

## Meta-Analysis Review Proves Animal Models In Stroke Research Are Flawed



Meta-analysis reviews, or systematic reviews, refer to the analysis of a large collection of previous results obtained from individual studies for the purpose of integrating and comparing these findings. The use of such reviews has become an important tool in medical research since by pooling together these results, one can assess for the validity of experimental approaches. For the purpose of assessing the validity of a model, such as the use of an animal for the understanding of a human disease, such reviews are proven very useful since any inconsistency would suggest the inadequacy of this model.

A Meta-analysis review on the use of animal models for the treatment of stroke in humans was published last week ([Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy](#)) in the journals PLoS (Public Library of Science) Biology together with a commentary article ([Can Animal Models of Disease Reliably Inform Human Studies?](#)) in PLoS Medicine. Both publications describe various statistical techniques to estimate how many studies in this particular field have gone unreported due to ending with negative or non-significant results.

Using a database encompassing 16 different attempted therapies, which together account for 1,359 experiments and 19,956 animals experimented on, the report finds that only a very small fraction of the publications (2%) report no significant effects of treatment.

As mentioned by the authors, these numbers suggest that in the case of animal-use in stroke studies, a significant proportion of animal experimentation is not being reported in the literature. The authors' estimate that up to 214 other experiments, which would correspond to 3600 animals would have shown a negative or non-significant effect were never reported.

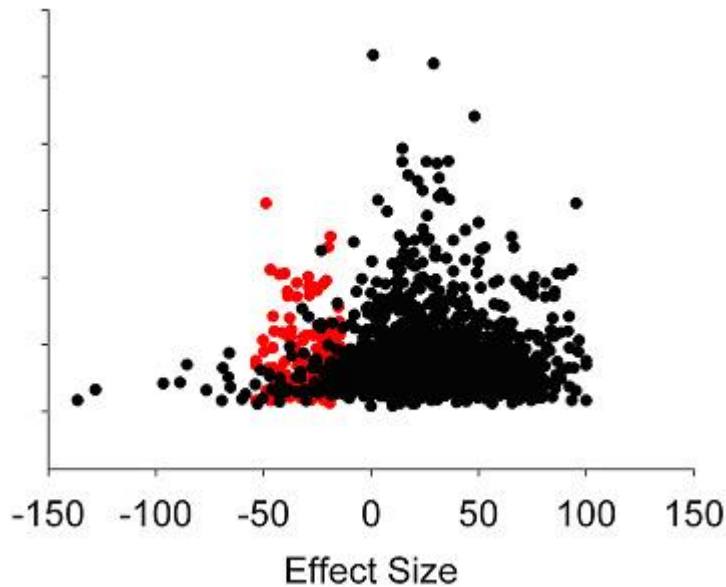


Figure 1 – A plot analysing the published effect of a treatment for stroke. The black dots are those studies that have been reported in the scientific literature and the red dots are calculated to be those studies that have not been reported. (Effect size is how much of a positive or negative effect the treatment has had)

This phenomenon where numerous experiments remain unpublished because they concluded of no interest, is defined as the ‘file drawer’ problem. The authors’ state:

*“This is the ‘file drawer problem’: at its most extreme, the 95% of studies that were truly neutral (that is, which reported no significant effects) remain in the files of the investigators, the 5% of experiments that were falsely positive are published, and reviewers conclude – falsely – that the literature represents biological truth.”*

Unfortunately such a reductionist approach which limits the publication to positive results does not take into account the necessity to know about negative results in order to avoid repeating such unnecessary experiments. This suggests that a large number of animals may be tested upon that are not mentioned in the literature. Such meta-analysis reviews illustrate not only the inadequacy of the animal model in stroke research but also the need to increase data sharing in medical research in general in order to limit unnecessary experiments. Since 95% of all animal procedures can lead to non-significant results that are not published or shared then shouldn’t alternatives be sought?

For the record, all therapies mentioned in the report showed some degree of overstating their effectiveness. On average all the therapies mentioned were overstated by at least a third.

The Dr Hadwen Trust has funded research on strokes that used Computational approaches to analyse human brain networks and their failure in disease conditions. This work has enabled scientists to understand not only how various connections in the brain are connected together and interact, but also how these areas are affected following a stroke ([www.scienceroom.org/brain-networks](http://www.scienceroom.org/brain-networks)).

The authors additionally conducted a meta-analysis review of previous publications that have searched for this “publication bias” in other animal studies. A total of 71 publications were identified, of which only 11 gave an overview of all studies undertaken in a particular subject area. Of those 11 publications, none looked for quantitative evidence of publication bias, 6 looked for evidence of publication bias at a qualitative level and 4 report that they found publication bias. Several studies indicate that in most cases negative or neutral animal experiments are not being disclosed simply because the scientists behind the experiments are not publishing their findings. The authors say: *“76% of unpublished projects were never submitted as a manuscript.”*

As a final message to all, the authors end their report by stating:

*“...Nonpublication of data raises ethical concerns, first because the animals used have not contributed to the sum of human knowledge, and second because participants in clinical trials may be put at unnecessary risk if efficacy in animals has been overstated.”*

***“It is unlikely that this publication bias in the basic sciences is restricted to the area we have studied... (emphasis ours).”***

This issue of limited availability of selected experimental data is not new to the scientific community. It is also reminiscent of the demand by most animal welfare groups to the European Commission to implement a system of data-sharing with the prohibition of the duplication of procedures in the revised Directive on the protection of animals used in experiments. Unfortunately, despite an increasing number of such publications underlining the issue, the requirement for data sharing has now been removed from the text. This is a disappointing result, since meta-analyses illustrate that Replacement starts with the analysis of existing data.