Gaussian process classification from multivariate spatio-temporal brain potential patterns in Alzheimer's disease

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Abstract

The diagnosis of Alzheimer's disease (AD) in routine clinical practice is most commonly based on subjective clinical interpretations. Event-related potentials (ERPs) have been shown to reflect neurodegenerative processes in AD and might qualify as affordable and thereby widely available markers to facilitate the objectivization of AD assessment. Here, we present a novel method combining multivariate pattern analysis (MVPA) and Gaussian process classification (GP) and aim to develop ERP markers for two crucial AD classification problems, i.e., the prediction of rapid cognitive decline (RCD) and the distinction between carriers and non-carriers of the $\epsilon 4$ allele of the apolipoprotein E gene, the main genetic risk factor for AD.

1 Introduction

Optimal decision making, including classification, operates by making the choice that minimises the expected loss. Calculating the expected loss requires a model. In this paper, we exploit the power of Bayesian nonparametric models, particularly the Gaussian Process [Rasmussen and Williams, 2006]. Nonparametric models ameliorate the difficulty of choosing the right model by offering an elegant framework in which model complexity, dealing with imprecise observations and propagating model uncertainty are all seamlessly handled. Furthermore, this methodology allows for an easy adjustment of predictions to compensate for variable class priors and provides full predictive uncertainty – both particularly helpful in clinical practice. Although potential advantages have already been stressed in the literature [Stahl *et al.*, 2012], this is – to the best of our knowledge – the very first electrophysiological ERP study to use GP, all fields of research taken into account.

Importantly, the proposed new MVPA-GP method does not only consider spatio-temporal patterns at distinct sites [Hahn *et al.*, 2013], and interregional spatial patterns [Challis *et al.*, 2015], but also multivariate interregional spatio-temporal patterns.

2 Methods

Sixty-three AD patients were recruited prospectively as part of the PRODEM Austria cohort study. Prediction of RCD (annual loss of $\geq$3 Mini-Mental State Examination points) was performed for subjects who returned at least for the 12-month follow-up assessment (N=48), whereas $\epsilon 4$ classification was performed for all subjects. We used an auditory oddball paradigm to elicit ERPs, recorded by EEG. ERPs represent a time- and phase-locked response to a stimulus. To take these distinct temporal patterns at various sites as well as their dependence into account, we adopted a special type of covariance matrix recently designed [Barachant and Congedo, 2014]. First, the averaged ERP data (19 channels; 1s) X_z of a given unlabeled patient z was vertically concatenated with the grand-average waveforms $\bar{X}_{(1)}$ and $\bar{X}_{(2)}$ of the two classes of patients, resulting in $X_z^{ST} = \left(\bar{X}_{(1)}, \bar{X}_{(2)}, X_z\right) =: (\bar{X}_{\cdot}, X_z)$ of dimensionaliy 57×256. Then, a spatio-temporal covariance matrix C_z^{ST} was estimated:

$$C_z^{ST} = \frac{1}{(T-1)} \begin{bmatrix} \bar{X}_{\cdot}\bar{X}_{\cdot}^{\intercal} & \left(X_z\bar{X}_{\cdot}^{\intercal}\right)^{\intercal} \\ X_z\bar{X}_{\cdot}^{\intercal} & X_zX_z^{\intercal} \end{bmatrix} \in \mathbb{R}^{57\times 57}$$

Feature selection was done by using (i) Kendall rank correlation of informative C_z^{ST} elements versus the binary class label, and (ii) automatic relevance determination within GP. A square exponential kernel and constant as well as sum of linear and constant mean functions were used for GP. Expectation propagation was applied to approximate the posterior density. To examine potential advantages of GP we compared it to a probabilistic reference method (logistic regression, LR) using identical MVPA features and leave-one-out cross-validation.

3 Results and Discussion

GP significantly outperformed LR in RCD as well as $\epsilon 4$ classification, with the highest AUC overall (0.802, $p<0.001$) being achieved using the newly developed spatio-temporal MVPA-GP method in the prediction of RCD. Furthermore, this spatio-temporal approach significantly outperformed a spatial MVPA-GP method we developed for electrophysiological signals based on Challis *et al.* [2015] in RCD classification (0.607 AUC, p=0.217). However, for the $\epsilon 4$ task, the method based on Challis *et al.* (0.735 AUC, p=0.002) yielded better results than spatio-temporal MVPA-GP (0.651 AUC, p=0.046). Although the number of AD patients included is among the highest of prospective longitudinal ERP studies, further investigations, with even larger sample sizes (including extensive external validation sets), should follow.

Acknowledgements

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References

[Barachant and Congedo, 2014] Alexandre Barachant and Marco Congedo. A plug&play p300 bci using information geometry. *arXiv preprint arXiv:1409.0107*, 2014.

[Challis *et al.*, 2015] Edward Challis, Peter Hurley, Laura Serra, Marco Bozzali, Seb Oliver, and Mara Cercignani. Gaussian process classification of alzheimer's disease and mild cognitive impairment from resting-state fmri. *NeuroImage*, 112:232–243, 2015.

[Hahn *et al.*, 2013] Tim Hahn, Andre F. Marquand, Michael M. Plichta, Ann-Christine Ehlis, Martin W. Schecklmann, Thomas Dresler, Tomasz A. Jarczok, Elisa Eirich, Christine Leonhard, Andreas Reif, Klaus-Peter Lesch, Michael J. Brammer, Janaina Mourao-Miranda, and Andreas J. Fallgatter. A novel approach to probabilistic biomarker-based classification using functional near-infrared spectroscopy. *Human Brain Mapping*, 34(5):1102–1114, 2013.

[Rasmussen and Williams, 2006] Carl E. Rasmussen and Chris Williams. *Gaussian Processes for Machine Learning*. The MIT Press, 2006.

[Stahl *et al.*, 2012] Daniel Stahl, Andrew Pickles, Mayada Elsabbagh, Mark H. Johnson, and Basis Team The. Novel machine learning methods for erp analysis: A validation from research on infants at risk for autism. *Developmental Neuropsychology*, 37(3):274–298, 2012.

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