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TRR 295 ReTune

Prediction of Stroke Outcome in Mice Based on Noninvasive MRI and Behavioral Testing.

Knab F*, Koch SP*, Major S, Farr TD, Mueller S, Euskirchen P, Eggers M, Kuffner MTC, Walter J, Berchtold D, Knauss S, Dreier JP, Meisel A, Endres M, Dirnagl U, Wenger N, Hoffmann CJ, Boehm-Sturm P*, Harms C*. Stroke. 2023 Nov; 54(11): 2895-2905. doi: 10.1161/STROKEAHA.123.043897. PMID: 37746704.

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Prediction of poststroke outcome using the degree of subacute deficit or magnetic resonance imaging is well studied in humans. While mice are the most used animals in preclinical stroke research, systematic analysis of outcome predictors is lacking.

We intended to incorporate heterogeneity into our retrospective study to broaden the applicability of our findings and prediction tools. We therefore analyzed the effect of 30, 45, and 60 min. of arterial occlusion on the variance of stroke volumes. Next, we built a heterogeneous cohort of 215 mice using data from 15 studies that included 45 min. of middle cerebral artery occlusion and various genotypes. Motor function was measured using a modified protocol for the staircase test of skilled reaching. Phases of subacute and residual deficit were defined. Magnetic resonance images of stroke lesions were coregistered on the Allen Mouse Brain Atlas to characterize stroke topology. Different random forest prediction models that either used motor-functional deficit or imaging parameters were generated for the subacute and residual deficits.

Variance of stroke volumes was increased by 45 min. of arterial occlusion compared with 60 min. The inclusion of various genotypes enhanced heterogeneity further. We detected both a subacute and residual motor-functional deficit after stroke in mice and different recovery trajectories could be observed. In mice with small cortical lesions, lesion volume was the best predictor of the subacute deficit. The residual deficit could be predicted most accurately by the degree of the subacute deficit. When using imaging parameters for the prediction of the residual deficit, including information about the lesion topology increased prediction accuracy. A subset of anatomic regions within the ischemic lesion had a particular impact on the prediction of long-term outcomes. Prediction accuracy depended on the degree of functional impairment.

In conclusion, we developed and validated a robust tool for the prediction of functional outcomes after experimental stroke in mice using a large and genetically heterogeneous cohort. In the future, using outcome prediction can improve the design of preclinical studies and guide intervention decisions.

Dr. Felix Knab & Dr. Stefan Paul Koch

Felix Knab has studied medicine at Charité Berlin and received his MD in the group of Christoph Harms. Currently, he is a neurology resident at the University Hospital of Tübingen and pursues a PhD in basic research of Parkinson's disease at the Hertie Institute for Clinical Brain Research. **Stefan Paul Koch** is a psychologist by training. During his PhD and postdoc at Charité, his focus changed to computational neurosciences. Since 2016, he is a senior researcher in the lab of Philipp Boehm-Sturm focusing on computational methods for preclinical neuroimaging.

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Philipp Boehm-Sturm is a physicist and professor for experimental imaging at the Charité with a research focus on magnetic resonance imaging in rodent models of neurological disease. He directs the technology platform "Experimental Imaging at the Charité for 3R" within Charité 3R. **Christoph Harms** is professor for molecular stroke research at the Charité Department of Experimental Neurology and the Center for Stroke Research Berlin. His group focuses on rodent stroke research, brain imaging and molecular stroke therapeutics.

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