Intelligent Digital Technology in Migraine Management: Examples from NTNU, Norway

Anker Stubberud

Department of Neuromedicine and Movement Science, NTNU, Trondheim

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Disclosures

Share-holder and part-time employee of Nordic Brain Tech AS

Patent holder for the Cerebri Biofeedback concept (PCT/EP2021/052512)

Lecture honoraria from TEVA

SMARTPHONE AND WEARABLE DIGITAL BIOFEEDBACK THERAPY

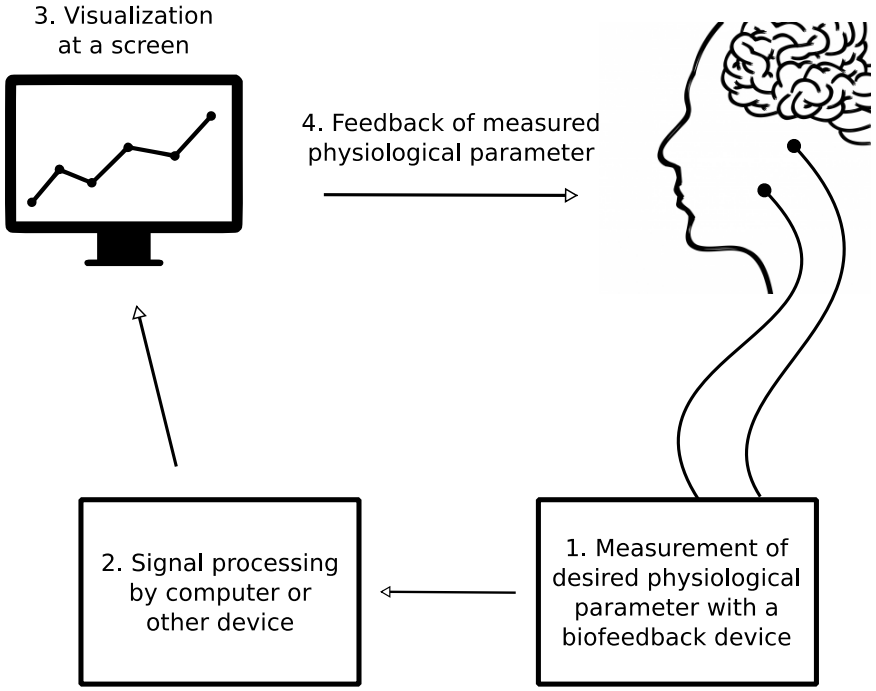
Biofeedback - Background

Moderate-quality evidence for medium effect size in adults[1]

Low-quality evidence for large effect in children and adolescents[2]

Inducing physiological change → beneficial biological adaptations

- Long-term alterations in autonomic tone
- Reduction of cortical excitability
- Resilience to extrinsic stressors



[1] Nestoriuc Y, Martin A. Efficacy of biofeedback for migraine: a meta-analysis. Pain. 2007 Mar 1;128(1-2):111-27.
[2] Stubberud A, Varkey E, McCrory DC, Pedersen SA, Linde M. Biofeedback as prophylaxis for pediatric migraine: a meta-analysis. Pediatrics. 2016 Aug 1;138(2).

Challenges

Biofeedback is not widely available despite being effective

The treatment is cost- and time-consuming and thus not used

Requires trained therapist and specialized equipment

Biofeedback app development at NTNU

Technical sensor validation[3]

- Fair to excellent agreement between wearables and stationary sensors (correlation coefficients ranging from 0.58 to 0.90)

Biofeedback algorithm[4]

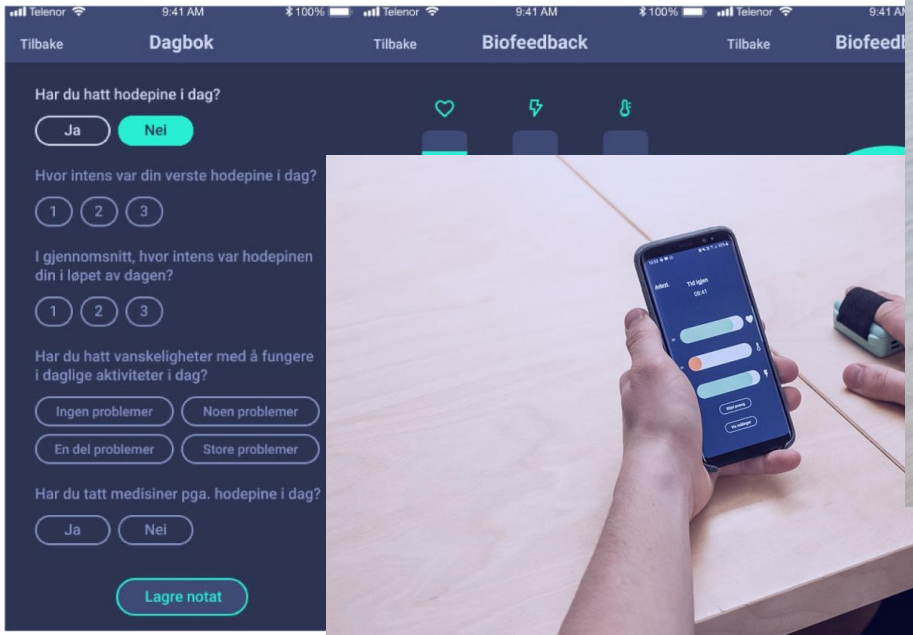
- Individualized combined feedback of trapezius surface EMG, peripheral skin temperature and heart rate

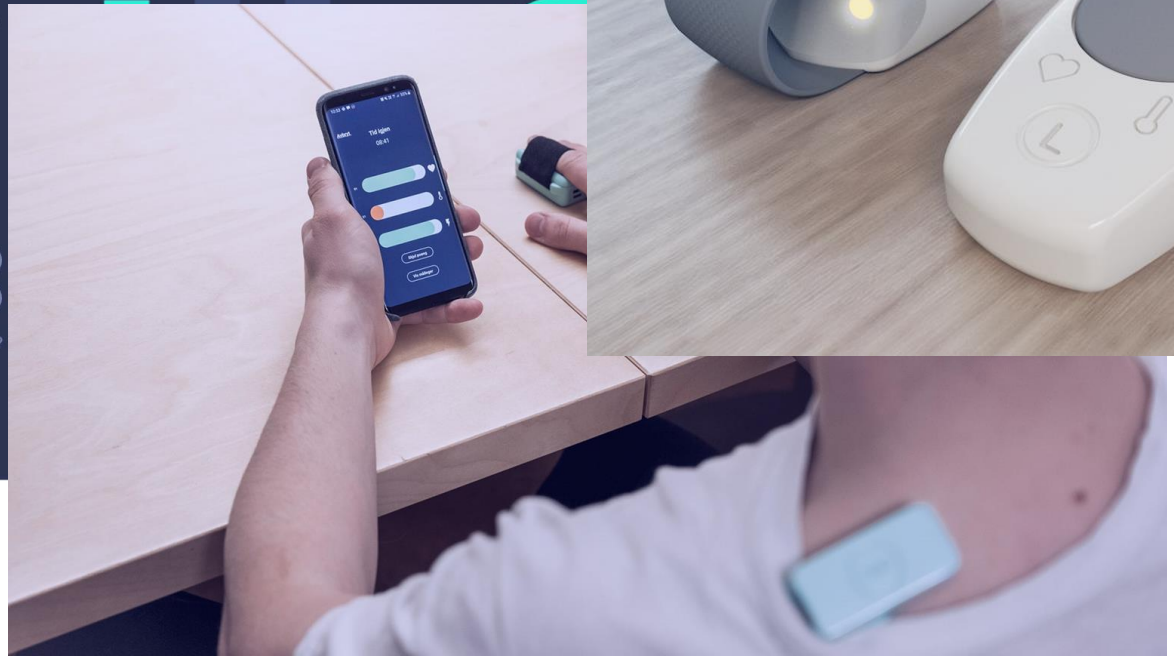
Usability testing and development[5]

- High scores on functionality, lower scores on engagement
- Acceptable adherence among adults 76% (SD 0.26) in one month

[3] Stubberud A et al. Wireless surface electromyography and skin temperature sensors for biofeedback treatment of headache: validation study with stationary control equipment. JMIR Biomedical Engineering. 2018 Feb 23;3(1):e9062.
[4] Stubberud A, Tronvik E, Olsen A, Gravdahl G, Linde M. Biofeedback treatment app for pediatric migraine: Development and usability study. Headache: The Journal of Head and Face Pain. 2020 May;60(5):889-901.
[5] Ingvaldsen SH, Tronvik E, Brenner E, Winnberg I, Olsen A, Gravdahl GB, Stubberud A. A Biofeedback App for Migraine: Development and Usability Study. JMIR formative research. 2021 Jul 28;5(7):e23229.

Biofeedback app setup





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Biofeedback app Pilot RCT

Self-administered biofeedback app for pediatric migraine[6]

- 23 adolescents with migraine. 16 randomized.
- Biofeedback app vs. “sham app”
- Poor adherence (40%) and high drop-out rates (7/23)
- Failed primary efficacy outcome. No significant improvement in migraine frequency
- Biofeedback group had a mean reduction of 1 migraine day/month (95% CI -4.0 to 9.0) compared to waiting list

[6] Stubberud A, Linde M, Brenner E, Heier M, Olsen A, Aamodt AH, Gravdahl GB, Tronvik E. Self-administered biofeedback treatment app for pediatric migraine: A randomized pilot study. Brain and Behavior. 2021 Feb;11(2):e01974.

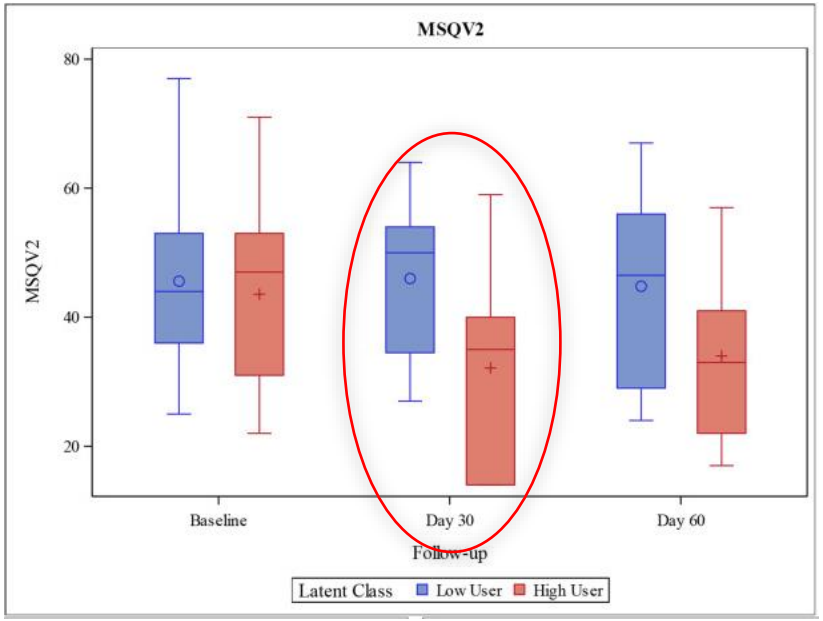
Similar findings

Heartrate variability biofeedback app[7]

- Failed primary efficacy outcome. No significant improvement in QoL
- Subgroup analysis: Improvement in QoL among high adherence users

Progressive muscle relaxation app[8]

- Non-significant decline in mean MIDAS scores compared with control group (−8.7 vs −22.7, *P* = .100)



[7] Minen MT, Corner S, Berk T, Levitan V, Friedman S, Adhikari S, Seng EB. Heartrate variability biofeedback for migraine using a smartphone application and sensor: A randomized controlled trial. General Hospital Psychiatry. 2021 Mar 1;69:41-9.
[8] Minen MT, Adhikari S, Padikkala J, Tasneem S, Bagheri A, Goldberg E, Powers S, Lipton RB. Smartphone-Delivered Progressive Muscle Relaxation for the Treatment of Migraine in Primary Care: A Randomized Controlled Trial. Headache: The Journal of Head and Face Pain. 2020 Nov;60(10):2232-46.

Cerebri biofeedback project

Planned RCT of Biofeedback app vs. wait-list control

12-week treatment program. “Therapist” included in software.

Outcomes

- Number of migraine days
- Responder rate
- Headache intensity
- Acute medication consumption

Enrollment from May 2022

Conclusion

Non-specific effect lost in the absence of regular sessions and therapist contact

mHealth behavioral migraine interventions may be effective among selected individuals with high adherence

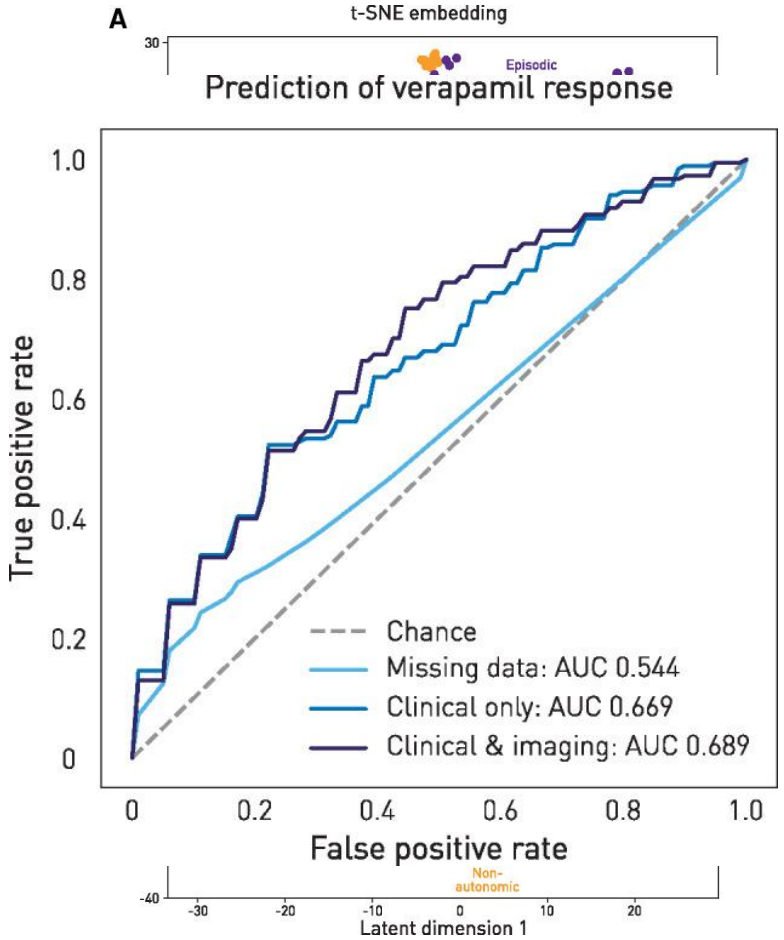
MACHINE LEARNING IN MIGRAINE MANAGEMENT

Machine learning in headache

Current knowledge on machine learning in headache

- Diagnostics and classification
- Absence of machine prescription

Machine phenotyping and verapamil responsiveness in cluster headache[9]

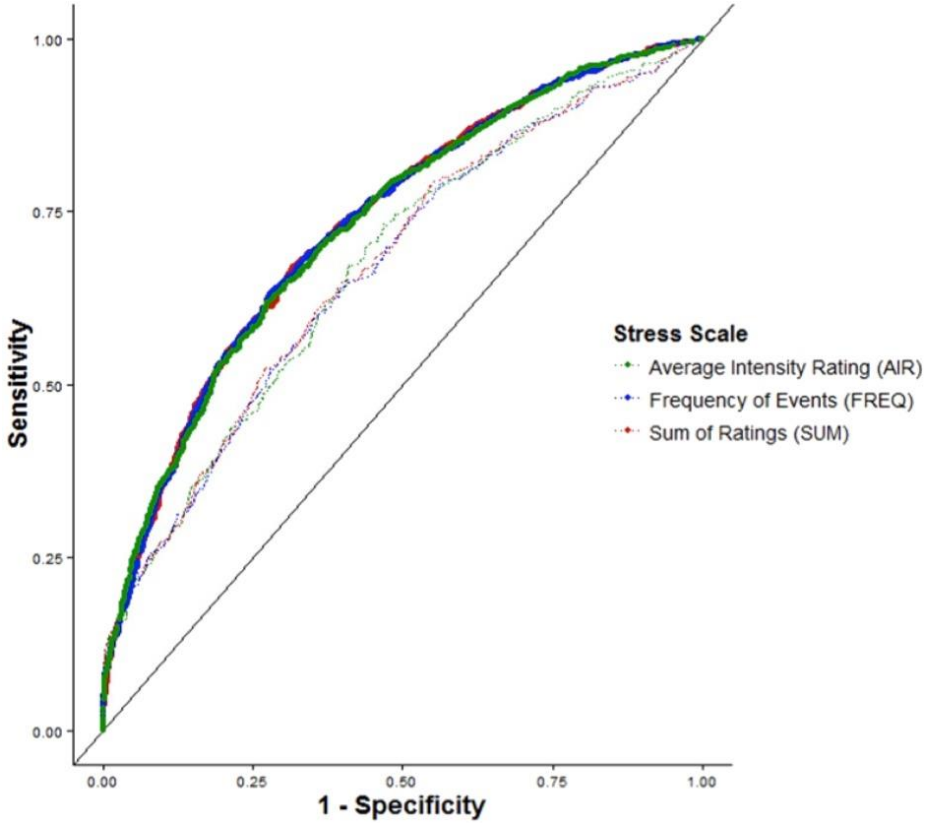


[9] Tso AR, Brudfors M, Danno D, Grangeon L, Cheema S, Matharu M, Nachev P. Machine phenotyping of cluster headache and its response to verapamil. Brain. 2021 Feb;144(2):655-64.

Migraine attack forecasting

Forecasting from perceived stress[10]

- N = 95 producing 4626 days of electronic diary data
- Input: Current headache status & current levels of stress
- Output: Presence/absence of headache
- Performance: AUC 0.65 (95% CI 0.6-0.67)



[10] Houle TT, Turner DP, Golding AN, Porter JA, Martin VT, Penzien DB, Tegeler CH. Forecasting individual headache attacks using perceived stress: development of a multivariable prediction model for persons with episodic migraine. Headache: The Journal of Head and Face Pain. 2017 Jul;57(7):1041-50.

Migraine attack forecasting

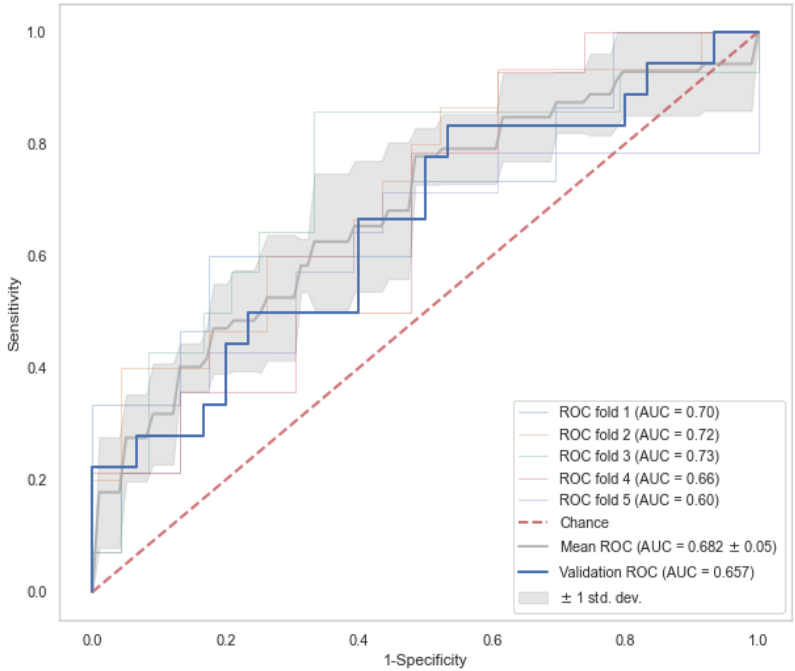
Forecasting from diary data and physiological measurements

N = 18 producing 295 days of data

Input: Diary data, premonitory symptoms, physiological data from biofeedback sessions

Output: Presence/absence of headache

Performance: AUC 0.657



NTNU

Machine prescription for chronic migraine

Stubberud A, Gray R, Tronvik E, Matharu M, Nachev P. Machine prescription for chronic migraine. medRxiv 2021.11.07.21265816; doi:https://doi.org/10.1101/2021.11.07.21265816

Background

- Difficult to predict treatment response at individual level
- Does the variation in clinical phenotype reflect different underlying causal mechanisms and responsiveness

Aims

- Can individualized treatment effects be estimated from patient characteristics?
- Is machine prescription superior to traditional heuristic treatment evaluation?

Machine prescription for chronic migraine

Study population (n = 1446)

- Chronic migraine
- 76 features (covariates)

- Gender, age
- Frequency, intensity
- Migrainous symptoms
- Cranial autonomic symptoms
- Aura

- Quality and location
- Headache triggers
- Family history
- Comorbidities

10 interventions

- Most of all commonly used migraine preventives

Outcomes

- Clinically meaningful response (50% reduction in headache frequency)

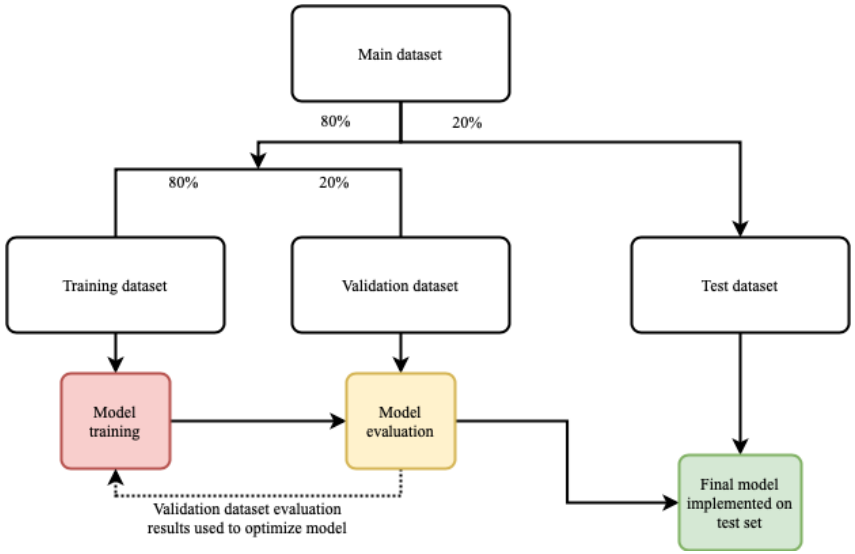
Modelling individualized treatment effects

Training, validation, test

Causal multitask gaussian process model

- Infers individualized treatment effects from high-dimensional data
- Predicts individualized treatment effects in unseen data

Conditional subgroup (patients predicted to respond) compared with average

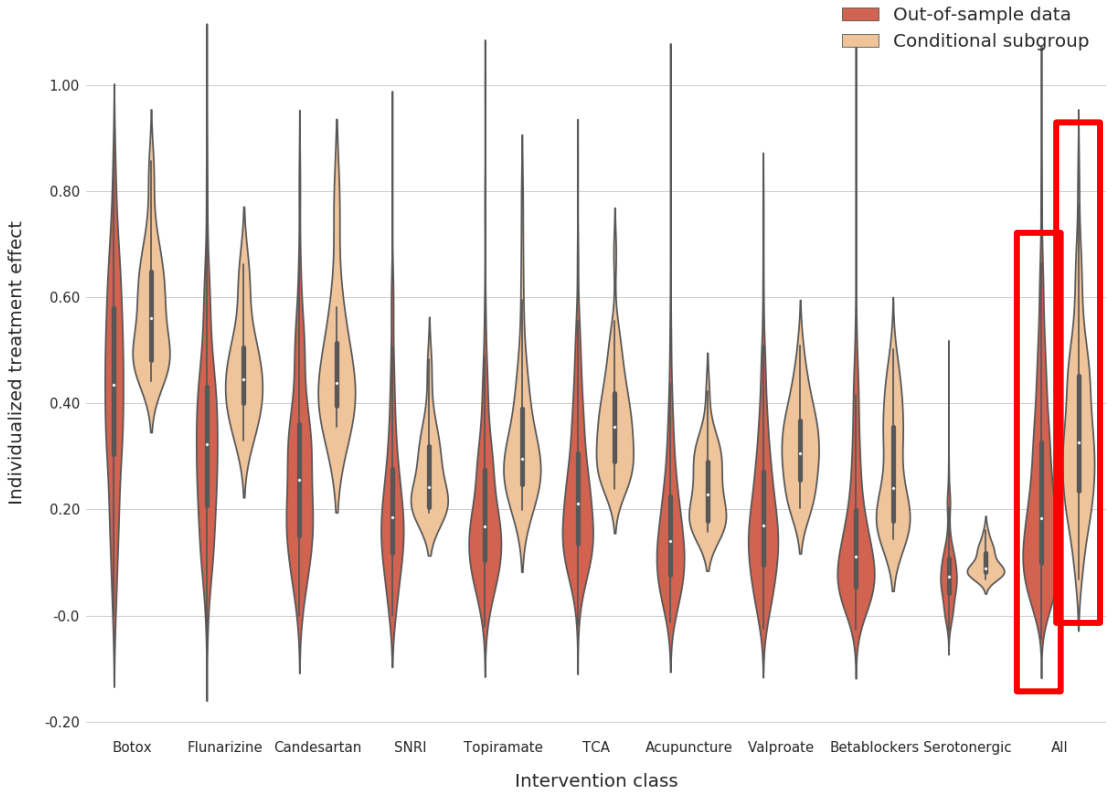


Individualized treatment effects

Average treatment effects – 0.06 to 0.44

Conditional average treatment effects – 0.09 to 0.56

Mean difference 0.034 (95% CI 0.003 to 0.065; p=0.033)



Impact and prescriptive modelling

Individualized treatment effects ≈ sequence of probabilites of treatment success

↓

$$\mathbb{P}\{X = k\} = p_1, k = 0$$
$$\mathbb{P}\{X = k\} = (1 - p_1)(p_2), k = 1$$
$$\mathbb{P}\{X = k\} = (1 - p_1) \dots (1 - p_k)(p_{k+1}), k \geq 2$$

↓

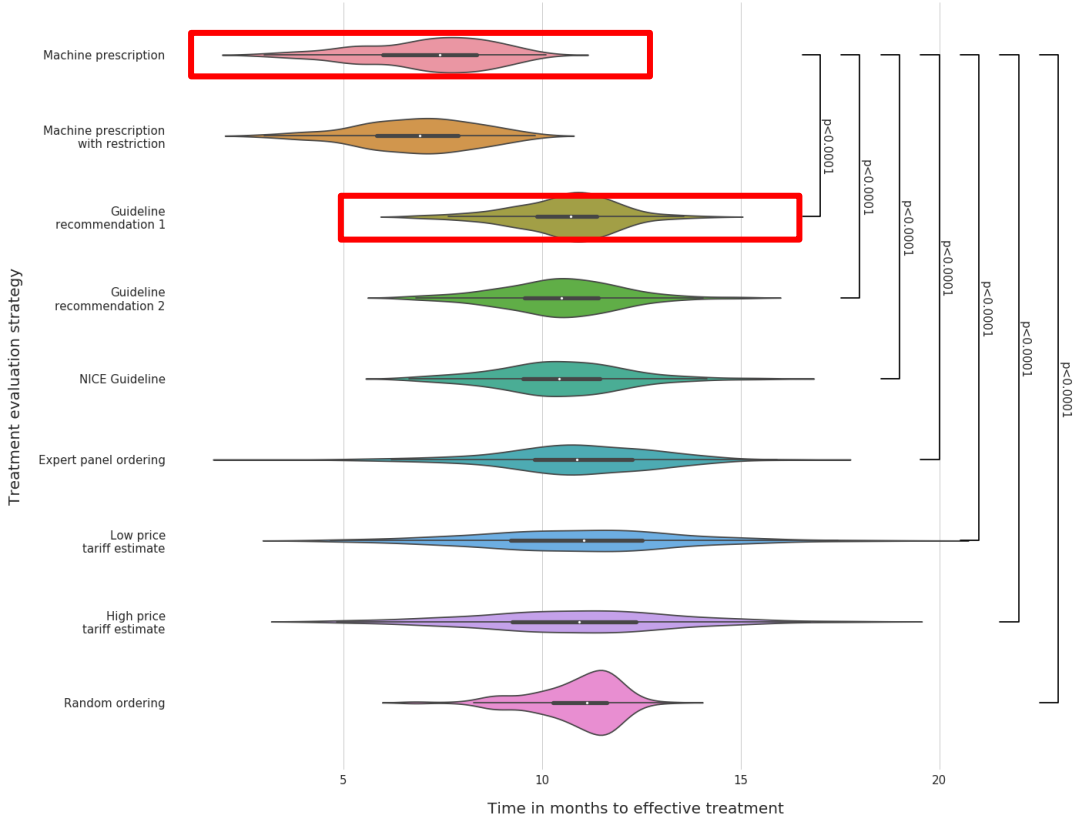
Expected number of months in pain = $(k + 1) \times 3\,months \times \mathbb{P}\{X = k\}$,
where *X* denotes number of failures before treatment success at trial *k+1*

Machine prescription vs. guidelines

Impact of machine prescription

-3.750 months; 95% CI -3.993 to -3.507; p<0.0001

Additional three-monthly cost -£2 to +£1



Conclusion

Machine learning can produce high accuracy forecasting models

Machine prescription can aid in choosing correct migraine therapy at the individual level

Model performance is likely to increase with optimal inclusivity and fidelity