

Powerful outcome measures in MS

In the search for new therapeutic agents for Multiple Sclerosis, use of sensitive and powerful outcome measures to maximize the ability of detecting treatment effects and need for more pathological specific outcome measures is becoming increasingly important. In this thesis, we explore the statistical power of several conventional and non-conventional MRI measures and investigate their feasibility as primary outcome in clinical trials of MS.

In multiple datasets, we validated the use of the statistical negative binomial distribution for modeling the number of contrast enhancing lesions, and illustrated the substantial gain in power when analyzing actual trial data for possible treatment effects. In subsequent studies we showed that both enhancing lesion volume as well as the number of T2 subtraction lesions are potentially more sensitive outcome measures compared to enhancing lesion counts, and required substantially smaller number of patients to significantly detect an anti-inflammatory treatment effect. For measures monitoring neuroprotection and repair, we analyzed the required sample size for placebo controlled clinical trials by means of parametric resampling and simulation procedures. The analyses showed that both the number of persistent black holes, representing focal neuronal damage, as well as cerebral atrophy applied in short interval trials, representing global neuronal damage, are feasible outcomes for future clinical trials, albeit they require potent drugs to obtain sufficient power. Magnetization transfer imaging, a measure pathological specific for myelin content, proved a highly feasible outcome measure, requiring a moderate number of patients. Ultimately, these results will contribute to the efficient practice of future clinical trials in MS.