Effects of Stem cell based therapy on acute neural injury

Ana Antonic, Emily Sena, Jennifer Lees,
Malcolm Macleod, David Howells

THE UNIVERSITY OF MELBOURNE

Collaborative Approach to Meta Analysis and
·C·A·M·A·R·A·D·E·S·
Review of Animal Data from Experimental Stroke

THE FLOREY

Aims

To combine the data from two published systematic reviews and meta-analyses of studies using stem cells to treat animal models of traumatic SCI and stroke and determine the effect of stem cells on neurobehavioural score in this larger dataset.

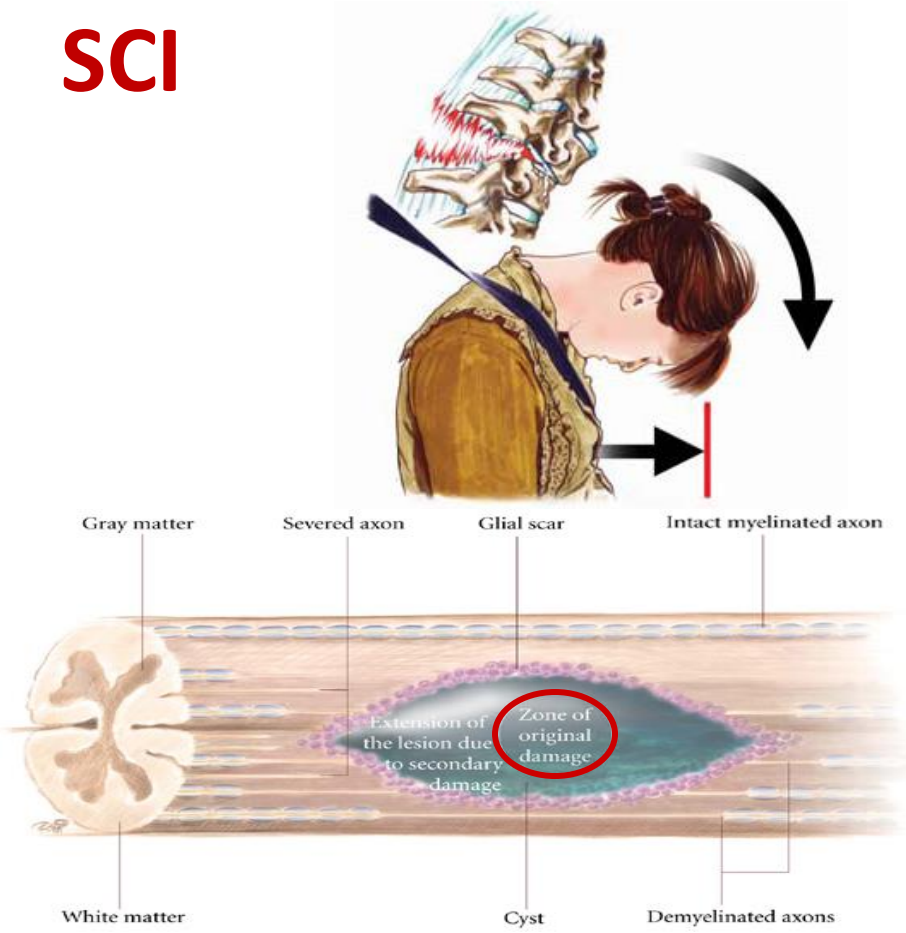
Objectives

To establish a summary estimate of the efficacy of stem cells in models of SCI and Stroke

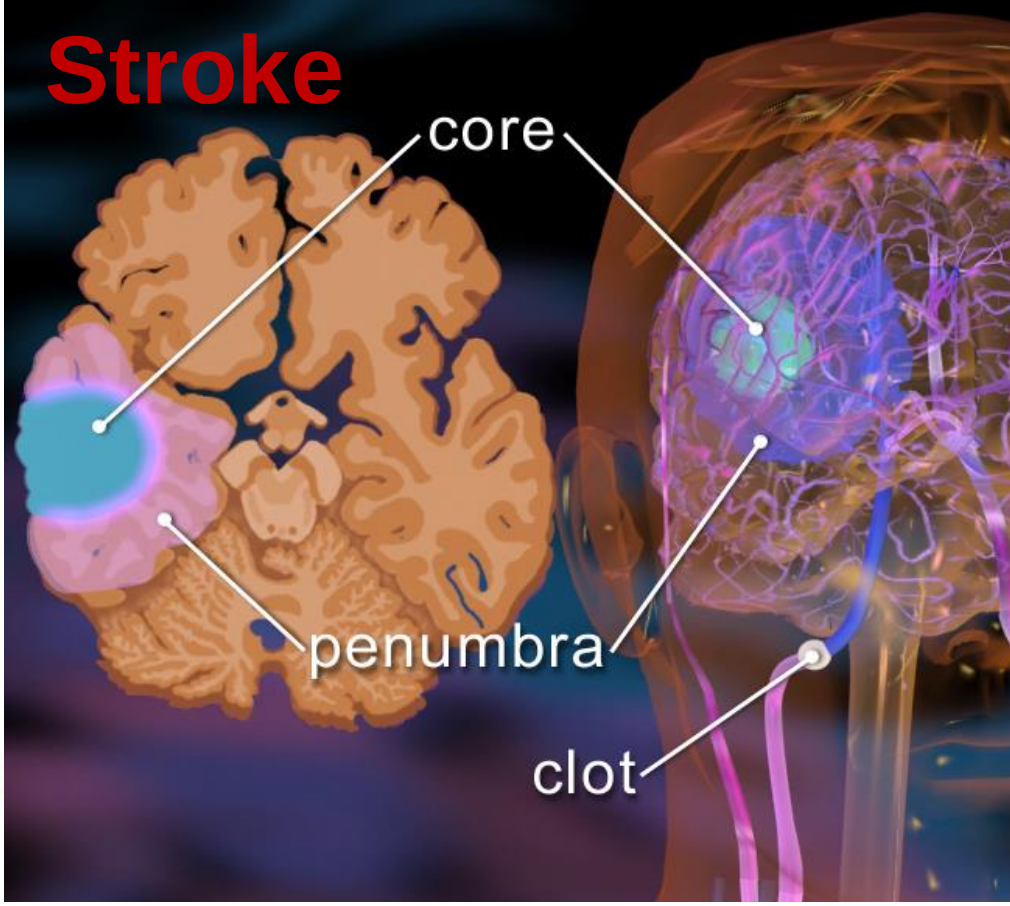
(i) Understanding similarities and differences between these two related diseases to further assess if stem cell therapy works

(ii) To ascertain the conditions under which efficacy was the greatest

SCI

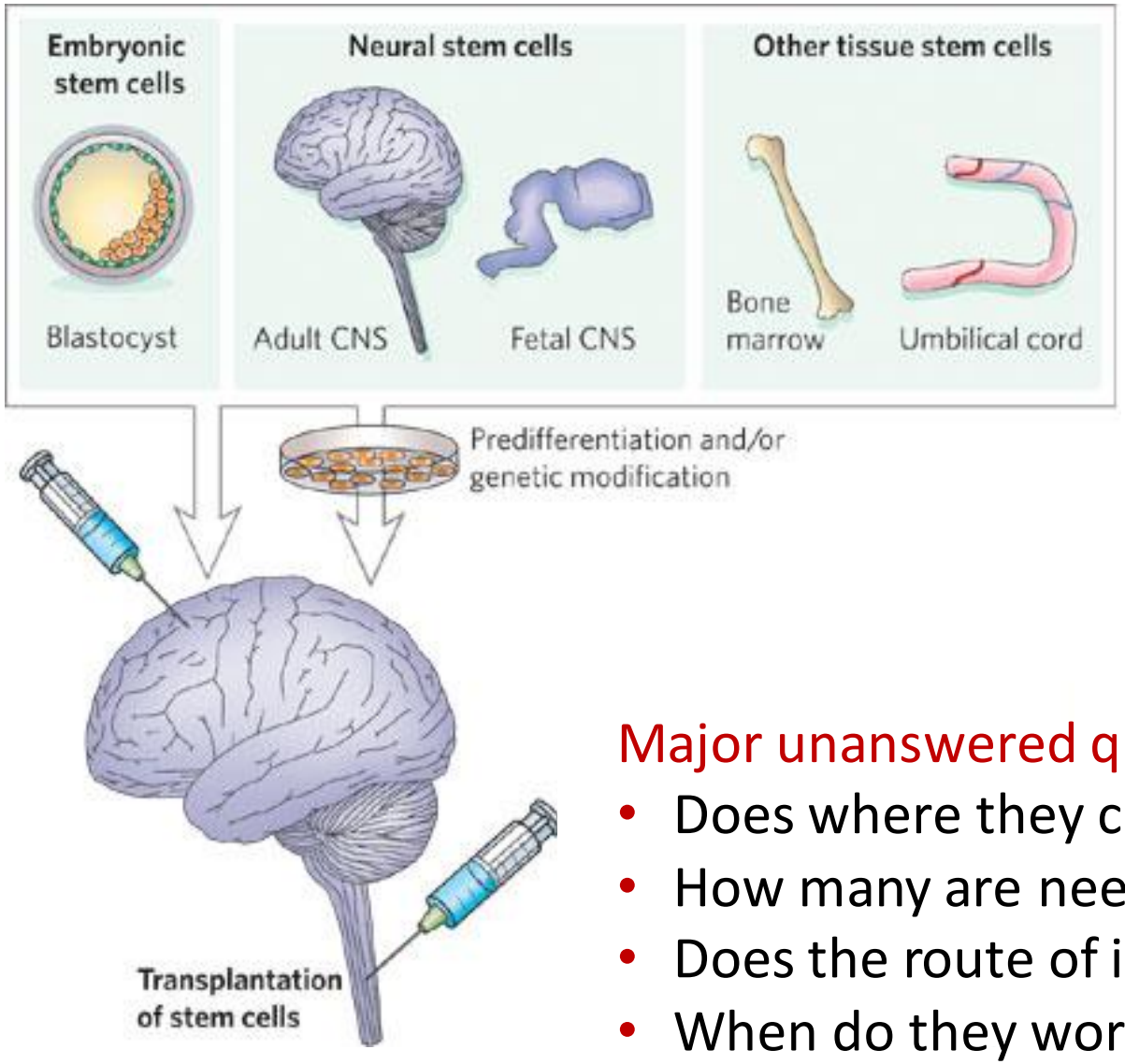


Stroke



Both are acute neurological diseases, and although caused by different processes, the underlying mechanisms of cell death and tissue loss are similar.

Stem cells as a potential treatment



Major unanswered questions

- Does where they come from matter?
- How many are needed?
- Does the route of implantation matter?
- When do they work

Methods

Combination of data from 2 published reviews of stem cell transplantation for treatment of traumatic spinal cord injury and stroke

Inclusion Criteria:

- All the studies included in the original reviews

Primary Outcome:

- Neurobehavioural score

Motor score sub-analysis (most homogeneous data)

- Rats
- With SCI injury created by an impactor or stroke by intraluminal filament/suture
- Assessed by BBB or NSS tests.

DerSimonian and Laird random effects meta-analysis and meta-regression was performed on the combined dataset

Overall analysis

527 experiments involving 8640 animals

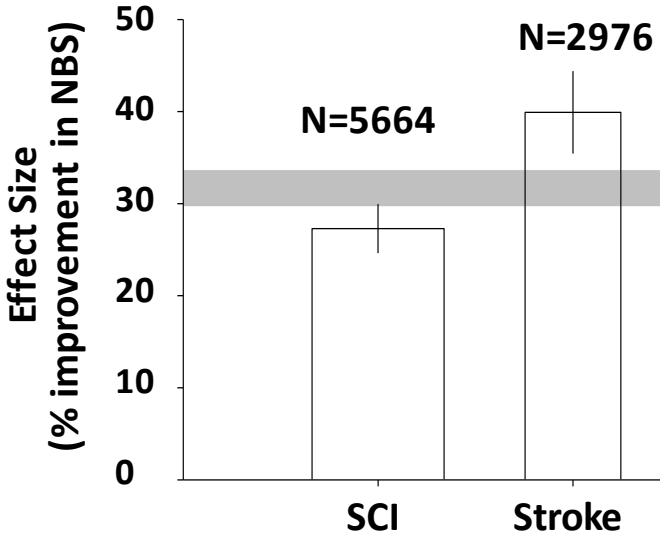
Overall improvement in outcome 31.7% (95% CI 29.6 – 34%)

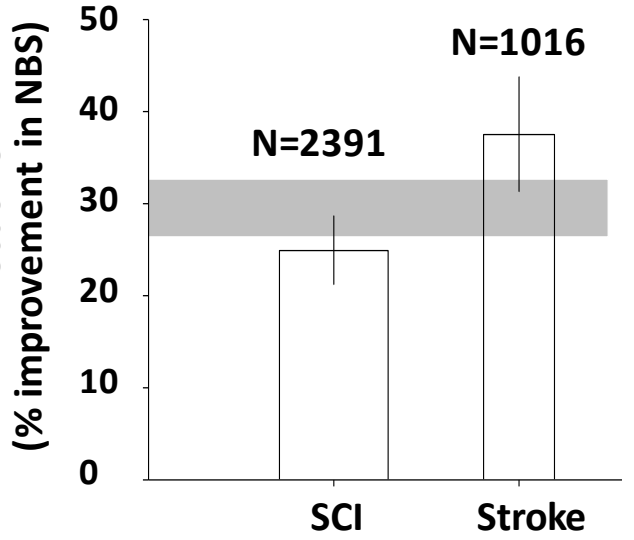
Subset analysis

200 experiments involving 3704 animals

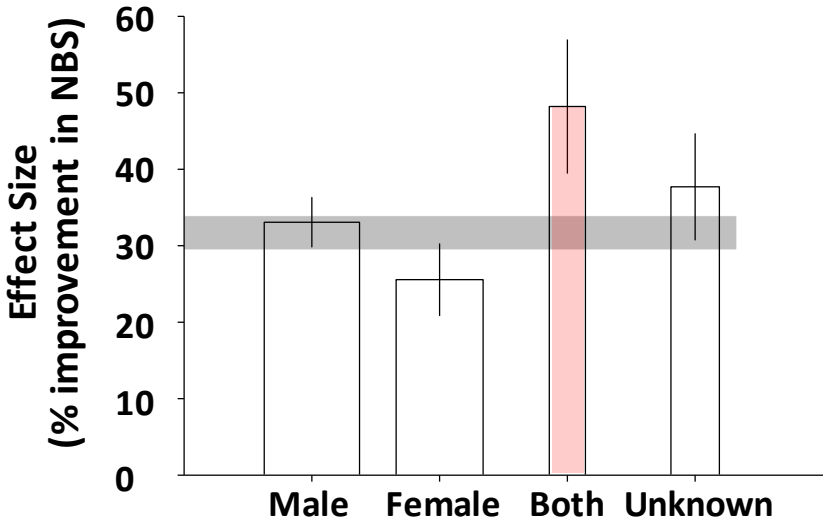
Overall improvement in outcome 29.5% (95% CI 26.4-32.6%)

Stem cells are more effective after stroke than SCI

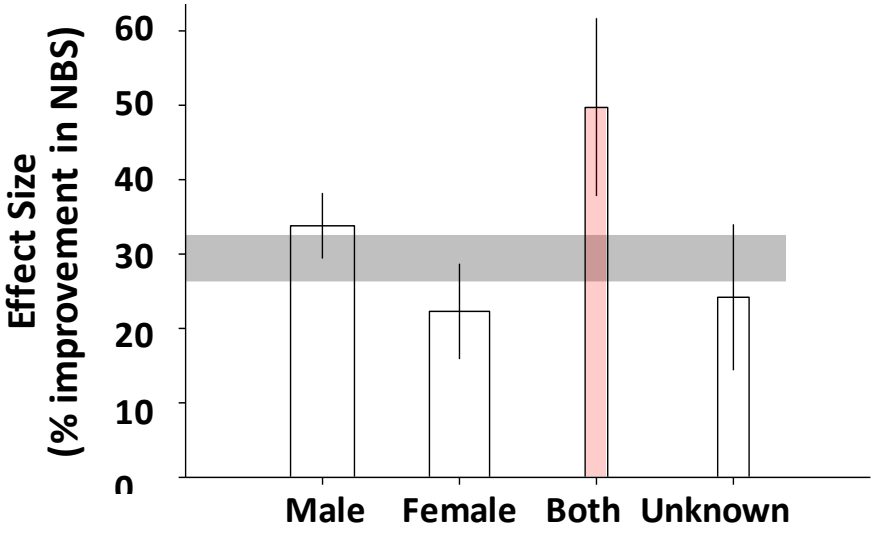




Stem cells are more effective in male than female animals

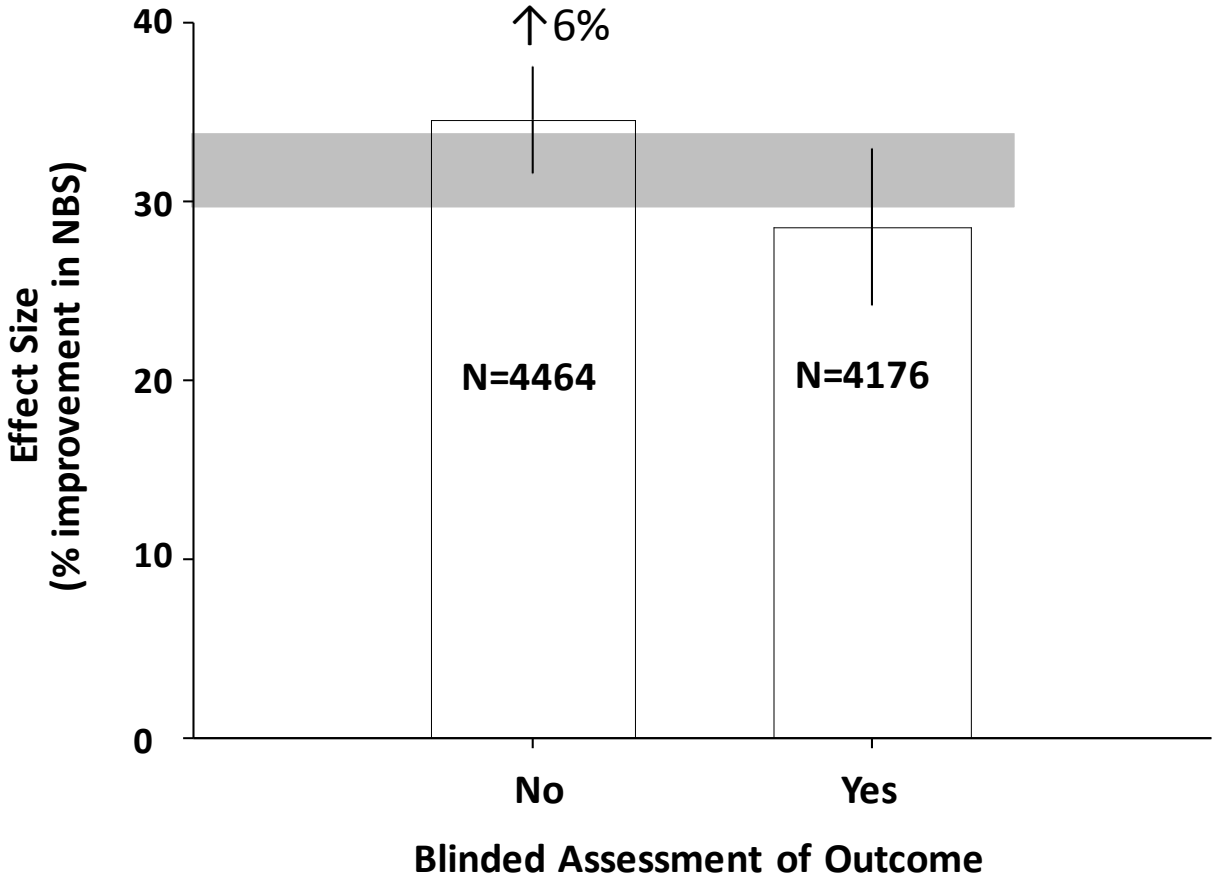


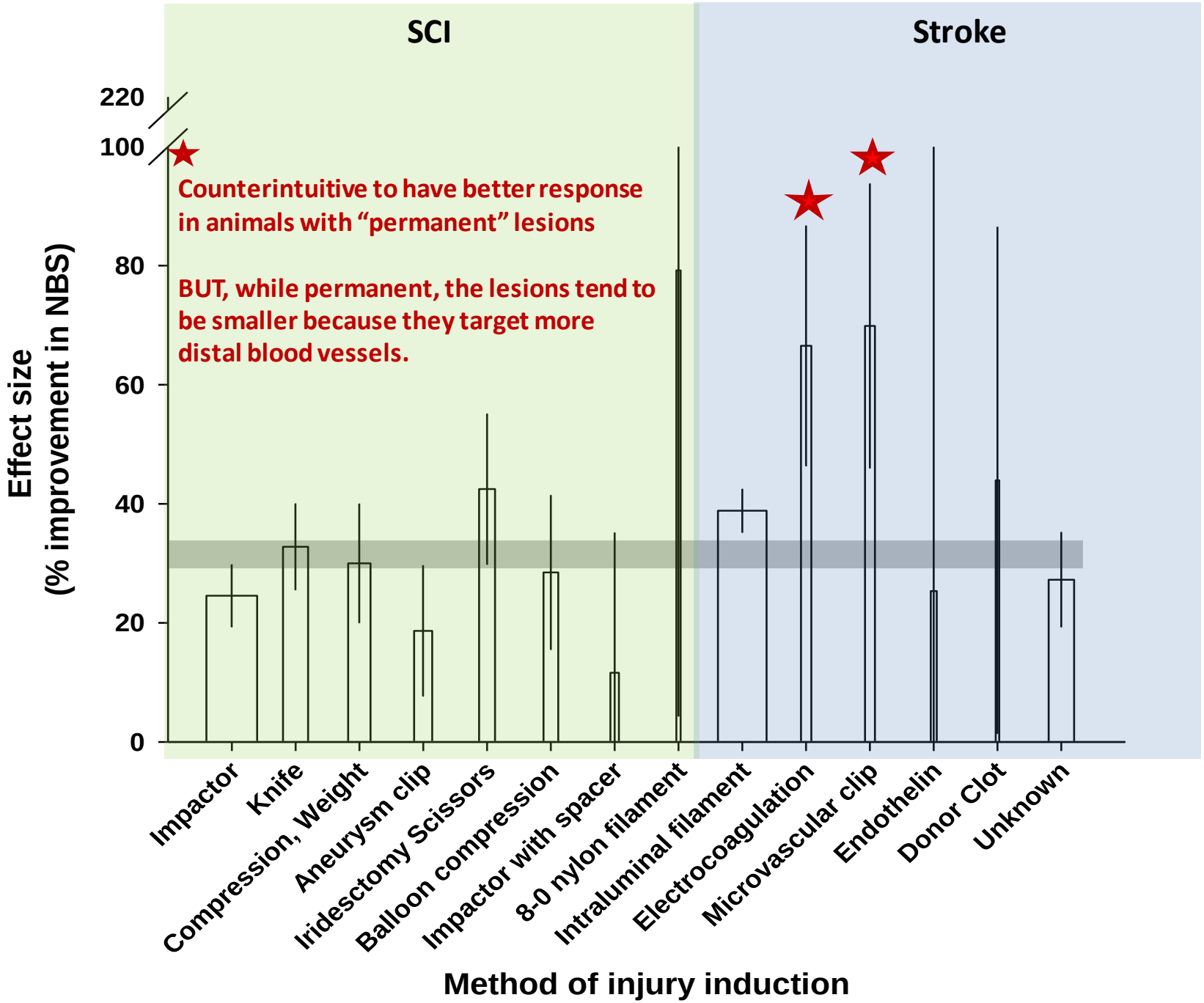
Overall analysis



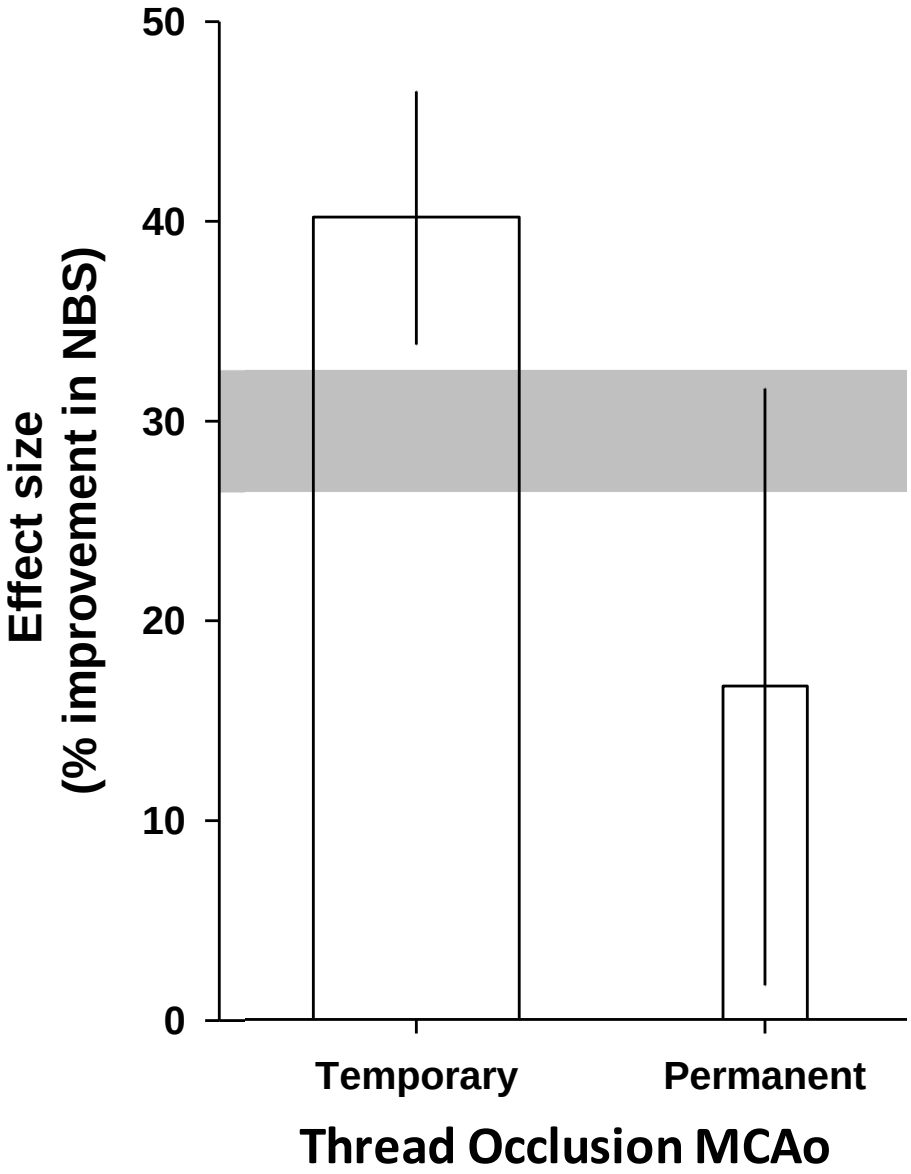
Subset analysis

~50% of studies reported measures to avoid bias, only lack of blinding contributed to inflation of effect size



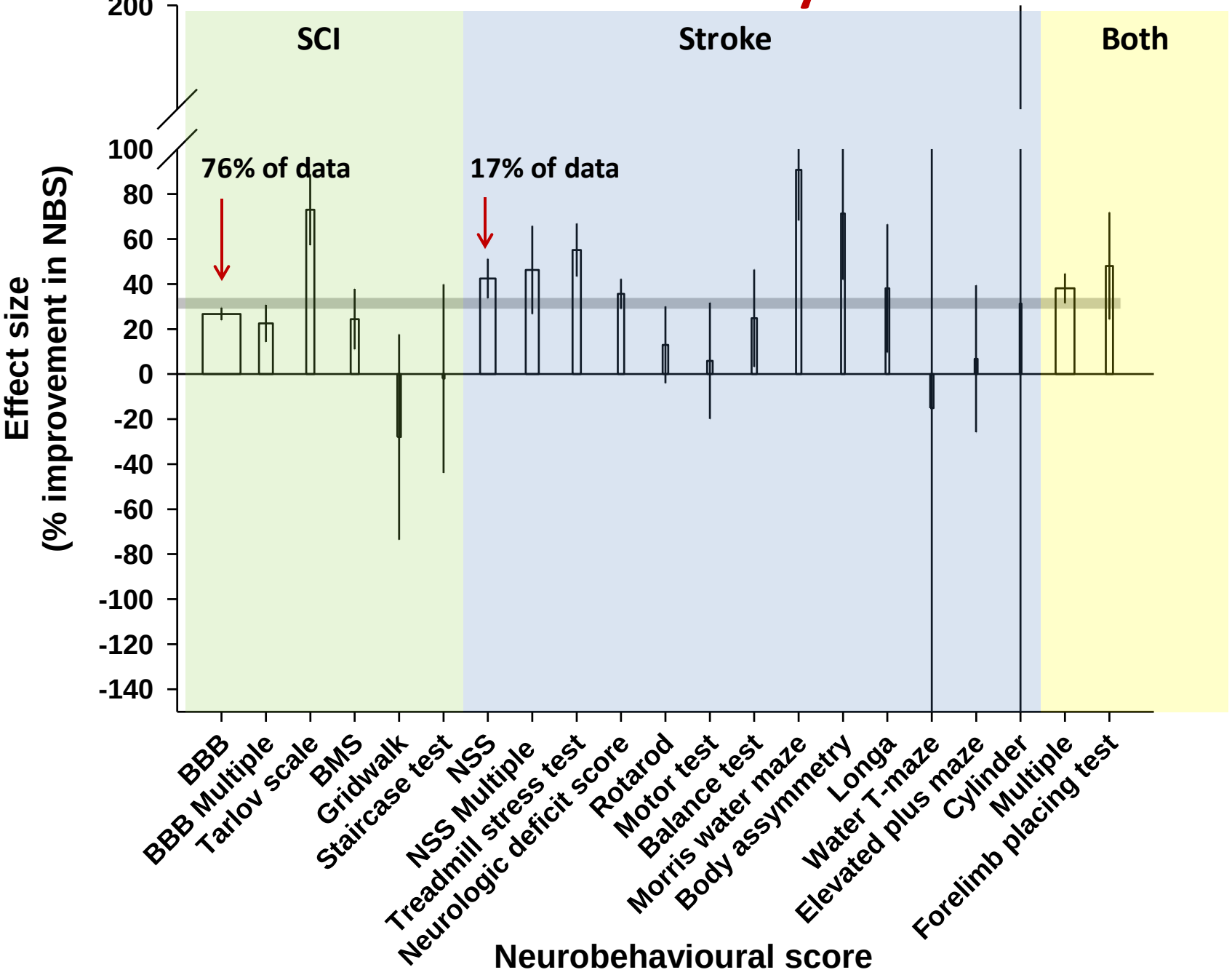

SCI
Stroke
220
100
80
60
40
20
0
Effect size
(% improvement in NBS)
Counterintuitive to have better response in animals with "permanent" lesions
BUT, while permanent, the lesions tend to be smaller because they target more distal blood vessels.
Impactor
Knife
Compression, Weight
Aneurysm clip
Iridesctomy Scissors
Balloon compression
Impactor with spacer
8-0 nylon filament
Intraluminal filament
Electrocoagulation
Microvascular clip
Endothelin
Donor Clot
Unknown
Method of injury induction

Subset analysis (Stroke)

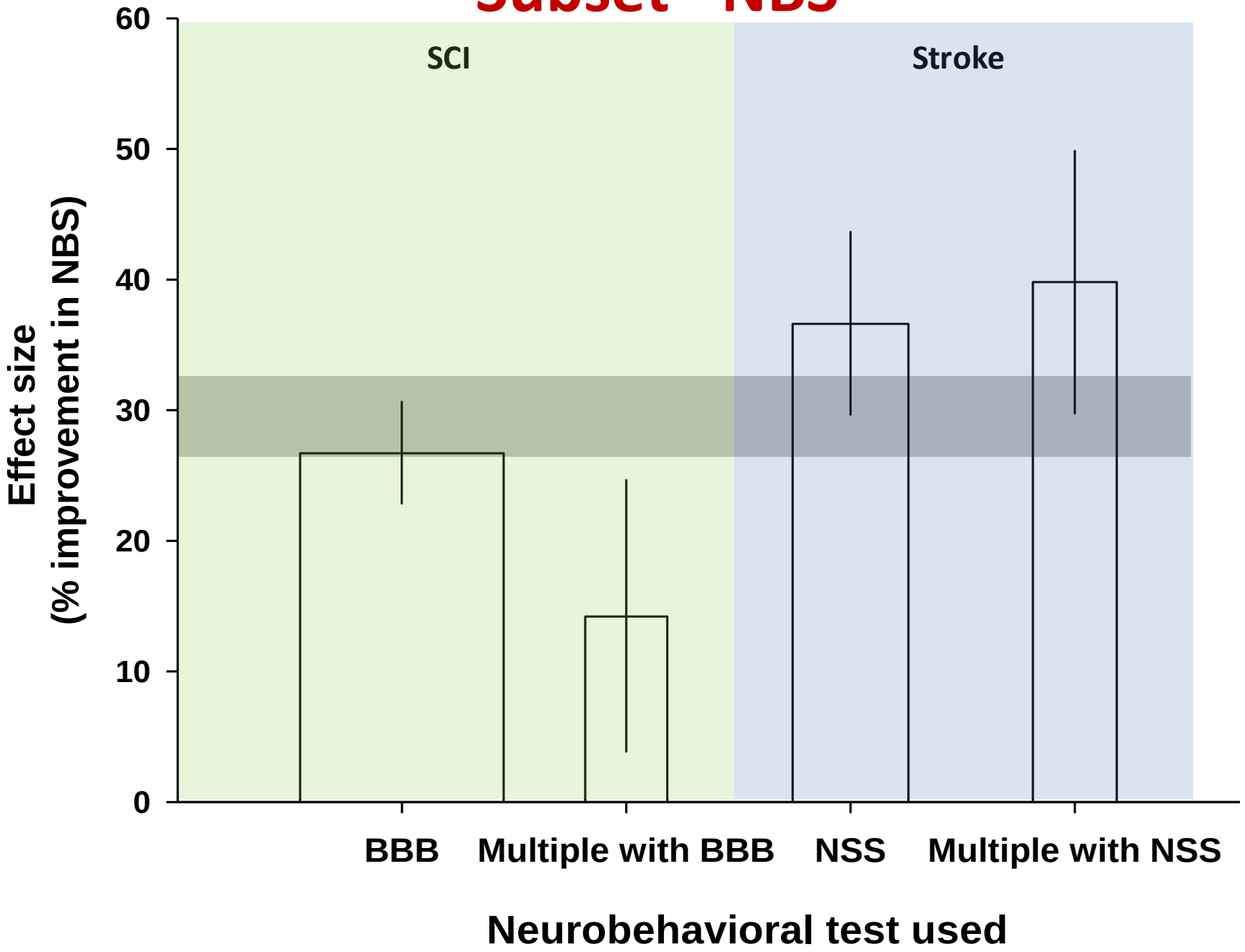


Same degree of initial ischemia but no capacity for reperfusion and recovery in “permanent” animals

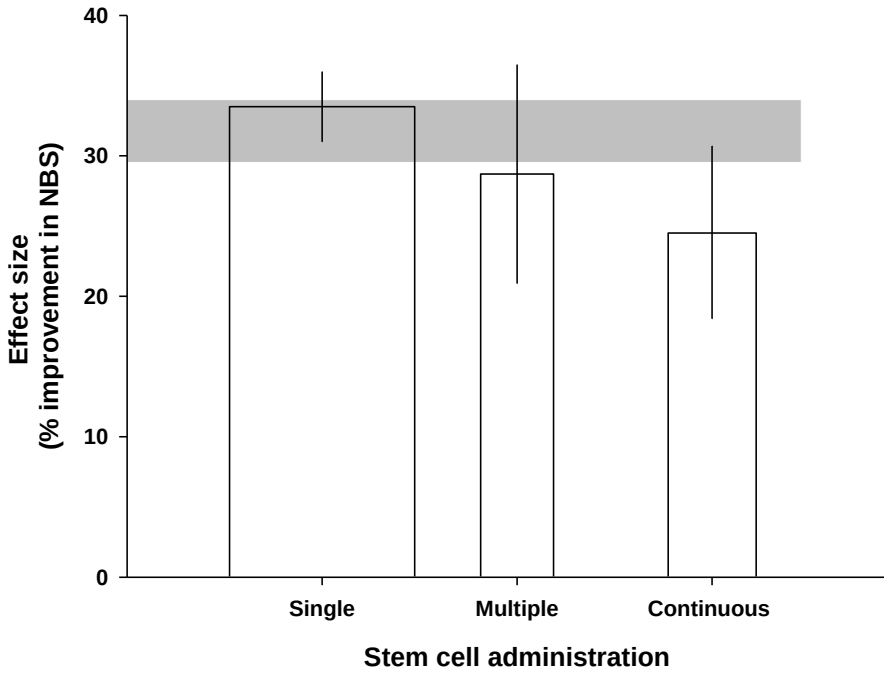
Overall analysis



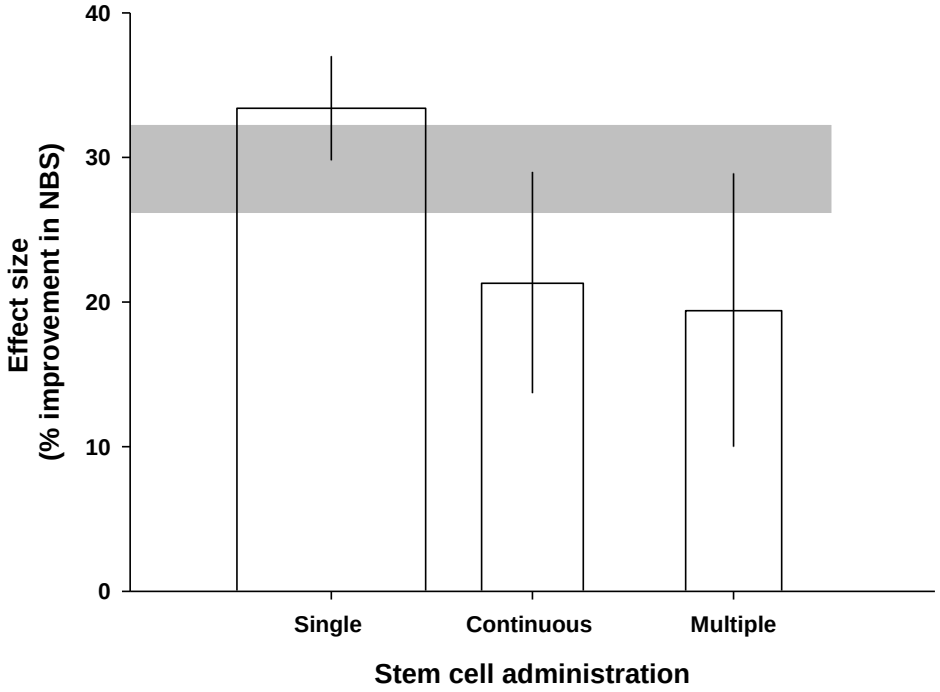
Subset - NBS


SCI
Stroke
60
50
40
30
20
10
0
Effect size
(% improvement in NBS)
BBB
Multiple with BBB
NSS
Multiple with NSS
Neurobehavioral test used

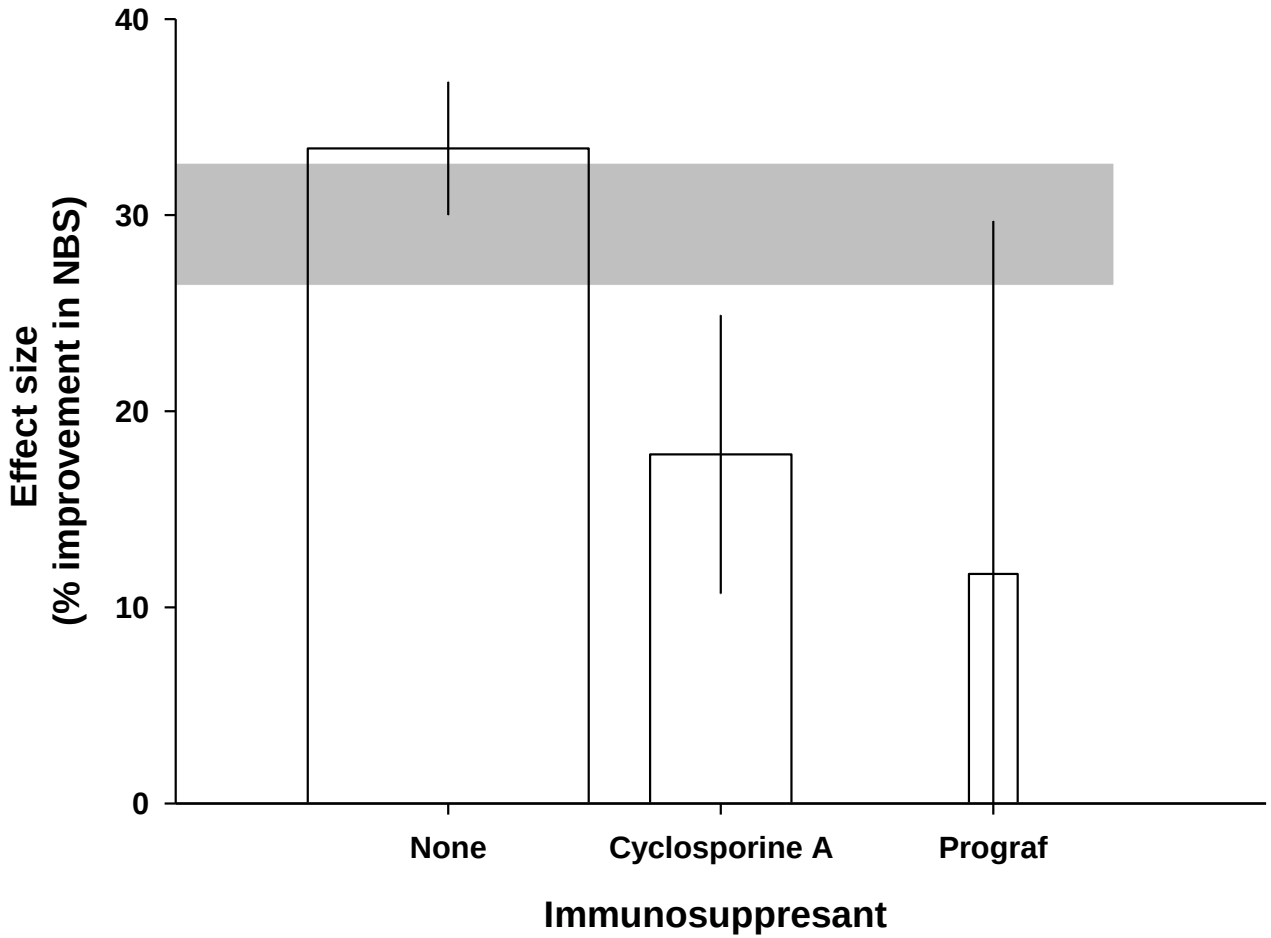
Overall analysis



Subset analysis

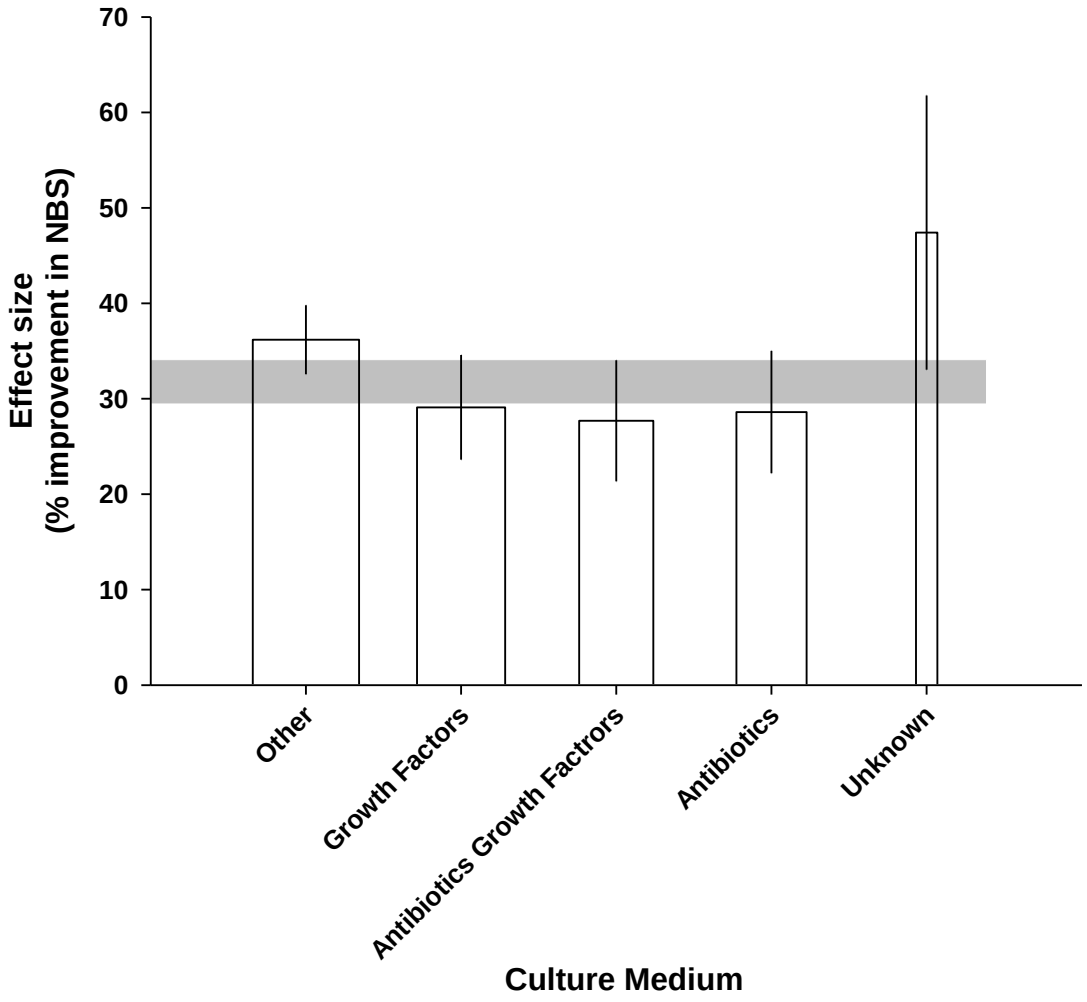


Subset - Immunosuppression

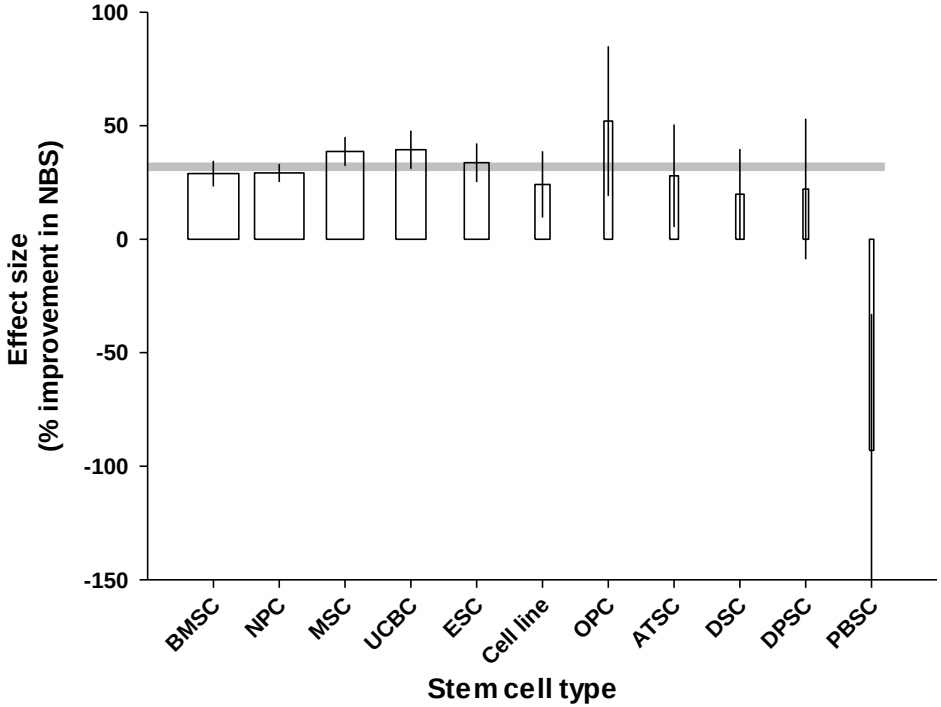


Stem cell biology

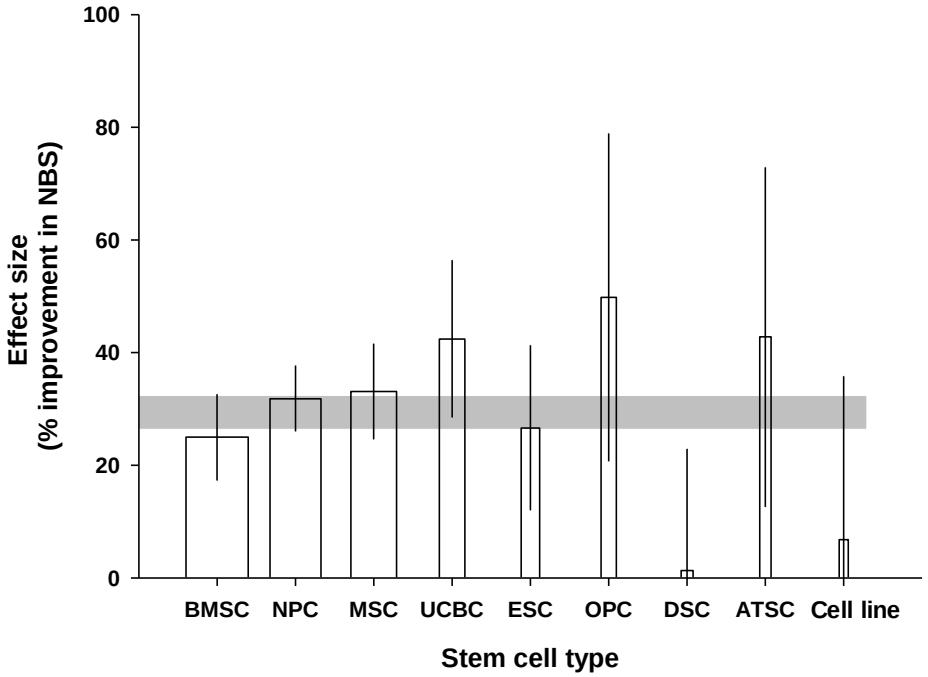
Overall analysis



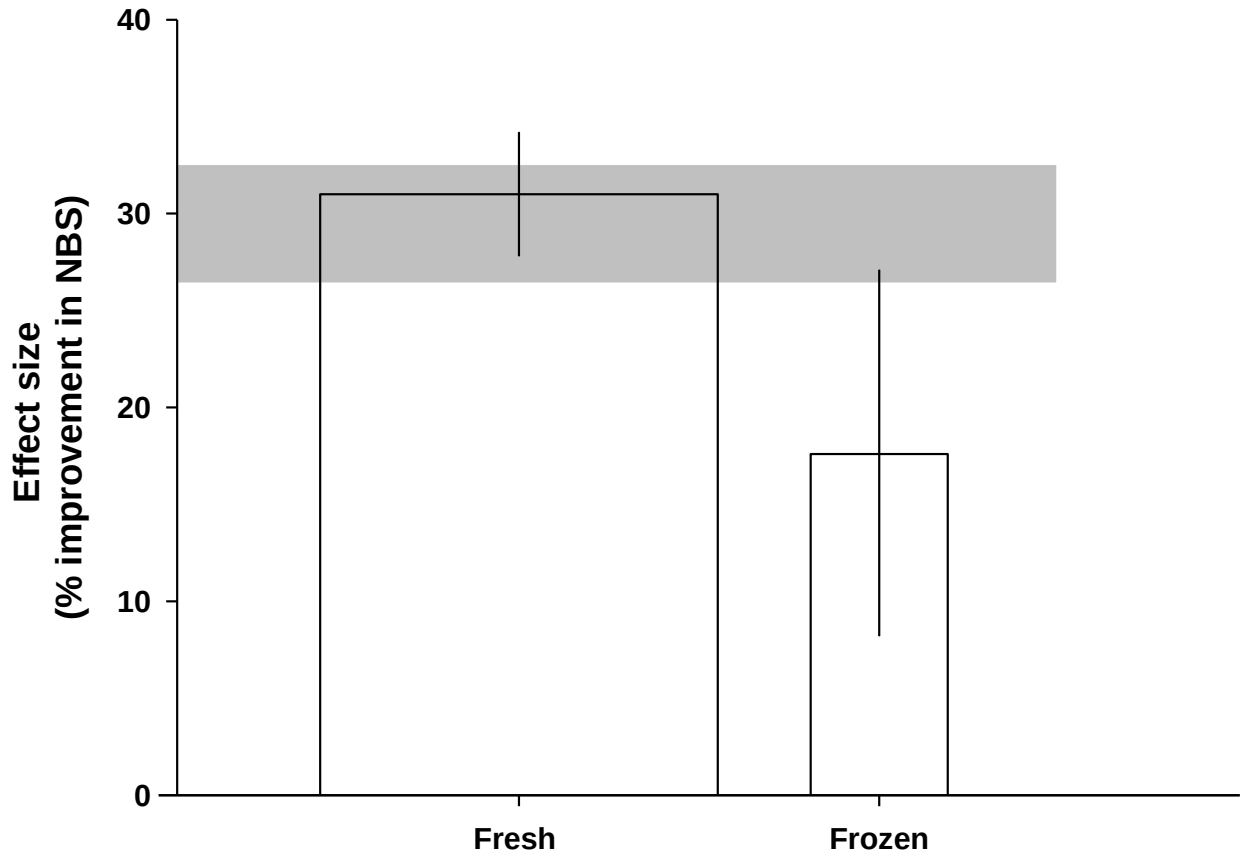
Overall analysis

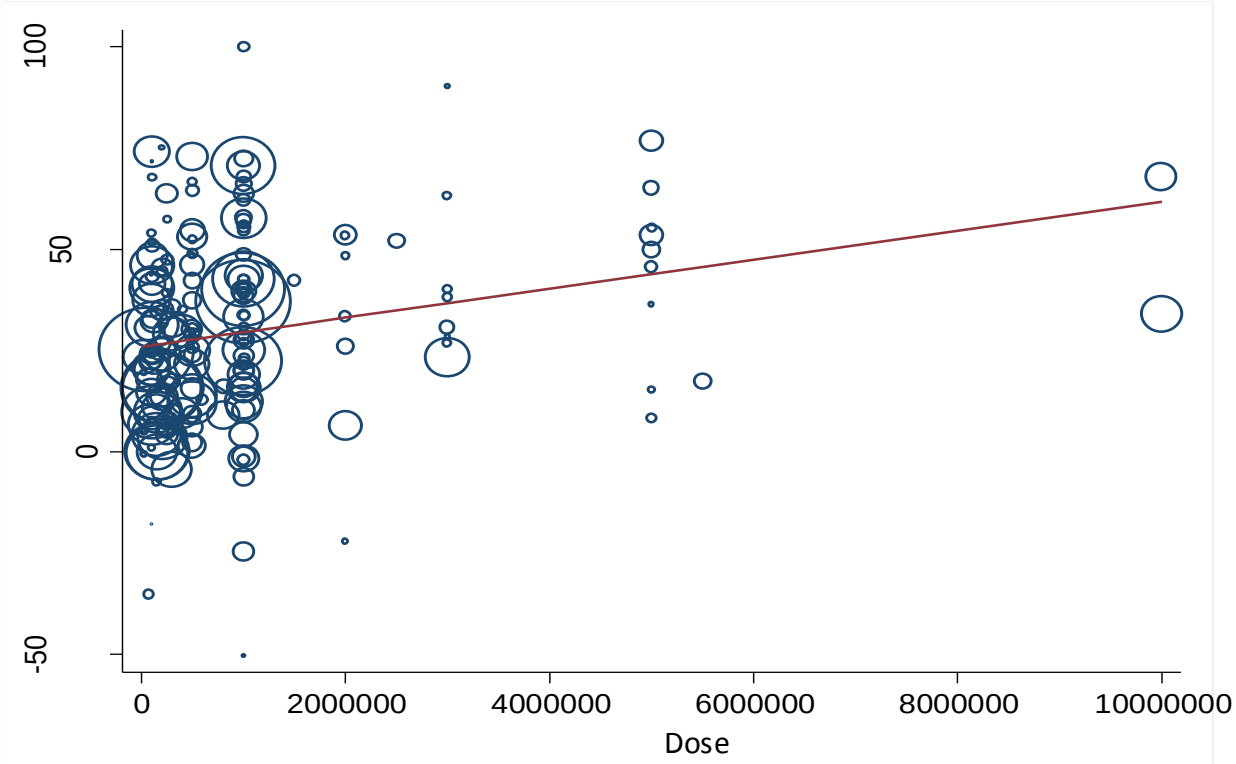


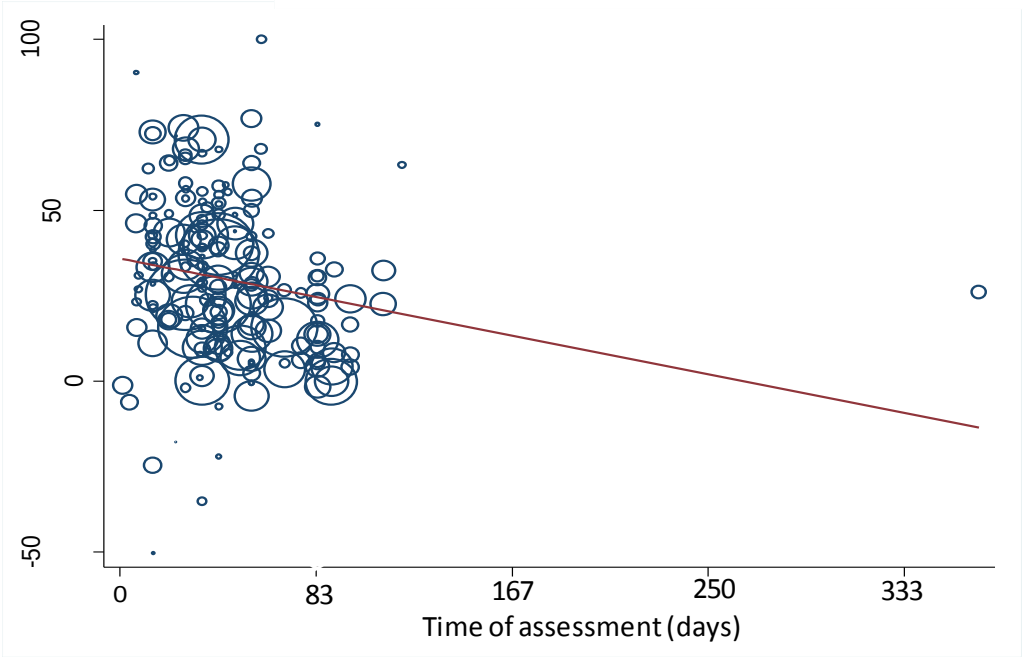
Subset analysis

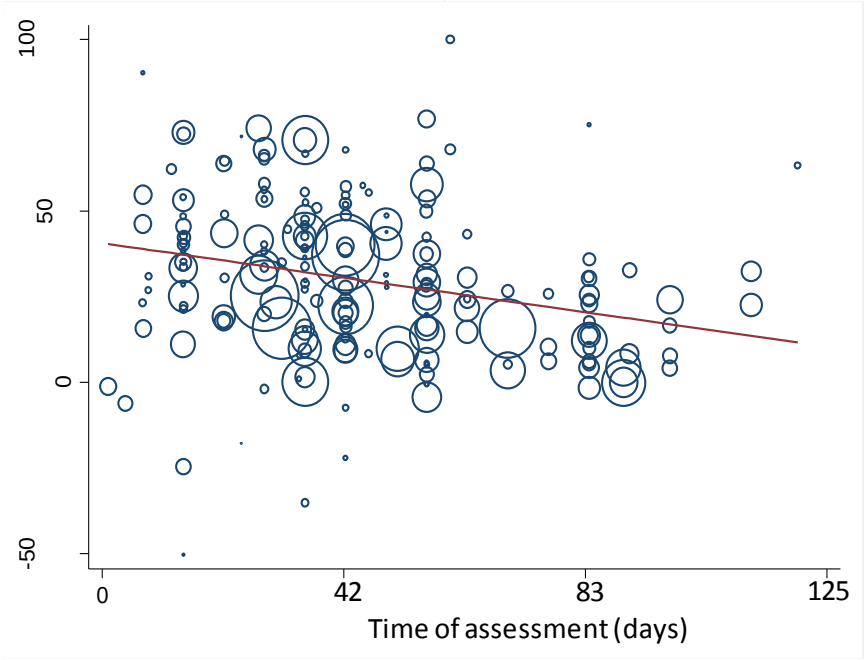


Subset - Fresh vs Frozen cells




100
50
0
-50
0
2000000
4000000
6000000
8000000
10000000
Dose


100
50
0
-50
0
83
167
250
333
Time of assessment (days)


100
50
0
-50
0
42
83
125
Time of assessment (days)

Summary

Stem cells appear to improve neurobehavioral outcome in the combined spinal cord injury and stroke dataset (overall effect size 31.7%).

Stem cells are more effective in improving neurobehavioral outcome in experimental models of stroke.

Stem cell biology accounted for more observed heterogeneity in the combined dataset compared to the individual analyses.

Conclusions

The effects of stem cells seem confounded by large heterogeneity in behavioural testing methodologies used suggesting that application of a core assessment protocol might be beneficial.

More preclinical work still seems to be needed to assess the impact of stem cell transplantation on these two acute neurological injuries before developing clinical trial protocols for testing efficacy of this treatment in humans.

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Everyone in Howells Lab