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Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases

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Abstract

Animal studies generate valuable hypotheses that lead to the conduct of preventive or therapeutic clinical trials. We assessed whether there is evidence for excess statistical significance in results of animal studies on neurological disorders, suggesting biases. We used data from meta-analyses of interventions deposited in Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies (CAMARADES). The number of observed studies with statistically significant results (O) was compared with the expected number (E), based on the statistical power of each study under different assumptions for the plausible effect size. We assessed 4,445 datasets synthesized in 160 meta-analyses on Alzheimer disease (n = 2), experimental autoimmune encephalomyelitis (n = 34), focal ischemia (n = 16), intracerebral hemorrhage (n = 61), Parkinson disease (n = 45), and spinal cord injury (n = 2). 112 meta-analyses (70%) found nominally ($p\leq0.05$) statistically significant summary fixed effects. Assuming the effect size in the most precise study to be a plausible effect, 919 out of 4,445 nominally significant results were expected versus 1,719 observed ($p<10^{-9}$). Excess significance was present across all neurological disorders, in all subgroups defined by methodological characteristics, and also according to alternative plausible effects. Asymmetry tests also showed evidence of small-study effects in 74 (46%) meta-analyses. Significantly effective interventions with more than 500 animals, and no hints of bias were seen in eight (5%) meta-analyses. Overall, there are too many animal studies with statistically significant results in the literature of neurological disorders. This observation suggests strong biases, with selective analysis and outcome reporting biases being plausible explanations, and provides novel evidence on how these biases might influence the whole research domain of neurological animal literature.

Author Summary

Studies have shown that the results of animal biomedical experiments fail to translate into human clinical trials; this could be attributed either to real differences in the underlying biology between humans and animals, to shortcomings in the experimental design, or to bias in the reporting of results from the animal studies. We use a statistical technique to evaluate whether the number of published animal studies with “positive” (statistically significant) results is too large to be true. We assess 4,445 animal studies for 160 candidate treatments of neurological disorders, and observe that 1,719 of them have a “positive” result, whereas only 919 studies would a priori be expected to have such a result. According to our methodology, only eight of the 160 evaluated treatments should have been subsequently tested in humans. In summary, we judge that there are too many animal studies with “positive” results in the neurological disorder literature, and we discuss the reasons and potential remedies for this phenomenon.

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Abbreviations: AD, Alzheimer disease; CAMARADES, Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies; E, number of expected studies with statistically significant results; EAE, experimental autoimmune encephalomyelitis; ICH, intracerebral hemorrhage; IQR, interquartile range; MBP, myelin basic protein; NOS, nitric oxide species; O, number of observed studies with statistically significant results; PD, Parkinson disease; RCT, randomized clinical trial; SCI, spinal cord injury

Introduction