
Personalized Medication Response Prediction for Attention-Deficit Hyperactivity Disorder: Learning in the Model Space Versus Learning in the Data Space

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Author contribution statement

HW was responsible for performing feature extraction of the clinical data, literature search, causal factor model simplification, the software implementation of the learning in model space framework, and determined benchmarking protocol. PT provided the clinical context of ADHD, constructed the prior knowledge used by the Bayesian framework, aided development on the causal factor model, and designed the literature search protocol. PW aided HW on the literature search and written the background on ADHD. OD implemented the SVM and GP machine learning algorithms. BK constructed the linear mixed effects models. YS helped with the technical implementation of the Bayesian linear regression algorithm. PT provided the mathematical formulation of the learning in model space approach and guidance on software implementation. MC and TN suggested candidate modeling approaches compatible with the framework, suggested a number of conventional approaches to be evaluated, appraised the output of the Bayesian approach, and provided recommendations for the improvement of the implementation and the methodology to ensure fair comparisons. SI coordinated access to the clinical data, facilitated digitization of paper-based clinical records, and maintained the database. DC provided the clinical context of ADHD, suggested causal mechanisms for treatment response, and defined the scope of clinical data collection.

Keywords

attention-deficit hyperactivity disorder, Bayesian inference, machine learning, Methylphenidate, mixed-effects model, personalized medicine, prognosis, treatment response

Abstract

Word count: 327

Attention-Deficit Hyperactive Disorder (ADHD) is one of the most common mental health disorders amongst school-aged children with an estimated prevalence of 5% in the global population (1). Stimulants, particularly methylphenidate (MPH), are the first-line option in the treatment of ADHD (2, 3) and are prescribed to an increasing number of children and adolescents in the US and the UK every year (4, 5) though recent studies suggest that this is tailing off, e.g. Holden et al. (6).

Around 70% of children demonstrate a clinically significant treatment response to stimulant medication (7, 8, 9, 10). However, it is unclear which patient characteristics may moderate treatment effectiveness. As such, most existing research has focused on investigating univariate or multivariate correlations between a set of patient characteristics and the treatment outcome, with respect to dosage of one or several types of medication. The results of such studies are often contradictory and inconclusive due to a combination of small sample sizes, low-quality data or a lack of available information on covariates.

In this paper, feature extraction techniques such as latent trait analysis were applied to reduce the dimension of on a large dataset of patient characteristics, including the responses to symptom-based questionnaires, developmental health factors, demographic variables such as age and gender, and socioeconomic factors such as parental income. We introduce a Bayesian modeling approach in a 'learning in the model space' framework that combines existing knowledge in the literature on factors that may potentially affect treatment response, with constraints imposed by a treatment response model. The model is personalized such that the variability among subjects is accounted for by a set of subject-specific parameters. For remission classification, this approach compares favorably with conventional methods such as support vector machines and mixed effect models on a range of performance measures. For instance, the proposed approach achieved an area under receiver operator characteristic curve of 82-84%, compared to 75-77% obtained from conventional regression or machine learning ('learning in the data space') methods.

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