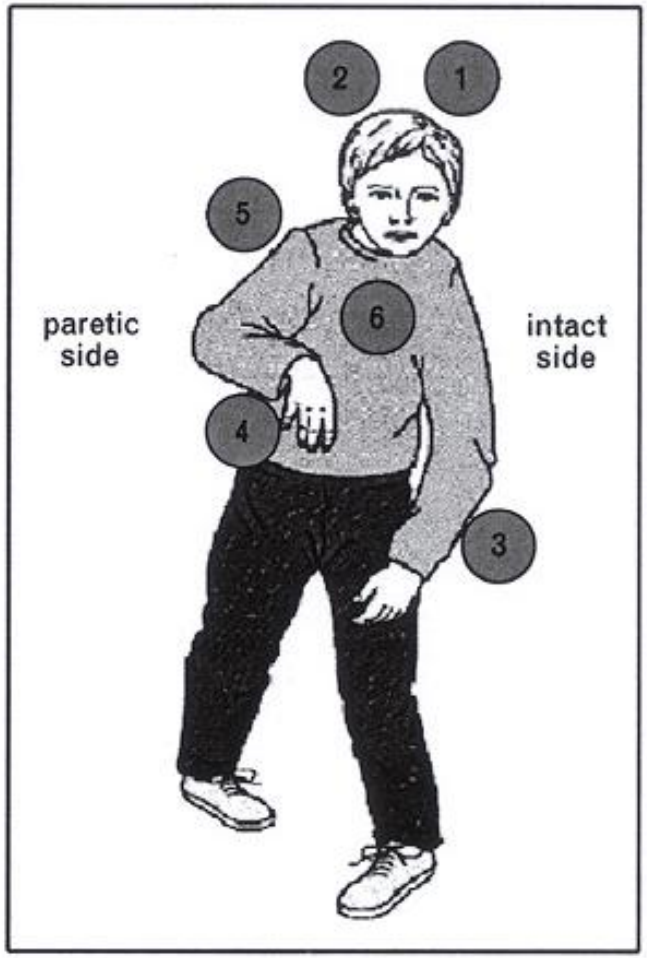
Experimental strategies in neurorehabilitation



1. Cortical stimulation to enhance acitivity of the motor cortex of the affected hemisphere
2. Downregulation of activity of the motor cotex in the intact hemisphere
3. Decreased somatosensory input from the intact hand (i.e. anaesthesia) to enhance sensorimotor function of the paretic hand
4. Somatosensory stimulation of the paretic hand
5. Transient anaesthesia of the paretic upper arm to enhance function of the paretic hand
6. Neuromodulatory pharmacological interventions to enhance effects of rehabilitative treatment and training

Hummel & Cohen (2005)

Influence of drugs on neuronal plasticity

„plus“	„minus“
calciumantagonists cholinergics (e.g. scopolamine) cholinesterase inhibitors (e.g. physostigmine) dopamine and DA-agonists catecholamines (e.g. norepinephrine) Amphetamine tricyclic antidepressants with intrinsic ?Ö-adrenergic effects (e.g. desipramine, nortryptiline)	phenothiazines (e.g. chlorpromazine, levomepromazine, perazine) butyrophenones (e.g. haloperidol) GABAergic substances (e.g. benzodiazepine, barbiturate) Phenytoin ?&$_1$-blocking agents (e.g. prazosin, phenoxybenzamin) ?&$_2$-agonists (clonidine) SSRIs (trazodone) aethylic alcohol

Pharmacological approaches in neurorehabilitation

- It is a long matter of debate to what extent pharmacologic strategies may serve as a useful adjunct therapy in neurorehabilitation
- Several lines of evidence suggest that recovery after injury to the cerebral cortex can be modulated through the effects of certain neurotransmitters on the CNS
- Some neuropharmacologic medications, especially when combined with practice, may hasten or incrementally improve motor, language, and cognitive outcomes

Neurotransmitters and Motor Activity:

The role of monoamines:

- Executive motor regions are rich in monoaminergic receptors
- Increased brain concentrations of monoamines may promote motor learning, with norepinephrine playing the most important role for brain plasticity
- Monoaminergic drugs are the most widely studied drugs in neurorehabilitation

Norepinephrine

Drugs that increase norepinephrine release (yohimbine, idazoxan) enhance motor recovery (Goldstein et al, 1989)

In animals, direct intraventricular infusion of norepinephrine and amphetamines facilitates motor recovery (Boyeson et al, 1990; Feeney et al, 1998)

Dopamine

The brain dopamine system is crucial for motor learning (Jay et al, 2003; Wise et al, 2004; Bailey et al, 2000)

Levodopa increases learning abilities in healthy individuals: Acceleration of memory formation in young subjects and restoration of the ability to form a motor memory in elderly subjects (Flöel et al, 2005)

Serotonin (5-HT)

5-HT activates pyramidal cells and GABAergic inhibitory interneurons and may inhibit Purkinje cell firing (Goldstein, 2006)

5-HT enhances storage of long-term memory in sensorimotor synapses, long-term facilitation and growth factor gene expression (Jacobs et al, 1997; Barbas et al, 2003)

Other neurotransmitters

- Acetylcholine
  - Activation of the muscarinergic cholinergic receptor facilitates the induction of LTP in the rat dentate gyrus (Burgard et al, 1990)
  - Acetylcholine facilitates recovery in animal brain injury models (Feeney et al, 1987)
  - Scopolamine interferes with motor recovery after cortex infarction in rats (De Ryck et al, 1990)
- GABA
  - Stimulation of inhibitory GABAergic inputs to the hippocampus suppress the induction of LTP (Douglas et al, 1982)
  - GABA-agonists such as benzodiazepines also suppress LTP (Riches et al, 1986)
  - Diazepam impedes recovery after anterior-medial neocortex damage in the rat (Schallert et al, 1986)

Serotonergic agents

Selective Serotonin Reuptake Inhibitors

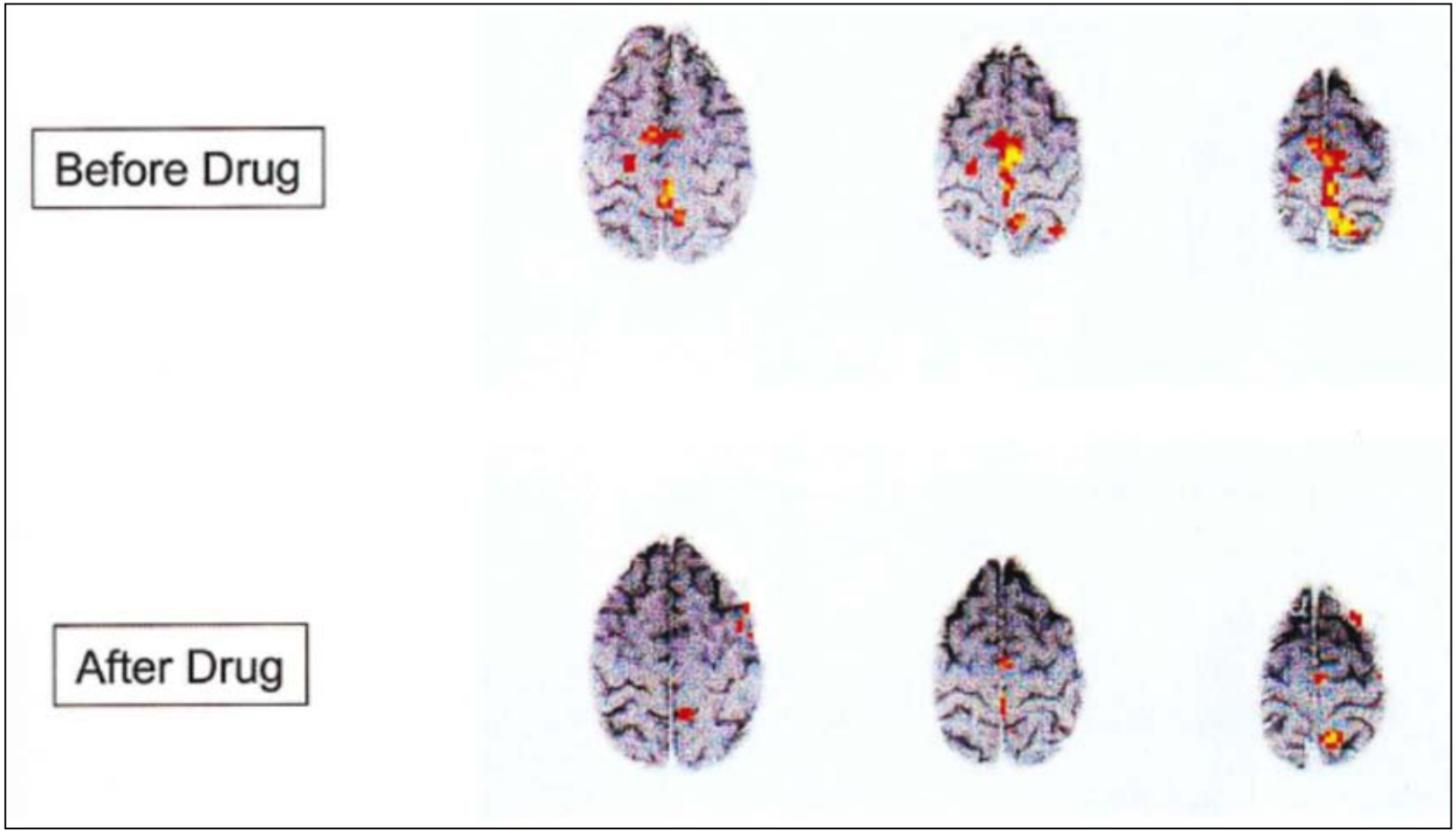
- Fluoxetine has shown to have a neuroprotective effect in the post-ischaemic brain through its anti-inflammatory effects and has improved ischaemia-induced spatial cognitive deficits by increasing hippocampal neurogenesis after stroke in rats
  - Lim et al. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-infl ammatory effect. Neurosci Res 2009; 87: 1037–45.
  - Li et al. Chronic fluoxetine treatment improves ischemia-induced spatial cognitive defi cits through increasing hippocampalneurogenesis after stroke. J Neurosci Res 2009; 87: 112–22
- In humans, trials with SSRIs in stroke patients showed promising results
- Effects of SSRIs on mood are likely, as shown by the additional changes in depression scores in some studies. However, it is not believed that SSRIs act only through antidepressant mechanisms on motor recovery

Prospective randomised placebo-controlled trials of SSRIs in motor recovery after ischaemic stroke

	Drug(s)	Dose, regimen, and treatment duration	Number of patients	Trial design	Time of inclusion after stroke	Clinical outcome criteria	Other outcome criteria	Patients in rehabilitation programme	Main results
Dam et al[12]	Fluoxetine and maprotiline	Fluoxetine 20 mg once per day for 90 days	48	Parallel groups (three groups)	1–6 months	Graded neurological scale (HSS)	None	Yes	10·7% improvement in HSS score
Pariente et al[13]	Fluoxetine	20 mg (single dose)	8	Crossover	15–30 days	Finger tapping and dynamometer	Functional MRI; hyperactivation of motor cortices	Yes	20–30% finger tapping and dynamometer improvement
Zittel et al[14]	Citalopram	40 mg (single dose)	8	Crossover	More than 6 months	Motor dexterity with nine-hole-peg test	None	Yes	11·4% improvement in nine-hole -peg test
Acler et al[15]	Citalopram	10 mg once per day for 30 days	20	Parallel groups (two groups)	Not reported	NIHSS score	TMS: modulation of cortical excitability	Yes	38·8% improvement of NIHSS score

- Dam et al, 1996: **Fluoxetine facilitates recovery in poststroke patients undergoing rehabilitation (Barthel Index)**
- Pariente et al, 2001: **Motor performance (finger tapping speed, hand strength) improved with fluoxetine, associated with increased contralateral M1 activation during voluntary movement of the paretc hand on fMRI**
- Zittel et al, 2008: **Citalopram significantly improved performance of the nine-hole peg test for the paretic hand but not for the unaffected hand**
- Acler et al, 2009: **Citalopram led to significant improvements in NIHSS and a decrease of motor excitability over the unaffected hemisphere (as studied by transcranial magnetic stimulation)**

Functional neuroimaging techniques visualize physiological activity of medications and their potential for modulating cerebral reorganization: An fMRI study with fluoxetine



20 ° of voluntary repetitive ankle dorsiflexion at 0.5 Hz in a healthy volunteer before and 3 hours after a single fluoxetine dose (10 mg): Activity became more focussed in primary sensorimotor cortex in the leg presentation and in SMA, suggesting greater synaptic activity induced by the SSRI (Bruce H. Dobkin „The Clinical Science of Neurological Rehabilitation“, 2003)

Lancet Neurol 2011; 10: 123–30

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

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

- Fluoxetine (20 mg/d) or placebo for 3 months starting 5–10 days after stroke onset; all patients had physiotherapy (N=113)
- Largest clinical trial conducted so far
- In patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine + physiotherapy enhanced motor recovery after 3 months (measured by Fugl-Meyer motor scale, Rankin Scale)

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

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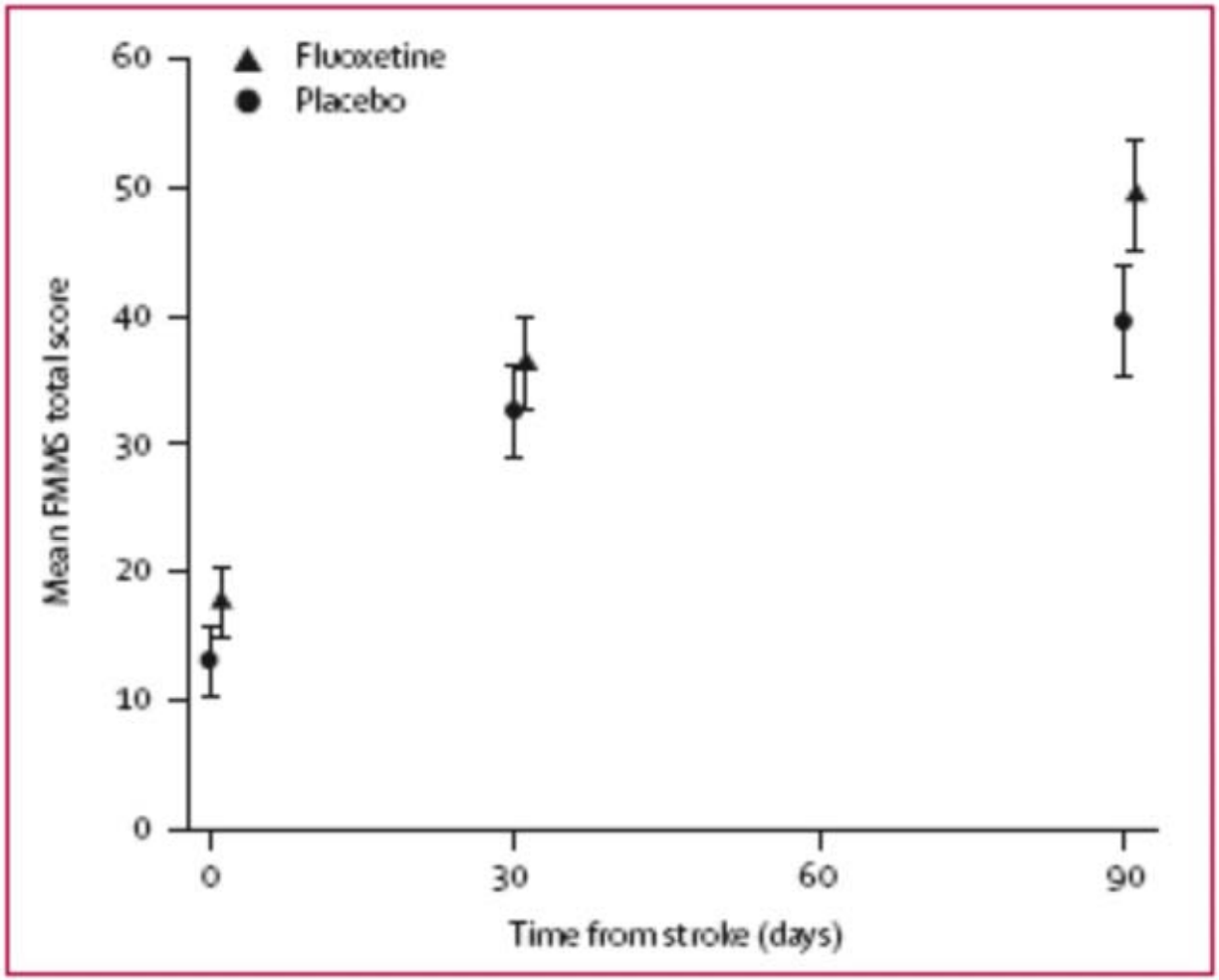


Figure 2: Adjusted mean Fugl-Meyer motor scale (FMMS) total scores at days 0, 30, and 90

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

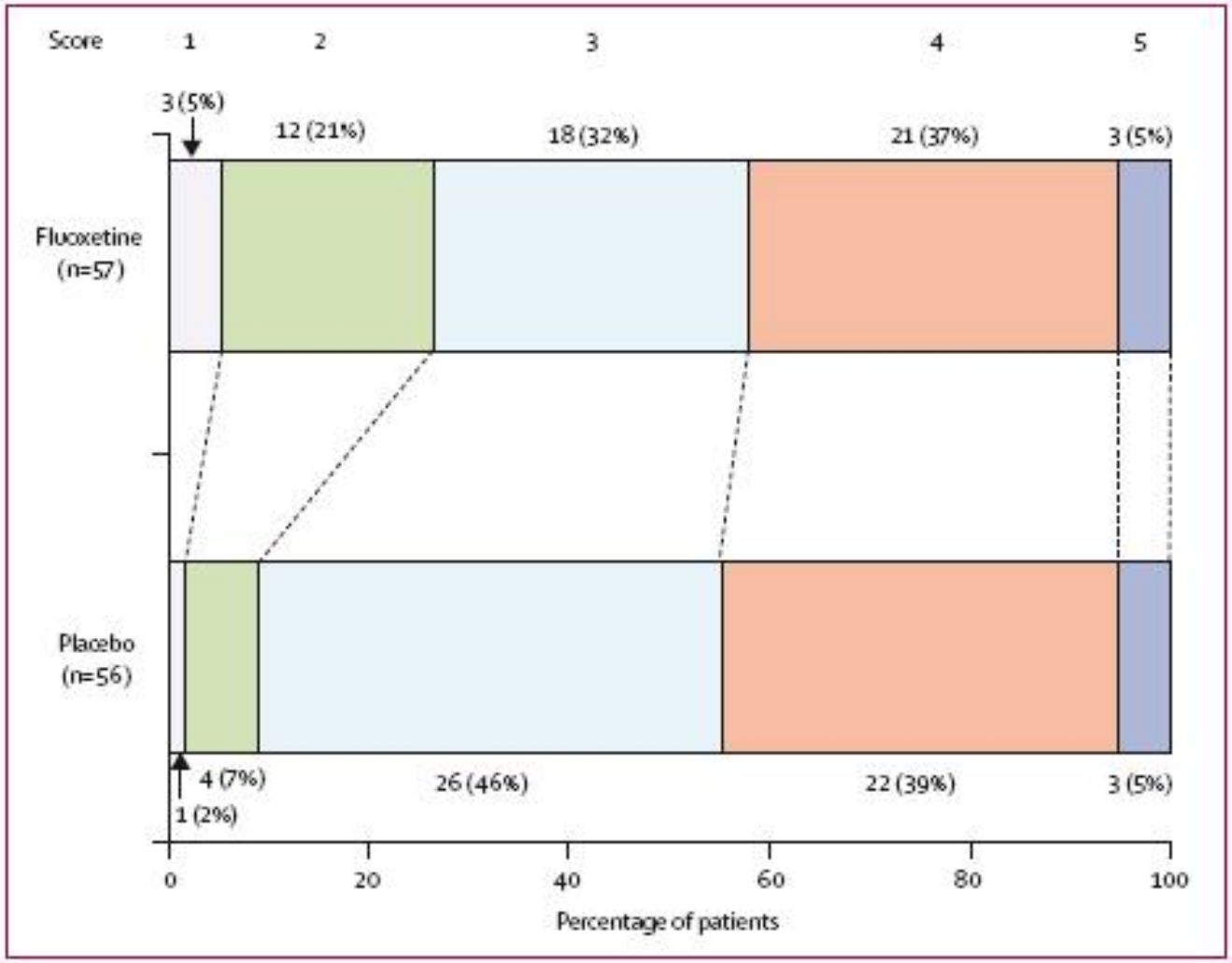


Figure 3: Distribution of modified Rankin scale scores at day 90
Data are number (%).

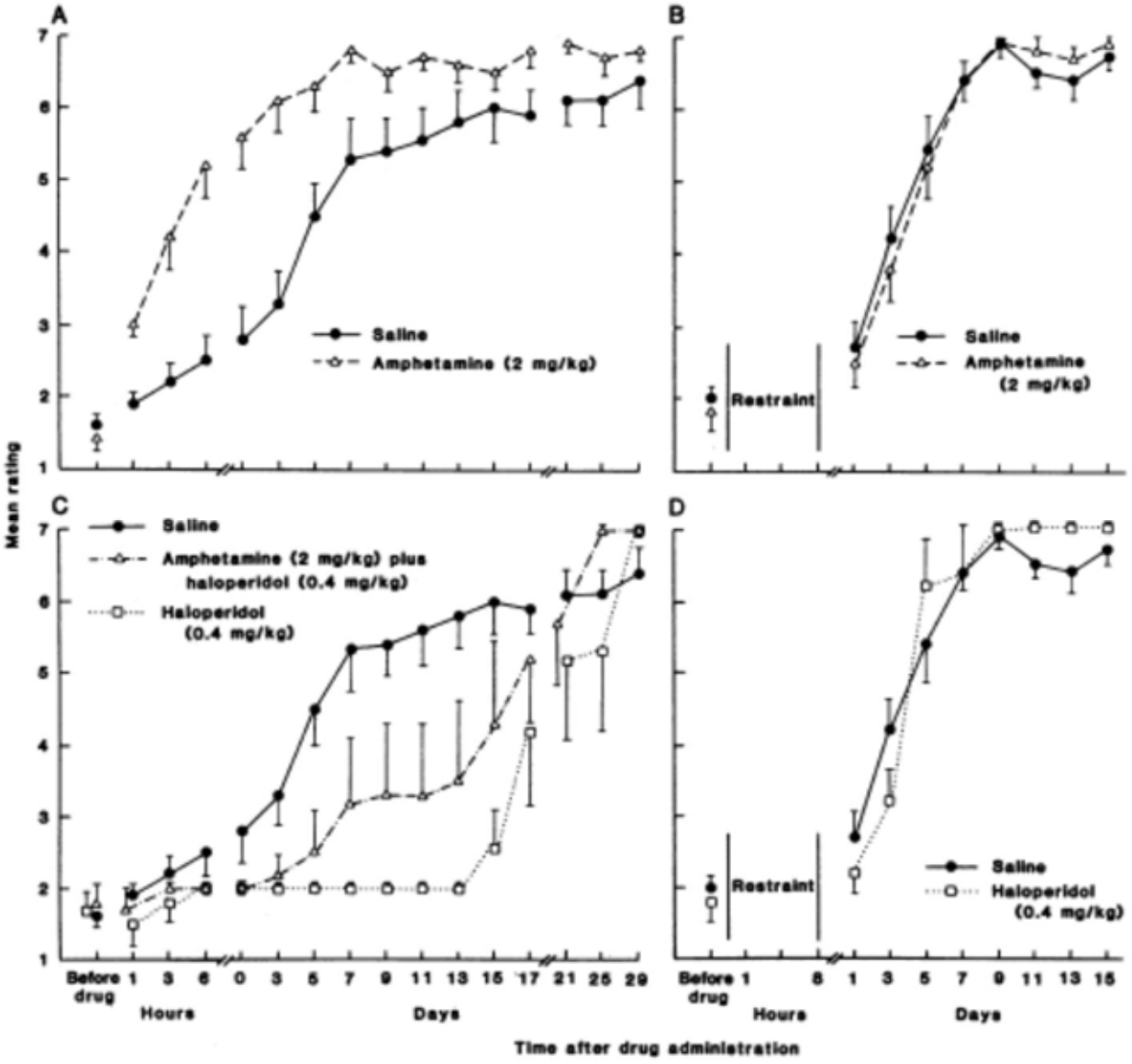
Amphetamine

Amphetamine

- D-Amphetamine is the best studied drug in neurorehabilitation
- Amphetamine is a potent modulator of neurological function and cortical excitation
- The drug primarily acts through norepinephrine and dopamine mechanisms to enhance arousal and attention, and thus, to facilitate learning of motor skills
- Reports suggesting that amphetamine promotes recovery after brain injury date back to the 1940-ies:
  - Maling et al, 1946: „Righting and other postural activity in low-decebrate and in spinal cats after d-amphetamine. J Neurophysiol 1946;9:379 –386.
- Interest renewed in the 1980's with a pivotal paper by Feeney and co-workers:
  - Feeney et al. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. Science 1982;217:855–857.

Feeney et al, 1982:

Hemiplegic rats (unilateral suction ablation of the somatic sensorimotor cortex) were treated with d-amphetamine paired with training on a locomotor task



Enduring acceleration of recovery after a single dose of amphetamine 24 hours after injury (A)

The behavioral improvement was blocked by preventing locomotion during drug intoxication (B)

Improvement was also blocked by administering haloperidol (C) or by preventing locomotion (D)

These observations have been replicated in a large number of animal studies, e. g.:

- Hurwitz et al. Amphetamine **promotes recovery from sensory-motor integration deficit after thrombotic infarction of the primary somatosensory rat cortex**. Stroke 1991;22:648–654.
- Adkins & Jones. D-amphetamine **enhances skilled reaching after ischemic cortical lesions in rats.** Neurosci Lett 2005;380:214–218.
- Barbay et al. A single injection of D-amphetamine **facilitates improvements in motor training following a focal cortical infarct in squirrel monkeys**. Neurorehabil Neural Repair 2006;20:455–458.
- Ramic et al. **Axonal plasticity is associated with motor recovery following amphetamine treatment** combined with rehabilitation after brain injury in the adult rat. Brain Res 2006;1111:176–186.
- Rasmussen et al. Acute but not delayed amphetamine treatment **improves behavioral outcome in a rat embolic stroke model.** Neurol Res. 2011 Sep;33(7):774-82.
- Liu et al. Post-treatment with amphetamine **enhances reinnervation of the ipsilateral side cortex in stroke rats.** Neuroimage. 2011 May 1;56(1):280-9.

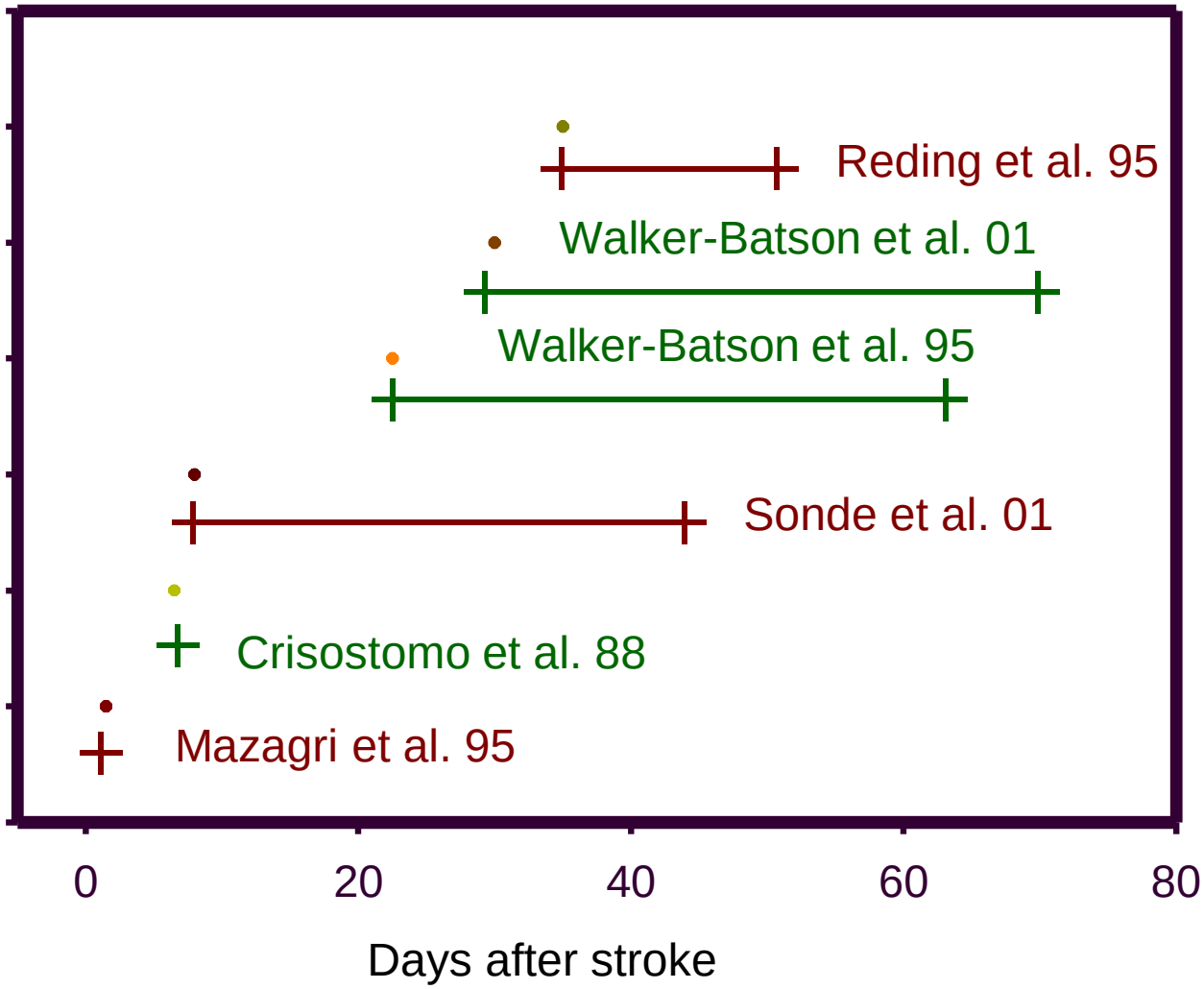
Effects of amphetamines (+ physiotherapy) on poststroke motor recovery in humans: Double-blind, placebo-controlled trials *(Goldstein, Stroke 2009)*

Study	n	Stroke-Treatment Interval	*d*-Amphetamine Dose/Treatment Frequency	Drug-Therapy Session Interval (Duration)	Outcome Assessment
Cristostomo et al, 1988[6]	8	<10 days	10 mg, one session	<3 hour (45 minutes)	1 day
Reding et al, 1995[7]	21	>1 month	10 mg daily for 14 days, then 5 mg daily for 3 days	Same day (? Duration)	1 month
Walker-Batson et al, 1995[8]	10	16–30 days	10 mg every 4 days for 10 sessions	"Peak of drug action" (? Duration)	1 week and 1 year
Sonde et al, 2001[11]	39	5–10 days	10 mg twice weekly*	1 hour (30 minutes)	3 months
Martinsson et al, 2003[12]	30	<96 hours	5 or 10 mg once or twice daily for 5 days	Same day (15 minutes vs 30–45 minutes)	3 months and 1 year
Treig et al, 2003[10]	24	<6 weeks	10 mg every 4 days for 10 sessions	1 hour (45 minutes)	90 days and 1 year
Gladstone et al, 2006[13]	71	5–10 days	10 mg twice weekly for 10 sessions	90 minutes (1 hour)	6 weeks and 3 months

*dl-amphetamine.
**Duration of physiotherapy varied (both groups received *d*-amphetamine).

- Inconsistent findings
- Attributable to potentially critical differences in trial design?
  - Small patient samples in most studies
  - Differences in: Stroke location and severity, dose regimen, treatment window (stroke-treatment interval), type, intensity and duration of physiotherapy

D-AMPHETAMINE: CLINAL STUDIES



D-AMPHETAMINE
IN STROKE REHABILITATION
???

WHEN?
WHICH DOSE?
HOW LONG?
+/- PHYSIOTHERAPY?

Critical review of randomised controlled trials of amphetamine in stroke *(Sprigg and Barth, J Neurol Sci 2009)*

- Eleven trials (n=329)
- Amphetamine treatment was associated with
  - Non-significant trends to increased death (OR 2.78 (95% CI, 0.75–10.23), n=329, 11 trials)
  - Improved motor scores (weighted mean difference 3.28 (95% CI ?0.48–7.04) n=257, 9 trials)
  - No effect on the combined outcome of death and dependency (OR 1.15 (95% CI 0.65–2.06, n=206, 5 trials)
  - Increased systolic blood pressure (weighted mean difference 9.3 mmHg, 95% CI 3.3–15.3, n=106, 3 trials) and heart rate (weighted mean difference 7.6 bpm, 95% CI 1.8–13.4, n=106, 3 trials).
- Despite variations in treatment regimes, outcomes and follow-up duration there was no evidence of significant heterogeneity or publication bias
- Author´s conclusion:
  - No evidence exists at present to support the use of amphetamine after stroke
  - Doubts remain over safety and there are significant haemodynamic effects, the consequences of which are unknown

Dopaminergic agents

Levodopa

- Findings from placebo-controlled studies in stroke patients: conflicting results, but positive effects in most studies
  - Sonde & Lökk, 2007: No effect of Levodopa on motor functions in subacute stroke patients (N=25, 100mg/day for 2 weeks)
  - Floel et al, 2005: Single dose of 100mg levodopa levodopa was associated with more frequent TMS-evoked movements in chronic stroke patients
  - Restemeyer et al. 2007: No effects of single dose of 100mg levodopa in chronic stroke patients (N=10), neither in the clinical tests (nine-hole-peg test, dynamometer) nor in TMS results.
  - Rösser et al, 2008: Improvement of Procedural Motor Learning (N=18) in chronic stroke patients
  - Scheidtmann et al, 2001: Improvement of recovery after stroke (N=53)

Scheidtmann et al, Lancet 2001

Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study

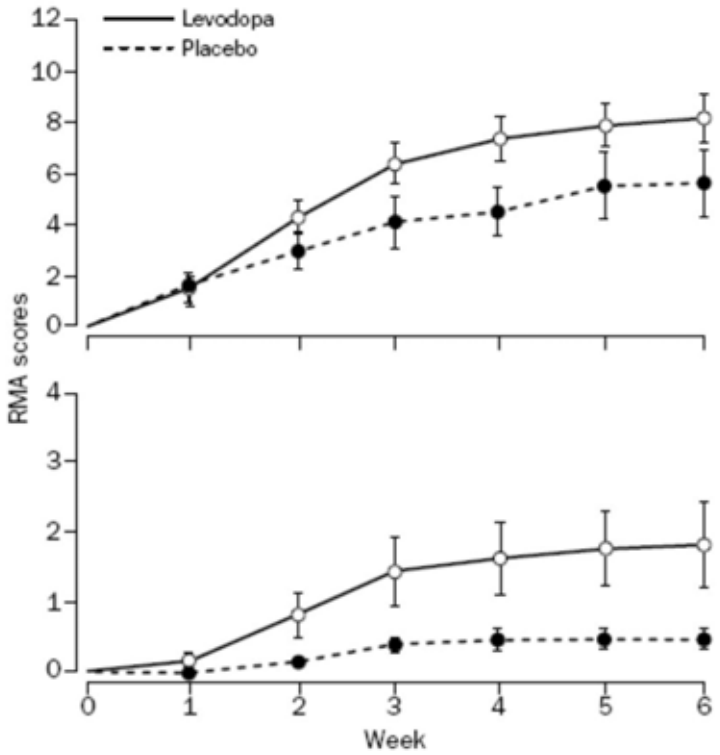


Figure 2: **Overall gain in motor function (upper) and in arm function (lower)**
RMA=Rivermead motor assessment. Error bars=SE. Overall gain in motor function at 3 weeks p<0·004 and at 6 weeks p<0·020. Gain in arm function at 3 weeks p<0·015 and at 6 weeks p<0·008.

N=53

Week 1-3: Levodopa 100 mg or placebo daily plus physiotherapy

Week 4-6: Physiotherapy only

Weekly assessment of motor function (Rivermead motor Assessment, RMA)

Motor recovery significantly improved after 3 weeks of drug intervention with levodopa (RMA improved by 6·4 points) compared with placebo (4·1)

Advantage of levodopa was maintained at study endpoint 3 weeks after levodopa was stopped

Result was independent of initial degree of impairment (p<0·004)

Other studies on dopaminergic agents

- Dopaminergic agents: Beneficial in neglect after stroke? Results from case studies:
  - Mukand et al, 2001: L-Dopa was beneficial for left neglect after stroke (n=4)
  - Fleet et al, 1987: Bromocriptine was effective in unilateral spatial neglect (n=2)
- Bromocriptine in traumatic brain injury:
  - McDowell et al, 1998: Improvement in executive function and dual-task performance, but not in working memory (n=24; double-blind, plaecbo-controlled)

Methylphenidate

- Methylphenidate increases dopaminergic activity
- Results of placebo-controlled trials suggest a potential benefit in stroke and TBI (traumatic brain injury) patients
  - Grade et al, 1998: Methylphenidate with physical therapy over a period of 3 weeks improved motor functions and decreased depression in patients early after stroke (n=21)
  - Whyte et al, 1997 (n=19), Whyte 2004 (n=34): Methylphenidate improved the speed of mental processing in TBI patients
  - Plenger et al, 1996: Methylphenidate was associated with better performance on tests of attention and motor performance in TBI patients (n=12)
- Moein et al, 2006: Methylphenidate soon after severe TBI seems to reduce the length of stay both in the intensive care unit and in hospital

Amantadine

- Early case reports and retrospective studies (Kraus et al, 1997; Nickels et al, 1994; Chandler et al, 1988) suggested beneficial effects of amantadine in TBI: ↓ agitation and aggression and attention, ? concentration and alertness
- Most placebo controlled studies confirmed these findings:
  - Meythaler et al, 2002: Amantadine improved disability and cognition in patients within the first 3 months after TBI (n=35)
  - Schneider et al, 1999: No beneficial effect of amantadine in TBI (n=10)
  - Kraus et al, 2005: Amantadine improved executive functioning in chronic TBI patients (n=22) and increased glucose metabolism in the left prefrontal cortex (PET performed in in 6 patients)
- Two reviews concluded that amantadine at doses of 200–400mg/d improves arousal and cognition in patients with TBI if administered 3 days to 5 months after the injury (Leone et al, 2005; Sawyer et al, 2008)

Giacino et al, NEJM 2012

Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

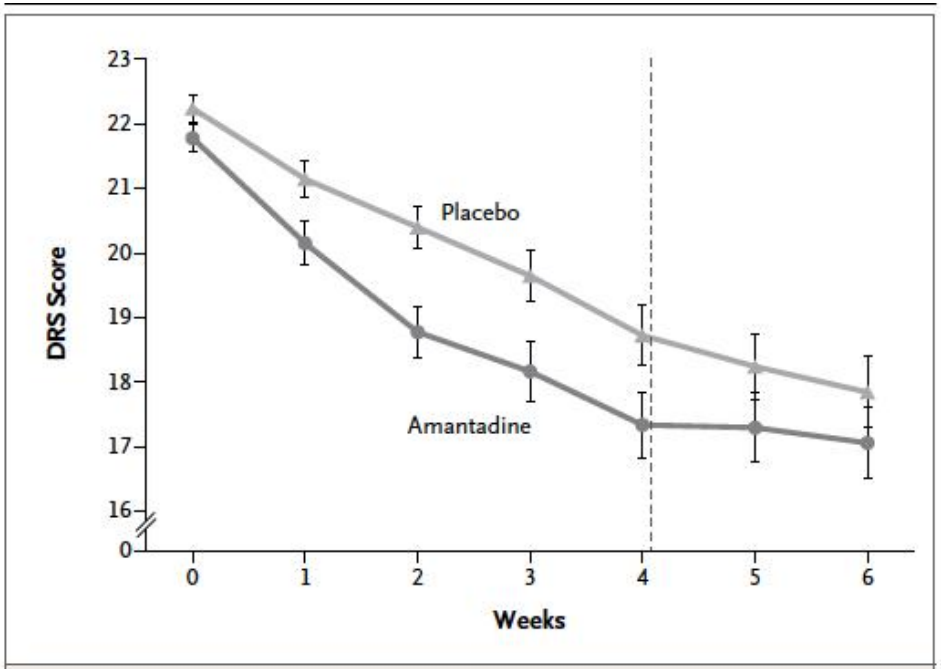


Figure 1. Mean Disability Rating Scale (DRS) Scores during the 6-Week Assessment Period, According to Study Group.

DRS scores range from 0 to 29; lower scores indicate less severe functional disability (see Fig. S7 in the Supplementary Appendix for the DRS syllabus). DRS scores improved significantly faster in the amantadine group than in the placebo group during the 4-week treatment interval. During the wash-out interval (weeks 5 and 6), the rate of recovery was significantly slower in the amantadine group, and mean DRS scores were similar for the two groups at the 6-week mark. I bars denote the standard error.

N=184

11 centers in 3 countries

Vegetative or minimally conscious state, 4-16 weeks after acute TBI

Amantadine (200-400mg/d, p.o.)

Week 1-4: Amantadine vs. Placebo
Week 5-6: wash-out

Disability Rating Scale (DRS, 0-29)

Difference in slope (week 1-4): 0.24 points per week
P=0.007

Overall improvement **in DRS scores between baseline and week 6 was *similar* in the two groups**

Reboxetine

Reboxetine

- Acts as a selective noradrenaline reuptake-inhibitor, with consective increase of norepinephrine levels in the synaptic cleft
- A limited number of small placebo-controlled trials suggest a beneficial effect on motor function
  - Plewnia et al, 2004: A single dose of 6 mg reboxetine improved motor skill acquisition in healthy individuals
  - Zittel et al, 2007: A single dose of 6 mg reboxetine induced a significant improvement of tapping speed and grip strength in chronic stroke patients (n=10)

Acetylcholine-Esterase-Inhibitors

Donepezil, Rivastigmine

- Given the well-established role of acetylcholine for cognitive and motor functions, an increase of brain acetylcholine levels appears to be a reasonable approach
- Placebo-controlled studies examined the effect of donepezil and rivastigmine on speech and cognition in stroke and TBI patients, with inconsistent findings:
  - Donepezil
    - Berthier et al, 1989: Donepezil (10 mg/d for 16 weeks) improved aphasia in 26 poststroke patients (n=26)
    - Zhang et al, 2004: Donepezil (10 mg/d for 10 weeks) improved short-term memory and sustained attention in chronic TBI patients (n=18)
  - Rivastigmine
    - Tenovuo et al, 2005: Rivastigmine (3–6mg/d for 12 weeks) in TBI patients (n=157) produced no effects on verbal memory and information processing

Piracetam

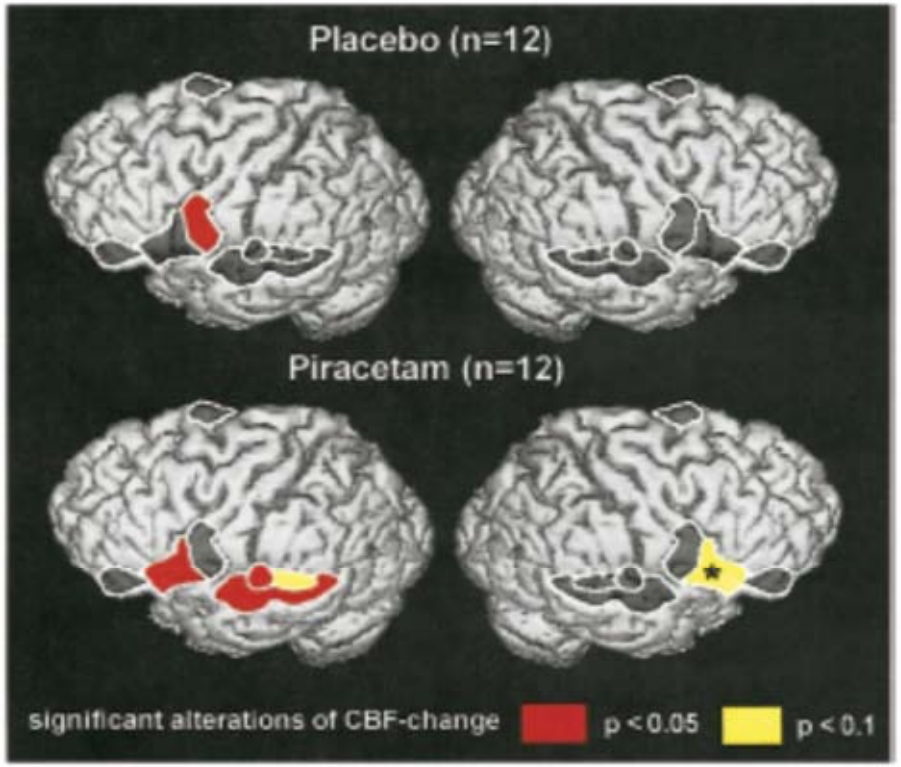
Piracetam

- Some evidence suggests that piracetam enhances glucose utilization and cellular metabolism in the brain
- The exact mode of action is unknown
- Placebo-controlled studies:
  - Enderby et al, 1994; Huber et al, 1997: Piracetam (4.800 mg/d) reduced aphasic symptoms in subacute stroke patients (n_{total}=203)
  - Kessler et al, 2000: Piracetam (4.800 mg/d for 6 weeks + language therapy) improved language skills in aphasic stroke patients (n=24) and increased activity (PET) in speech-relevant brain areas (left transverse temporal gyrus, Wernicke, Broca) during a word-repetition task
- A Cochrane Review concluded that „treatment with piracetam may be effective in the treatment of aphasia after stroke“ (Greener et al, 2001)

Piracetam Improves Activated Blood Flow and Facilitates Rehabilitation of Poststroke Aphasic Patients

J. Kessler, PhD; A. Thiel, MD; H. Karbe, MD; W.D. Heiss, MD

Stroke 2000: 31:2112-2116.



A significant enhancement of blood flow change at the end of treatment was observed only in the left hemisphere. In the piracetam group, rΔCBF was significantly higher in the left transverse temporal gyrus, left triangular part of inferior frontal gyrus, and left posterior superior temporal gyrus after the treatment period compared with the initial measures. The suppression effect of the right Broca area (area with asterisk) is compatible with successful language recovery. The placebo group showed an increase of activation effect only in the left vocalization area.

Conclusions (1)

- Cellular mechanisms underlying the effects on recovery of drugs that act on the CNS still remain largely speculative
- For most drugs evaluated in restorative neurology, the hypothesized main mechanism of action appears to be an increase of central norepinephrine levels (e. g. amphetamine, certain dopaminergic drugs)
- Some drugs (e. g. amphetamine) continue to show promising results for recovery of function in the majority of pre-clinical trials

Conclusions (2)

- There are some general principles that have emerged from experimental studies:
  - Responses to a drug may be state dependent (differential effects in healthy subjects versus those with brain lesions or comorbid psychiatric disorders)
  - Patients with similar clinical phenotype may respond to psychopharmacologic agents in different ways, depending on lesion location
  - Individual drugs can have varying effects based on the dosage (dose-effect relationship)
  - Timing of drug administration may be crucial
  - Effects of drugs seem to be dependent on concomitant behavioral experience (e.g. drug administration must be coupled with training)

Conclusions (3)

- In many cases, results of animal studies have not translated well to clinical trials, which have yielded mixed results
- Most studies in humans were performed in well-selected small patient groups, thus they rather serve as a proof-of-principle investigation
- To date, there is only limited evidence for supporting or refuting the use of centrally acting drugs given to enhance the effects of neurorehabilitation

Conclusions (4)

- Evidence from clinical trials suggest that the most promising pharmacological strategies may include:
  - Piracetam for poststroke aphasia
  - Levodopa for improvement of motor functions in stroke patients
  - Amantadine for improvement of cognitive functions and alertness after TBI
  - These drugs have minor side-effects and can, therefore, be considered reasonably well tolerated.
- Recent evidence also suggests that SSRIs may have beneficial effects on motor recovery in stroke patients
- To date, no clear evidence exists to support the use of amphetamine after stroke in humans (conflicting results in studies with humans; safety concerns)

Conclusions (5)

- Many factors related to the optimal design of clinical trials pairing drugs and behavioral experience have not yet been established
- Factors that remain to be elucidated include
  - Timing of treatment relative to injury onset
  - Timing, quality and quantity of the behavioral experience
  - Dosage regimens
  - Side effect profile (safety concerns)
- If one wishes to use a drug for a specific indication, for example aphasia or motor recovery, patients should be informed about the level of current evidence supporting such an approach

Conclusions (5)

- Functional imaging tools (fMRI, PET, TMS) allow evaluation of the effects of a drug on brain activity in greater detail; thus future studies with adequate design will be interesting
- Clinicians should know about negative effects of some commonly prescribed drugs in patients recovering from stroke (e. g. haloperidol); benzodiazepines and anticholinergics may also have hamper recovery, though sufficient data in humans are lacking

Thank you for your attention!