Recovery after brain damage and response to rehabilitation therapy: experimental design

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Cognitive Recovery After Head Injury.
Wong et al. (2001)

A database containing 319 patients with a broad range of coma duration was used to construct recovery curves for performance IQ. Recovery is influenced by severity, but is always faster early, with slower changes apparent over many months.

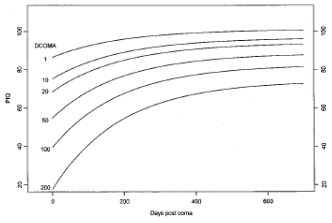
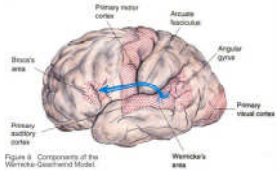


Figure 3. Recovery of PIQ.

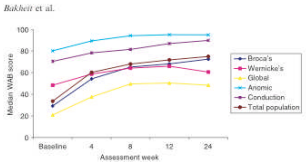
BRAIN INJURY, 15, 519 -530

Background: Aphasia After Stroke.

- Impaired language processing is common after damage to the superior temporal or posterior frontal lobes of the left hemisphere.
- Fluency and comprehension are affected in varying degrees depending on site of damage.
- Difficulty in producing object names "anomia" is the most common deficit and seen to some extent in most aphasics



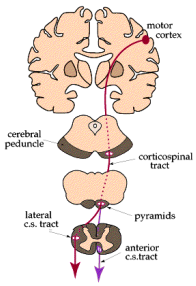
The classical model of language areas. Now known to be only partially correct.



Clinical Rehabilitation 2007; 21: 941–949

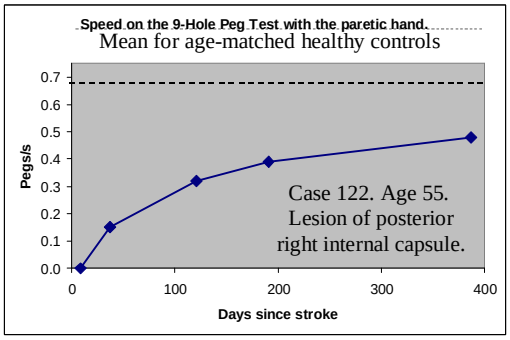
Background: Arm paresis after stroke

- Reduced use of one hand and arm (paresis) is a common long term problem after stroke.
- This is due to damage to the contralateral motor cortex or descending pathways (especially the internal capsule).
- When there is complete paralysis in the arm and leg it is called hemiplegia, but where there is some movement the correct term is hemiparesis.

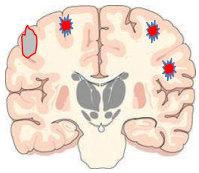


Rules of Recovery:

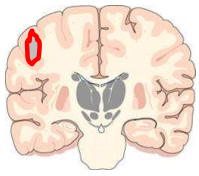
Fast early, slow late and spanning >6months.



General indications from imaging studies of recovery from aphasia and paresis.



Initially there is greater than normal activity in many brain areas.



During recovery there is a re- focussing to a more normal pattern. Often around the borders of the area of damage ("peri-lesional activation").

Studies of Changes in Brain Activation After Rehabilitation Therapy

- A difficult type of study to do well. They require:-
  - Repeated assessments
  - Methods to distinguish between effects of the passage of time ("spontaneous recovery") and treatment effects.
- Most studies to date have looked at short-term changes in chronic-stage patients where spontaneous recover is smallest.
- Behavioural methodology tends to be given less attention than neuroimaging.
  - As yet, there are no high quality randomised trials.

The Randomised Controlled Trial
Why is it the gold standard?

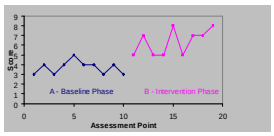
- Has high Internal Validity
  = High confidence in inference of causal relationship (that it was the treatment that did it).
- Has high External Validity
  = High confidence that the results will generalise to other members of the population.

The Randomised Controlled Trial

- The "gold standard" in medical clinical trials e.g. testing new drugs.
- But it is difficult to apply where there are individual differences in problems, individually determined treatments, and complex outcomes.
- It has been argued that RCTs are premature in cognitive neuroscience until individual differences and treatment effects are better understood e.g. therapy for visual neglect (Barrett et al., J Cog Neuroscience, 2006, 1223-1236).
- So far studies of neural effects of therapy have been limited to small N experimental studies of variable quality.

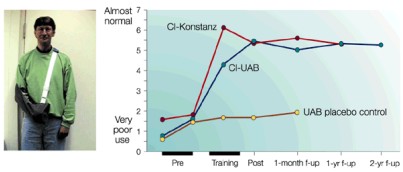
Weak Internal Validity of the uncontrolled before-after (AB) design.

- Unless the baseline is protracted and stable, there is no control for effects of passage of time.
- No control for placebo effects.



Intensive Treatment for Arm Paresis
Constraint Induced Movement Therapy (Taub et al., 2002)

- In this therapy a sling is worn on the other arm throughout the waking day. This overcomes the tendency to use the other hand by "forced use."
- This is maintained for 2 weeks of normal activities and combined with with intensive graded training in the use of the paretic limb for everyday functional tasks.
- A number of studies have shown that in some cases this results in a permanent increase in use of the affected arm.



Nature Reviews | Neuroscience

TMS study of cortical effects of Constraint Induced Movement Therapy
Liepert et al. (2000) *Stroke 31:1210-6*

- Thirteen patients with chronic stroke (>6 months)
- 3 had cortical lesions. 10 had internal capsule lesions.
- All had some residual finger movement.
- 12 days of CI therapy preceded and followed by TMS studies.

Liepert et al. (2000) *Stroke 31:1210-6*

Behavioural effects. Reported frequency of hand use (Motor Activity Log).

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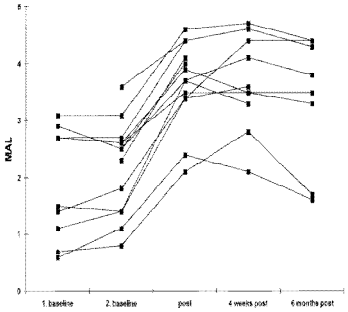
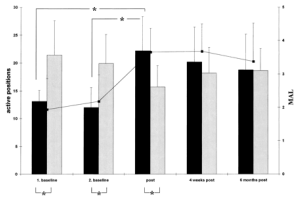


Figure 1. MAL scores 2 weeks and 1 day before treatment and 1 day, 4 weeks, and 6 months after treatment for each patient.

Liepert et al. (2000) *Stroke 31:1210-6*

TMS effects

- Before constraint induced therapy there was an average off 40% fewer TMS active sites across the damaged hemisphere than the intact hemisphere.
- After therapy, the situation was reversed, with 37% more active sites on the damaged side.
- This effect diminished over time but the paretic side remained more responsive than at baseline, and at 6 months after therapy.



Black bars = Number of active TMS positions in the damaged hemisphere. **P*<0.05
Grey bars = Active sites in the intact hemisphere.
Line = Patient's reports of the amount of use of the paretic hand.

Liepert et al. (2000) interpreted these results as evidence of restitution of cortical representation of the paretic limb in peri-lesional areas:-

•The reduced excitability of the damaged hemisphere before therapy was consistent with diminished representation of the paretic limb.

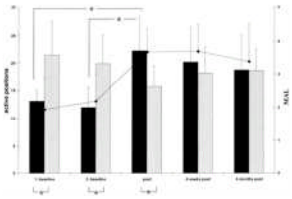
•The increased number of active sites after therapy was seen as a resolution of this abnormality and recovery of a normal balance between the hemispheres.

•In addition to enlargement of the excitable area there was a shift in its location suggesting recruitment of adjacent cortical areas – paralleling the animal study by Nudo et al. (1996) which demonstrated the formation of a new hand representation neighbouring the cortical lesion.

Critical Evaluation

An interesting study, but some reservations:-

- An AB uncontrolled design with a brief baseline.
- Very little information is given about the behavioural improvements
  - only subjective reports (MAL scores) are included in the paper
  - no information is given about objectively measured changes in motor performance.



Cornelissen et al. (2003)

Adult Brain Plasticity Elicted by Anomia Treatment. J Cog Neuroscience, 15, 444-461.

Used MEG to look for specific changes distinguishing between trained and untrained words.

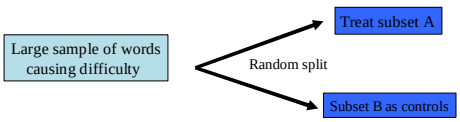
Three anomic patients 2, 8 & 14 years after stroke.

100 hard-to-name pictures selected for each individual.

50 of these used as control items and 50 used in training.

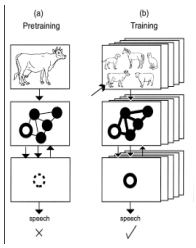
Two types of single case experiment in aphasia therapy research

- Before-After, AB studies
  - Weak internal validity unless controlled
- Split-set studies:-



- Can only be used where targets can be split into subsets.
- A powerful way of demonstrating specific effects of therapy.
- But not useful if therapy has a general effect.

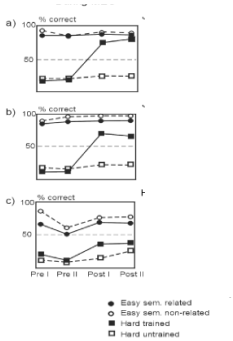
Cornelissen et al. (2003).
Contextual Priming Technique to train naming of 50/100 items



- Pictures presented in sets of 5 semantically related items.
- 5 attempts at repetition of each name presented as part of the set.
- Technique aims to elicit repetition priming + semantic priming.
- 3 hrs of therapy each week for 3 weeks.

Cornelissen et al. (2003).
Effect of therapy on trained and non-trained items

- All 3 patients showed statistically significant effects (weakest for patient c).

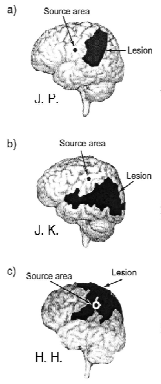


Cornelissen et al. (2003). MEG Procedure

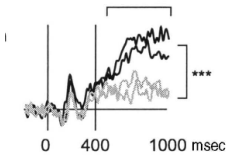
- Picture presented on screen for 150msec
- Question mark appears 3 sec later
- Patient attempts to name.

This rapid presentation & delayed naming paradigm was used to reduce movement artifact due to eye movements during picture inspection or facial muscle activation during attempts to produce a rapid response.

Cornelissen et al. (2003).
MEG Responses After Training



- For all 3 patients, only one source was found which was different for trained versus untrained words.
- In all cases it was in the remaining tissue of the left inferior parietal lobe.
- Only in one case did this overlap with changes related to proportion of correct answers (So the training effect on MEG was not just because more answers were correct).
- The differences between trained & untrained items emerged late after picture onset (300-600mSec).



Grey =pre-training
Black=post-training

Cornelissen et al. (2003).
Their Conclusions

The MEG results showed no evidence of increased right hemisphere participation following training, supporting the view that restoration of language-related networks in peri-lesional cortex is crucial for anomia recovery.

The late emergence of the training effect in the naming process suggested more effective phonological encoding and storage of the trained items through the engagement of a left hemispheric word-learning system.

Conclusions

- Studies of brain changes related to therapy are important but methodologically challenging.
- Published studies are small scale and have limited methodology.
- A focus on the neural aspects has lead to relative neglect of evaluation of behaviour change.
- But new and improved studies are now beginning to appear.