Pathophysiological aspects of mobility and activity in Parkinson's disease

Kiel 18.01.23

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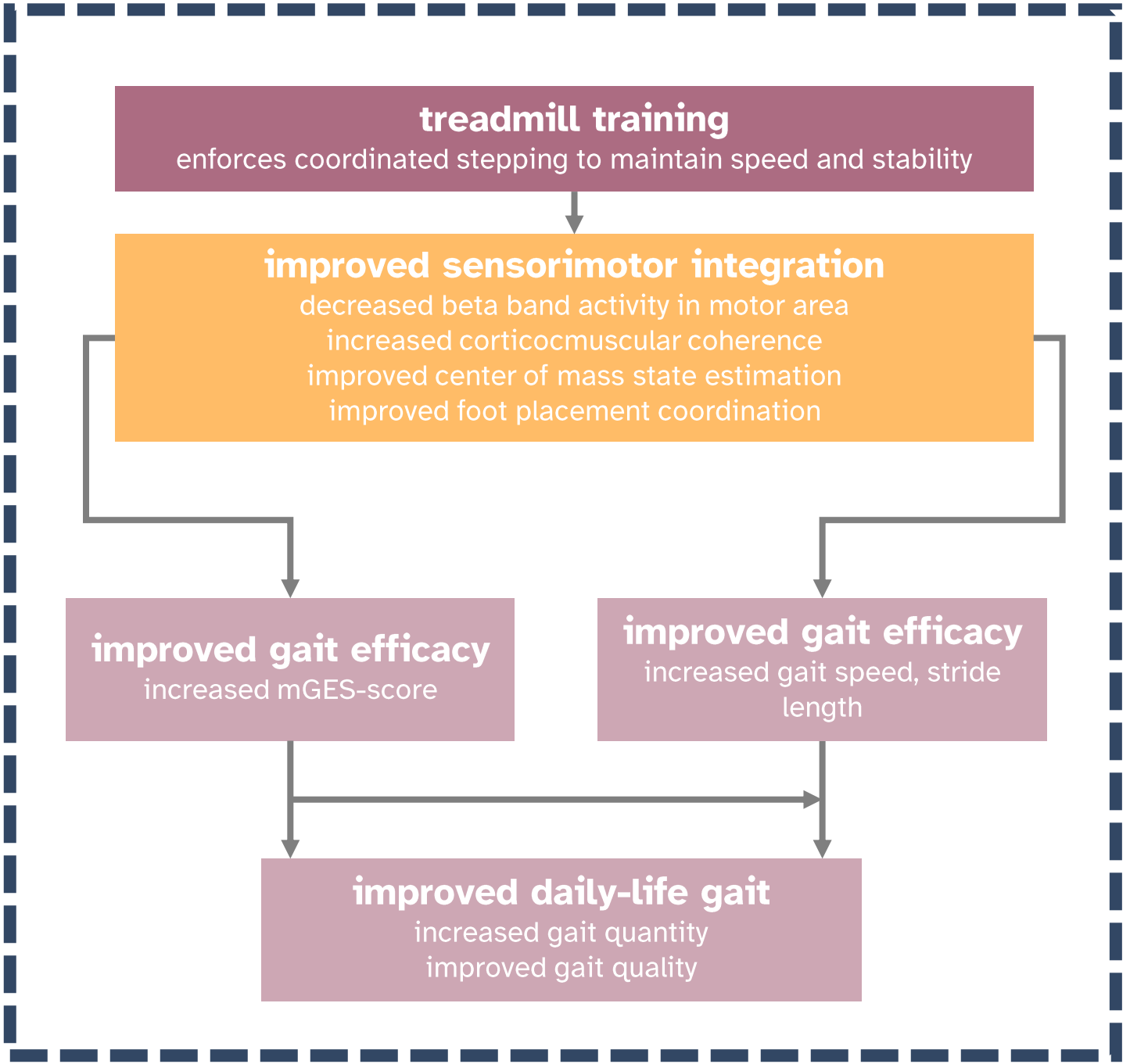
JPND call

→ Successful funding for three years with the **Step**s against the b**u**rden of **P**arkinson's Disease (**StepuP**) project

Overview

Pathophysiological aspects of mobility

a JPND project in Kiel



StepuP objectives

1. Understand the **biomechanical and neural mechanisms that underlie improvements in gait due to training** in people with PD

2. *Still secret*

3. *Still secret*

4. *Still secret*

Motivation

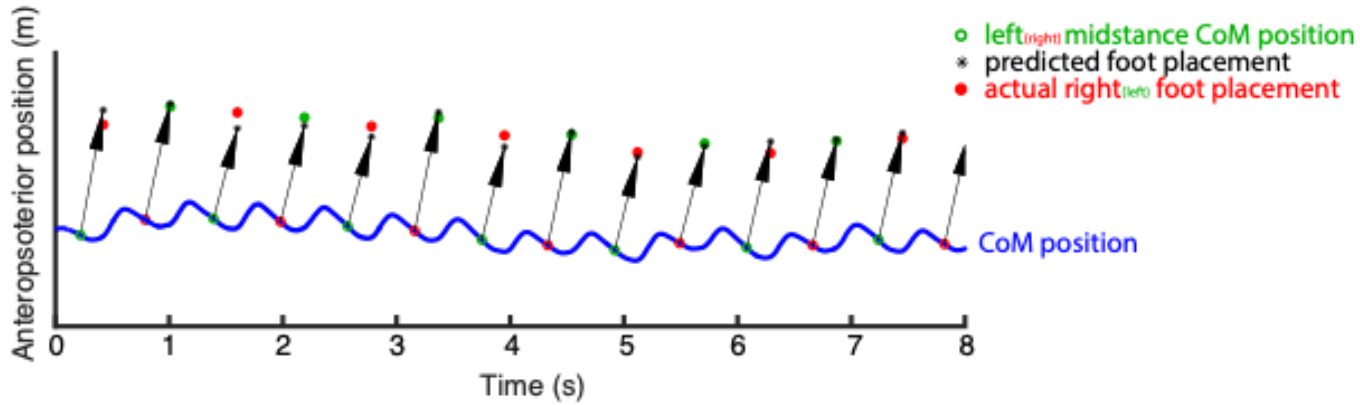
- PD often shows impaired gait (70%) which can cause falls (Allen ea., Parkinsons Dis, 2013)
- Early stakeholder survey on unmet needs in PD care

→ **improving gait** and **preventing falls**

  - 294 people with PD (88% & 88%)
  - 76 family members (91% & 93%), 16 clinicians (88% & 86%) and 29 caregivers (80% & 85%)

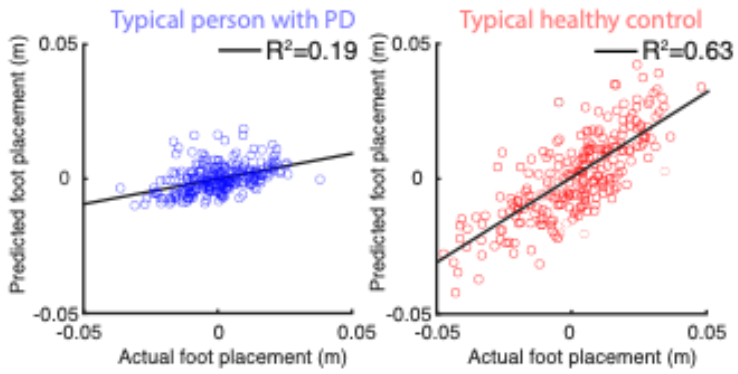
- Non-pharmacological interventions can reduce fall risk (Mirelmann ea., Lancet, 2016)
- Treadmill training (with perturbation) has been proven to improve mobility

Biomechanical aspects of walking in PD

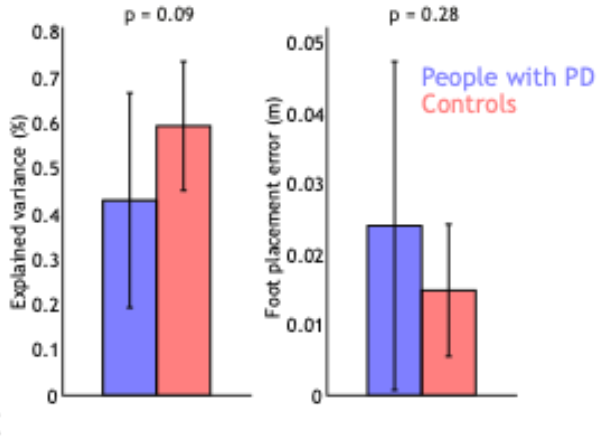


A

$$\text{foot placement} = \beta_1 \bullet P_{CoM} + \beta_{2l} \bullet v_{CoM} + \varepsilon$$



B

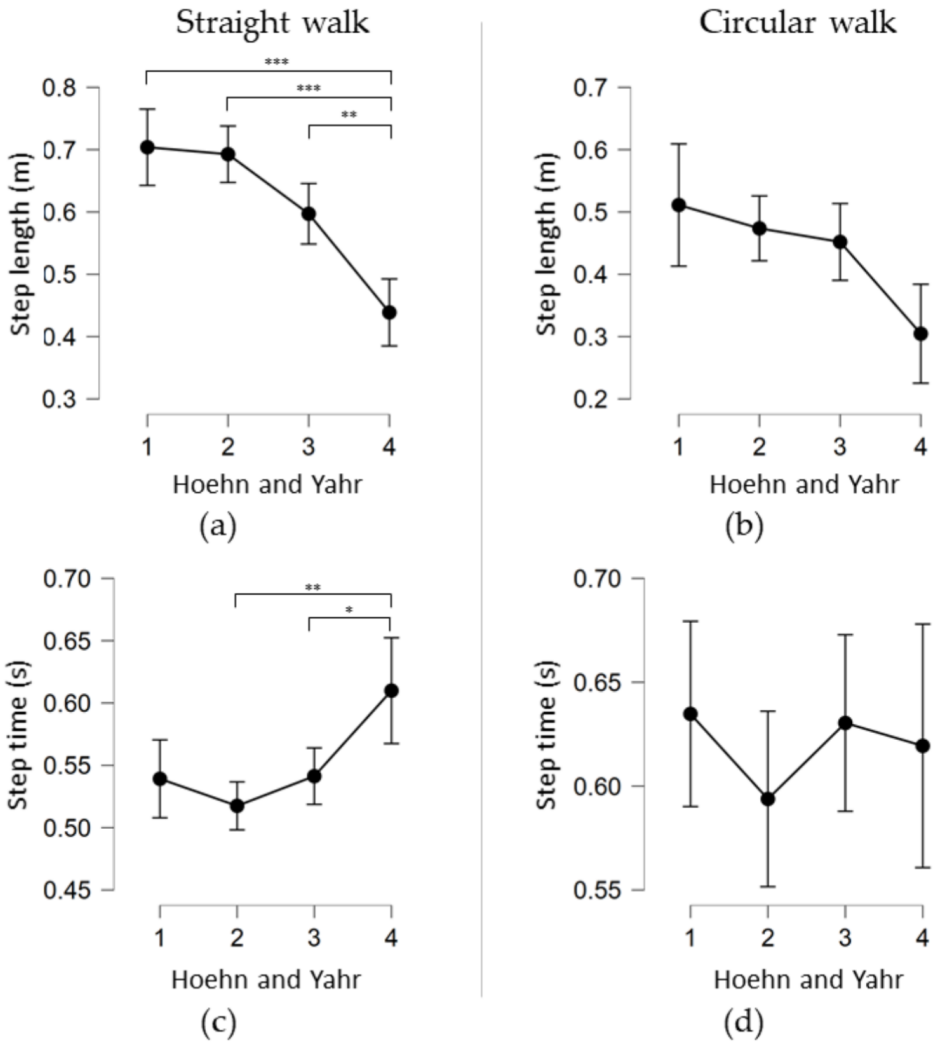


C

- Centre of mass must be repositioned with every step taken
- PD patients show worse adaptation of centre of mass correction while walking

Gait as a progression marker in PD

- Quantitative gait parameters decrease with more severe PD stages
- Different types of walking are affected differently
- Different aspects of walking show heterogenic results



Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis | Shen ea., Neurorehabilitation and Neural Repair, 2016

- “[…] Determine the effects of exercise training on the enhancement of balance and gait ability and reduction in falls for people with PD and to investigate potential factors contributing to the training effects on balance and gait ability of people with PD […]”.

- 25 RCTs
- **exercise training** against no intervention and placebo intervention
- Effects on **balance** and **gait** performance and **falls**

Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis | Shen ea., Neurorehabilitation and Neural Repair, 2016

Balance training:

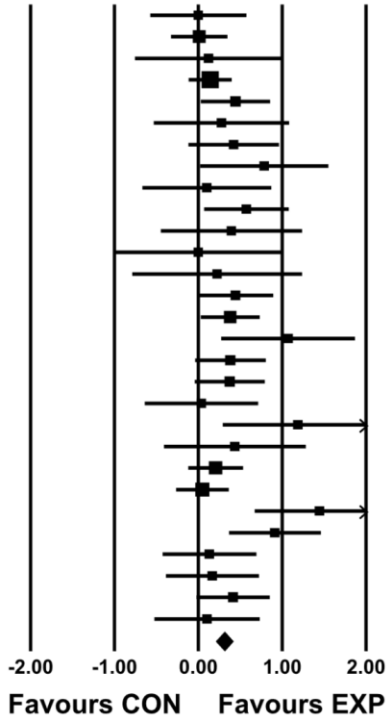
- control of the body's centre of mass with destabilizing movements and/or while standing on an unstable or small base of support

Gait training:

- walking exercises over ground or on a treadmill

A. Effects on postural stability in short-term (n=1881)

Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
Allen 2010	comfortable walking velocity (cm/s)	0.000	-0.575	0.575	1.000
Ashburn 2007	berg balance scale (0-56)	0.011	-0.327	0.349	0.948
Canning 2012	comfortable walking velocity (cm/s)	0.124	-0.757	1.004	0.783
Canning 2015	freezing of gait questionnaire	0.142	-0.116	0.399	0.281
Conradsson 2015	comfortable walking velocity (cm/s)	0.443	0.029	0.858	0.036
De Bruin 2010	comfortable walking velocity (cm/s)	0.276	-0.532	1.085	0.503
Duncan 2012	comfortable walking velocity (cm/s)	0.422	-0.120	0.963	0.127
Ebersbach 2010 (LSVT-BIG)	time_up and go test (s)	0.786	0.021	1.551	0.044
Ebersbach 2010 (Nordic walk)	time_up and go test (s)	0.101	-0.669	0.872	0.796
Ellis 2005	comfortable walking velocity (cm/s)	0.574	0.068	1.080	0.026
Fietzek 2014	freezing of gait questionnaire	0.395	-0.449	1.238	0.359
Fisher 2008 (Physiotherapy)	comfortable walking velocity (cm/s)	0.000	-1.010	1.010	1.000
Fisher 2008 (treadmill walk)	comfortable walking velocity (cm/s)	0.224	-0.789	1.238	0.665
Gao 2014	berg balance scale (0-56)	0.443	-0.007	0.894	0.054
Goodwin 2011	berg balance scale (0-56)	0.381	0.028	0.734	0.034
Hackney 2008	berg balance scale (0-56)	1.071	0.271	1.870	0.009
Li 2012 (balance ex)	time_up and go test (s)	0.383	-0.040	0.806	0.076
Li 2012 (strength ex)	time_up and go test (s)	0.375	-0.044	0.794	0.080
Liao 2014	time_up and go test (s)	0.037	-0.640	0.715	0.914
Mak 2008 (balance ex)	time_sit-to-stand (s)	1.188	0.289	2.087	0.010
Mak 2008 (common ex)	time_sit-to-stand (s)	0.435	-0.412	1.283	0.314
Morris 2015 (strength ex)	time_up and go test (s)	0.207	-0.122	0.536	0.218
Nieuwboer 2007	time_up and go test (s)	0.049	-0.266	0.364	0.760
Picelli 2012	berg balance scale (0-56)	1.445	0.670	2.220	0.000
Smania 2010	berg balance scale (0-56)	0.913	0.365	1.462	0.001
White 2009 (3h per wk)	2-min walking test (m)	0.132	-0.428	0.693	0.644
White 2009 (4.5h per wk)	2-min walking test (m)	0.167	-0.389	0.724	0.555
Wong-Yu 2015	comfortable walking velocity (cm/s)	0.414	-0.024	0.853	0.064
Yen 2011	sensory organization test_compoisite score	0.103	-0.527	0.733	0.748
		0.303	0.211	0.395	0.000

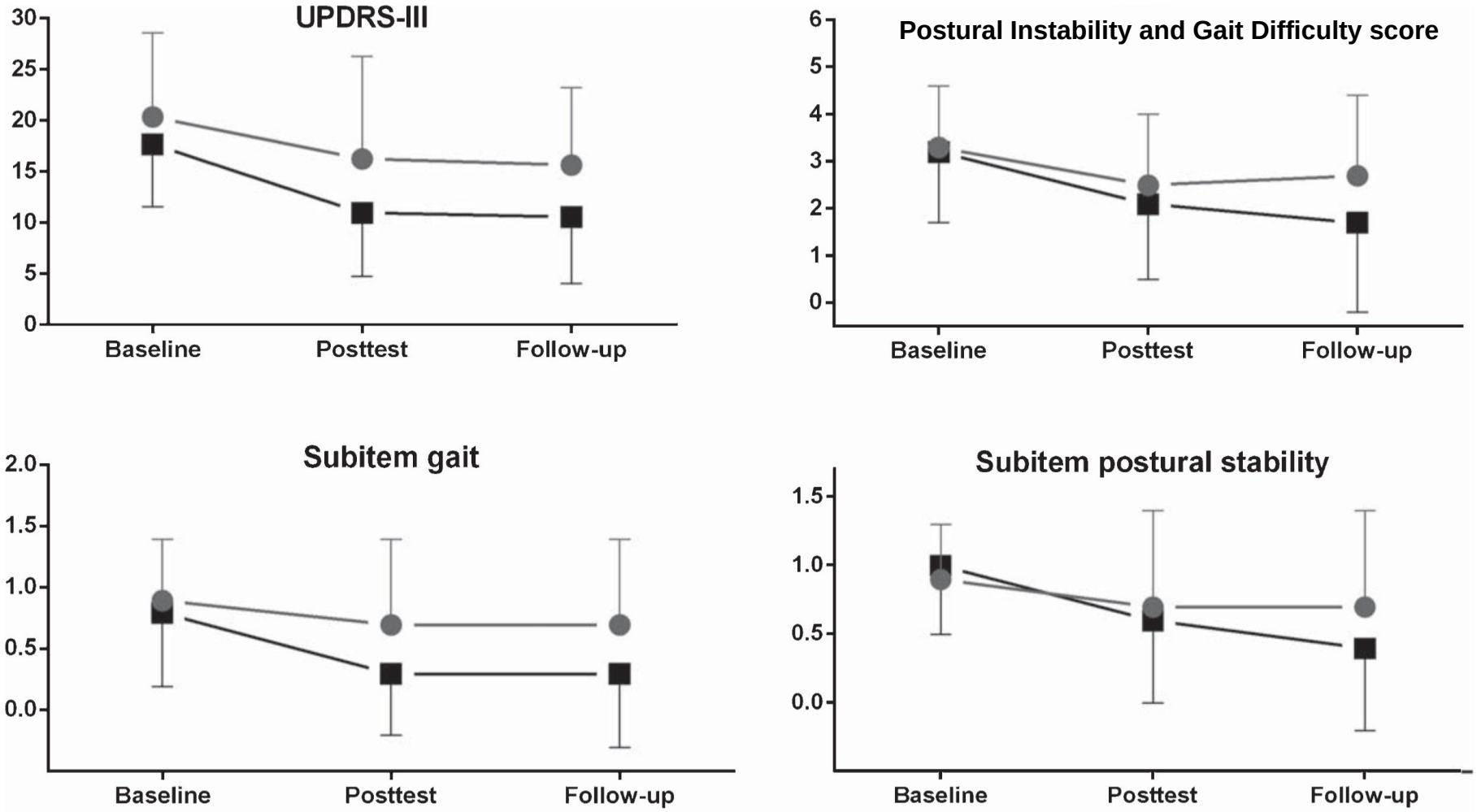


Fixed-effects model of meta-analysis: I^2=22%, df=28, P>0.05

Perturbation Treadmill Training Improves Clinical Characteristics of Gait and Balance in Parkinson's Disease | Gaßner ea., Journal of Parkinson's Disease, 2019

- RCT with 43 PD's
- Perturbation Treadmill Training vs conventional Treadmill Training
- Outcomes at Baseline, 8 and 12 weeks after intervention
- Exercise vs. best medical treatment

Perturbation Treadmill Training Improves Clinical Characteristics of Gait and Balance in Parkinson's Disease | Gaßner ea., Journal of Parkinson's Disease, 2019



Treadmill training

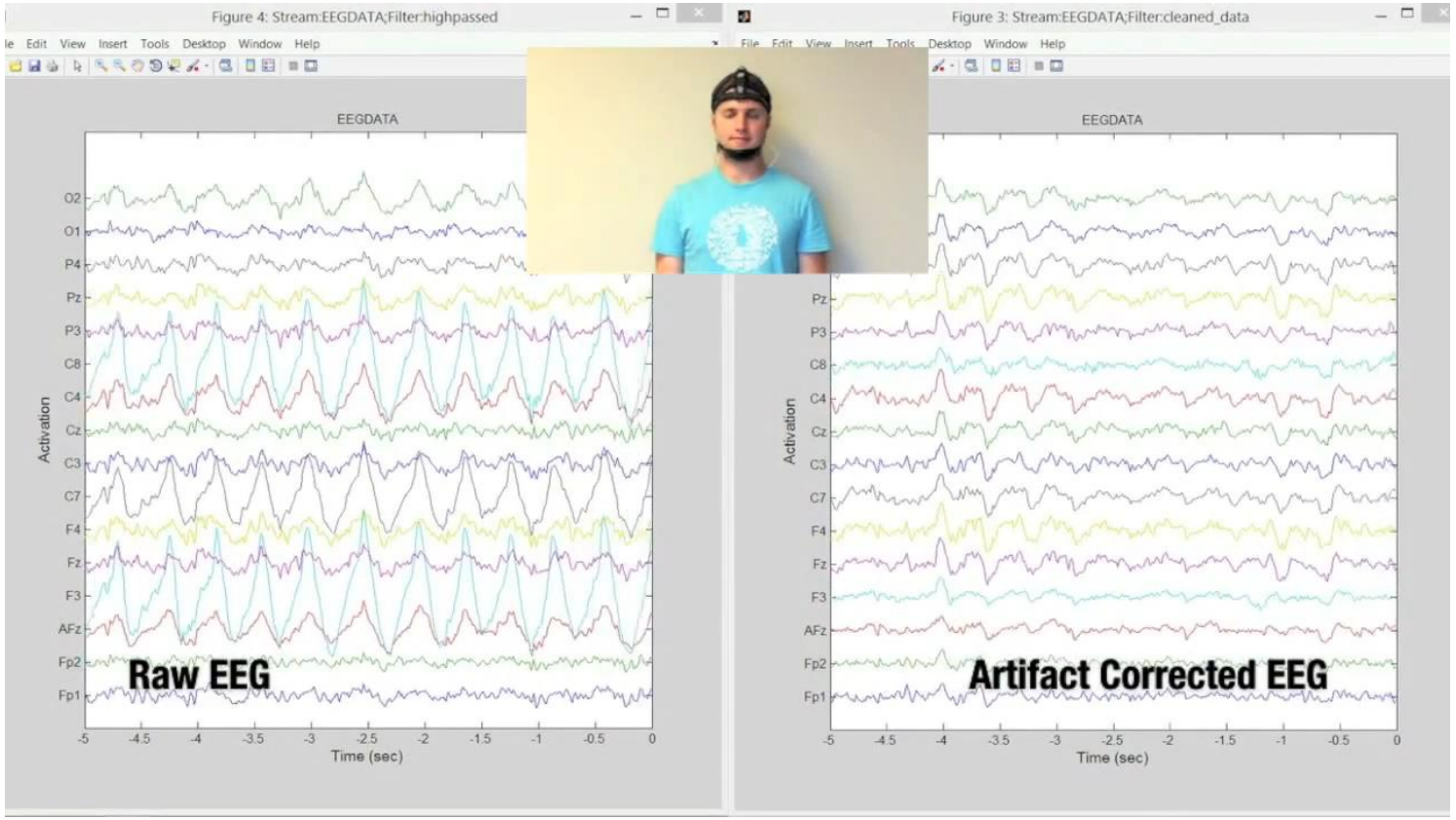
Video is curtesy of Helen J. Huang from the University of central Florida

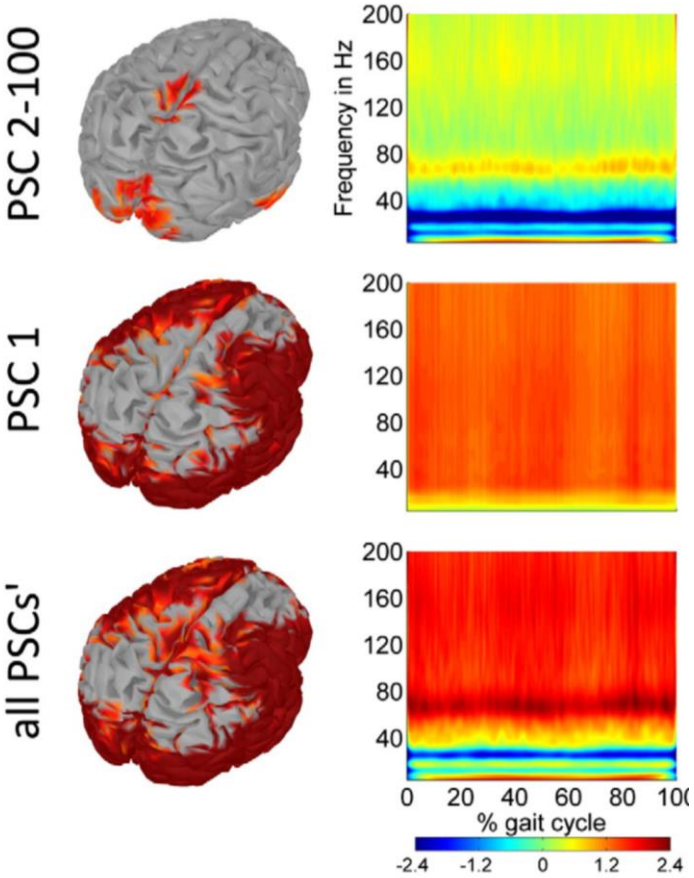
Recap

- PD patients show impaired gait
- Can be trained → Feedback mechanisms improve
- Treadmill-training holds promising results
- Adding perturbations might be even more effective

But: How does training work on a neural level?

“Mobile EEG”

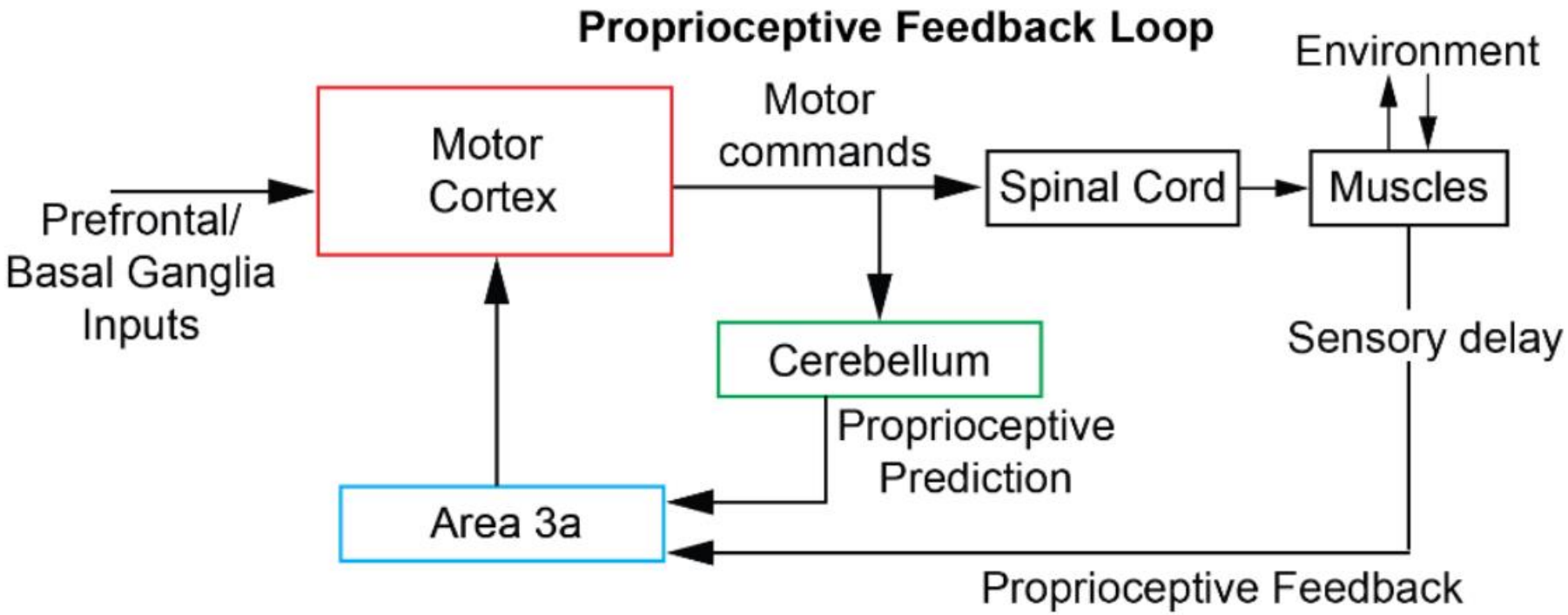




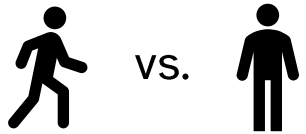
Seeber ea., NeuroImage, 2015

Dynamical Feedback Control: Motor Cortex as an Optimal Feedback Controller Based on Neural Dynamics |Versteeg ea., bioarXiv, 2022

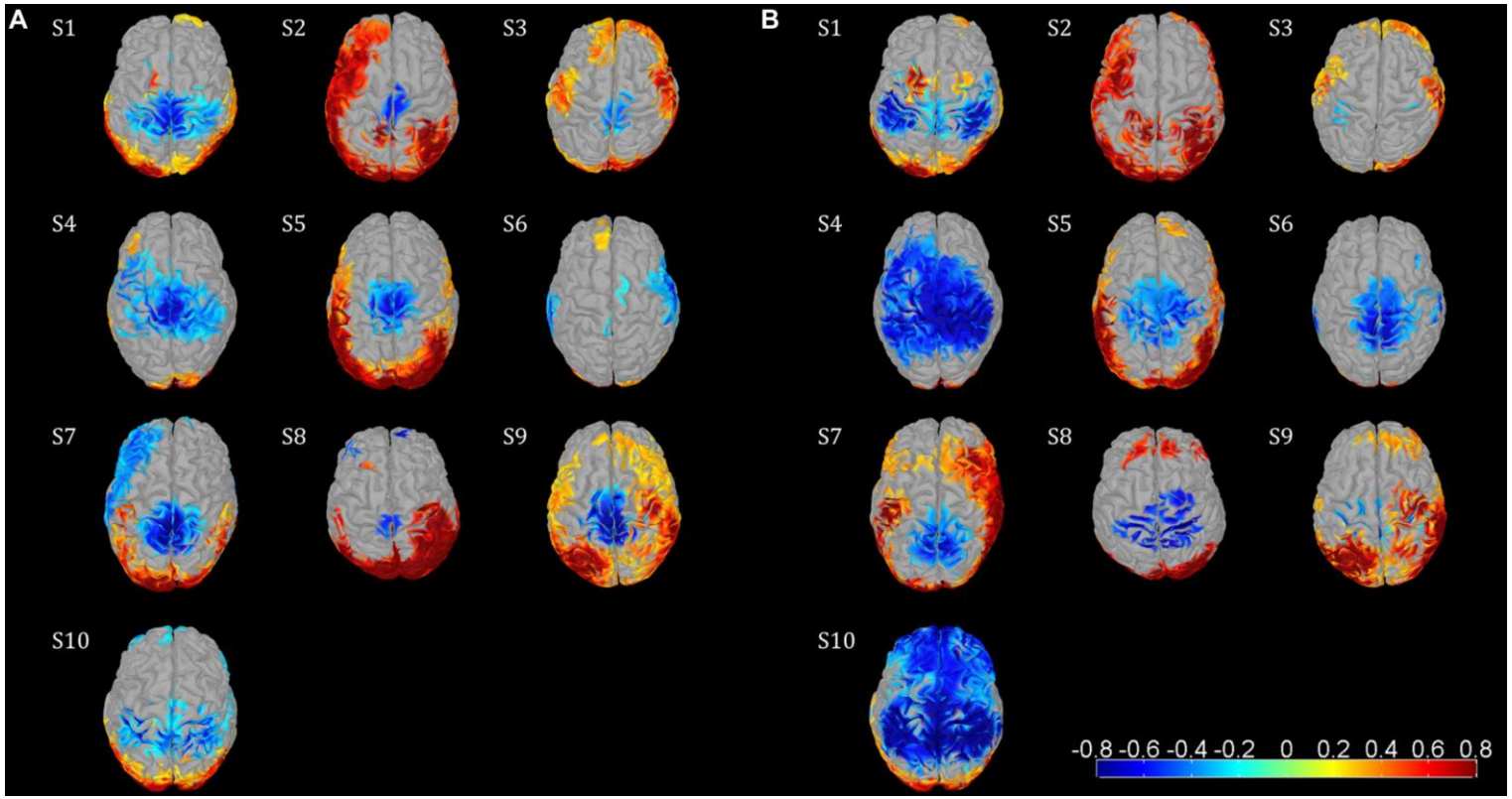
- **M1 as main feedback controller in motor control**



EEG beta suppression and low gamma modulation are different elements of human upright walking | Seeber ea., Frontiers, 2014

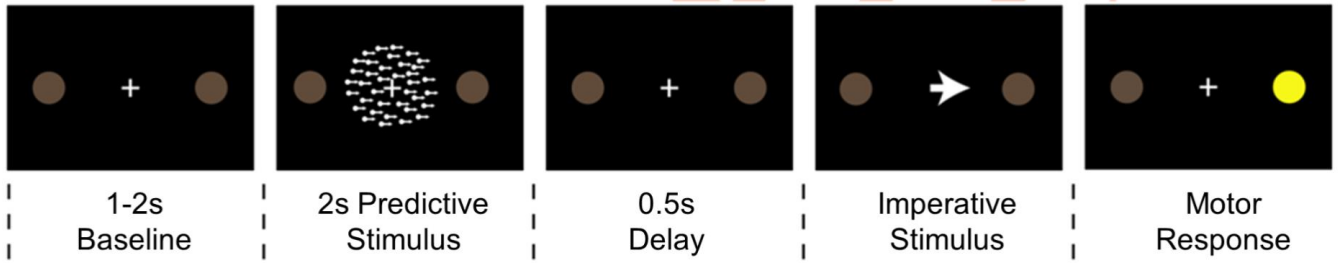
α  vs. β

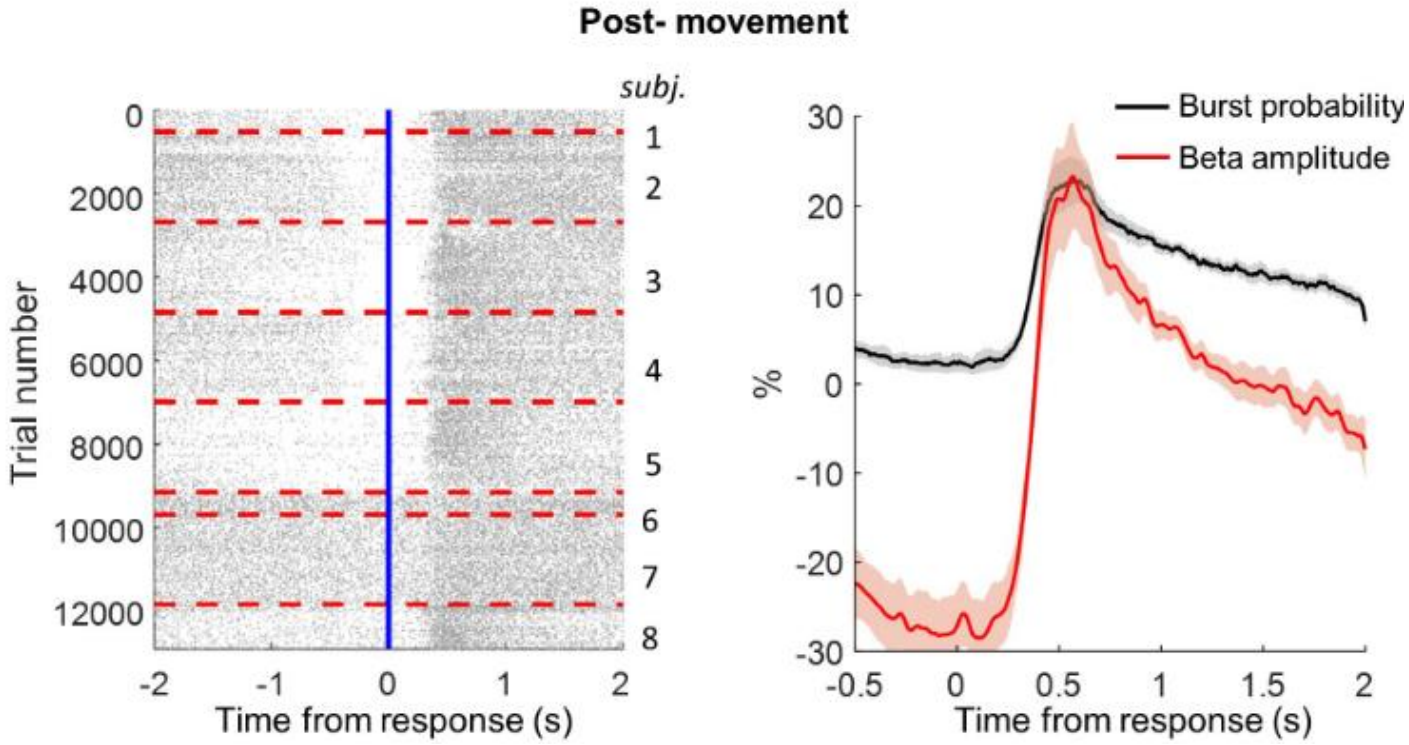
- Mu and beta in M1
- Less event related desynchronisation in more challenging task



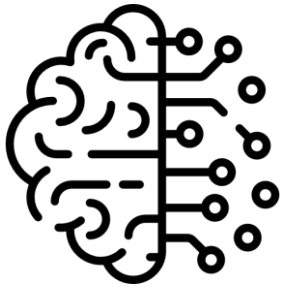
Human motor cortical beta bursts relate to movement planning and response errors | Little ea., PLOS Biology, 2019

- Error processing on a neural basis
- Beta as significant predictor post movement for error
- Beta bursts are associated with delayed motor initiation and correct responses





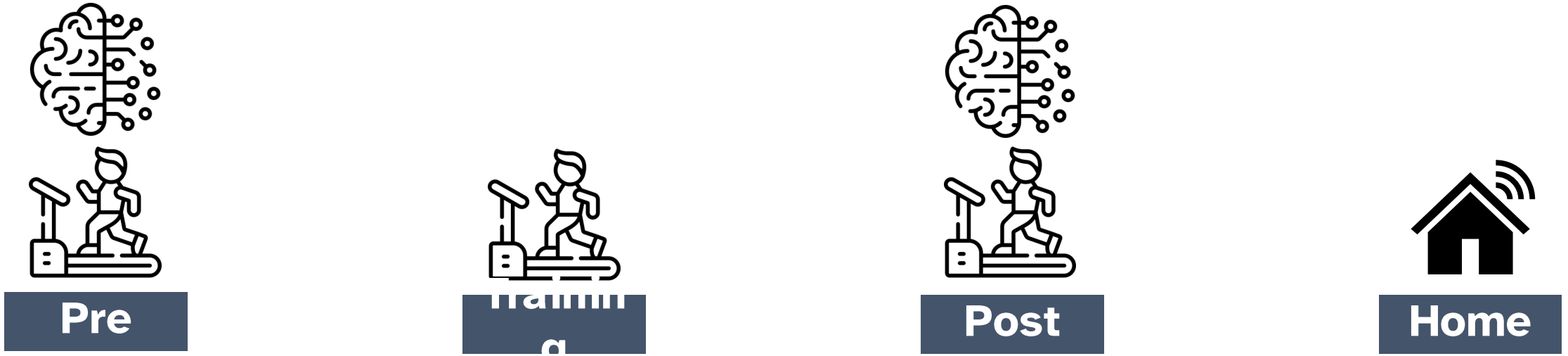
Recap



- Mobile EEG is very possible
- Cortical involvement in motor control (M1) as feedback controller
- Beta band is involved in motor tasks like walking and error processing

→ Unclear how unsuccessful walking looks like in the brain and what changes after training

What is the best treadmill training



Center	Training intervention	control	duration
Bologna	Speed-dependent treadmill training (SDTT)	Placebo	4 weeks
Tel Aviv	SDTT + VR-triggered perturbations	SDTT	4 weeks
Sydney	SDTT + multi-directional perturbations	SDTT	4 weeks
Kiel	**SDTT + anterior-posterior perturbations**	**SDTT**	**2-3 weeks**

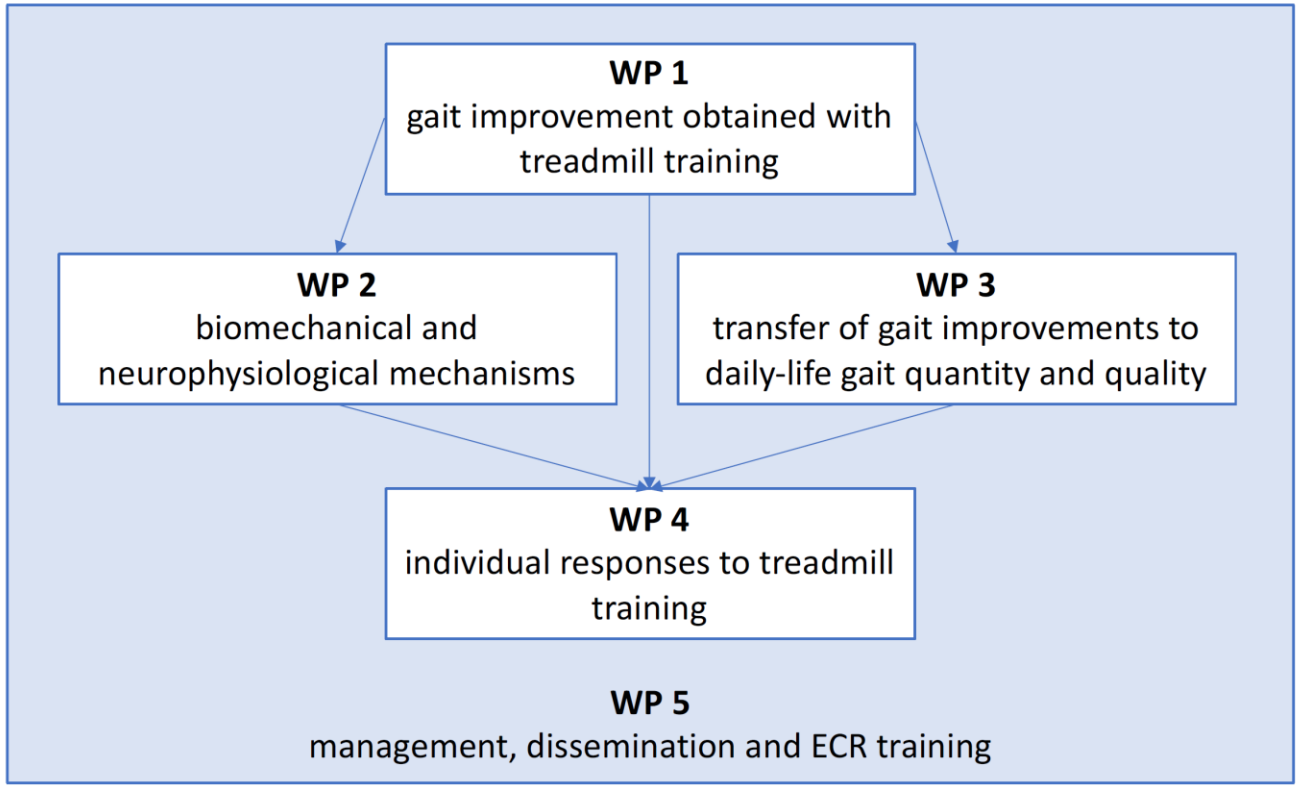
StepuP overview

Secret objectives:

2. Assess to what extent improvements in gait due to treadmill training **transfer to daily life** mobility

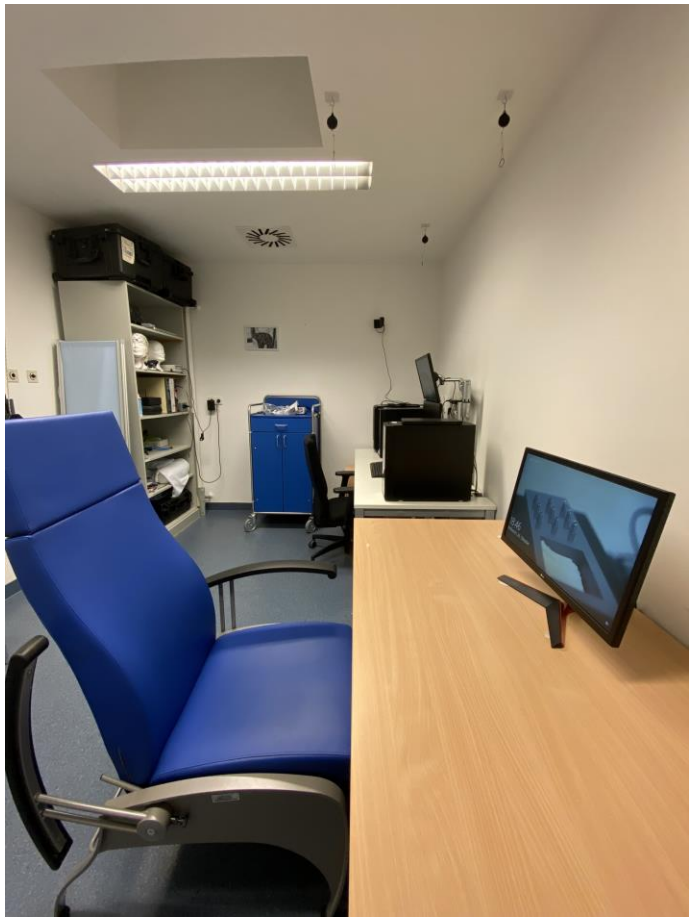
3. Understand the mechanisms that underpin transfer from improvements in gait to **improvements of mobility in daily life** in people with PD

4. Understand **for whom treadmill training does improve lab-based gait characteristics** and for whom it does not and understand for whom treadmill training does **improve mobility in daily life** and for whom it does not.



Why Kiel?

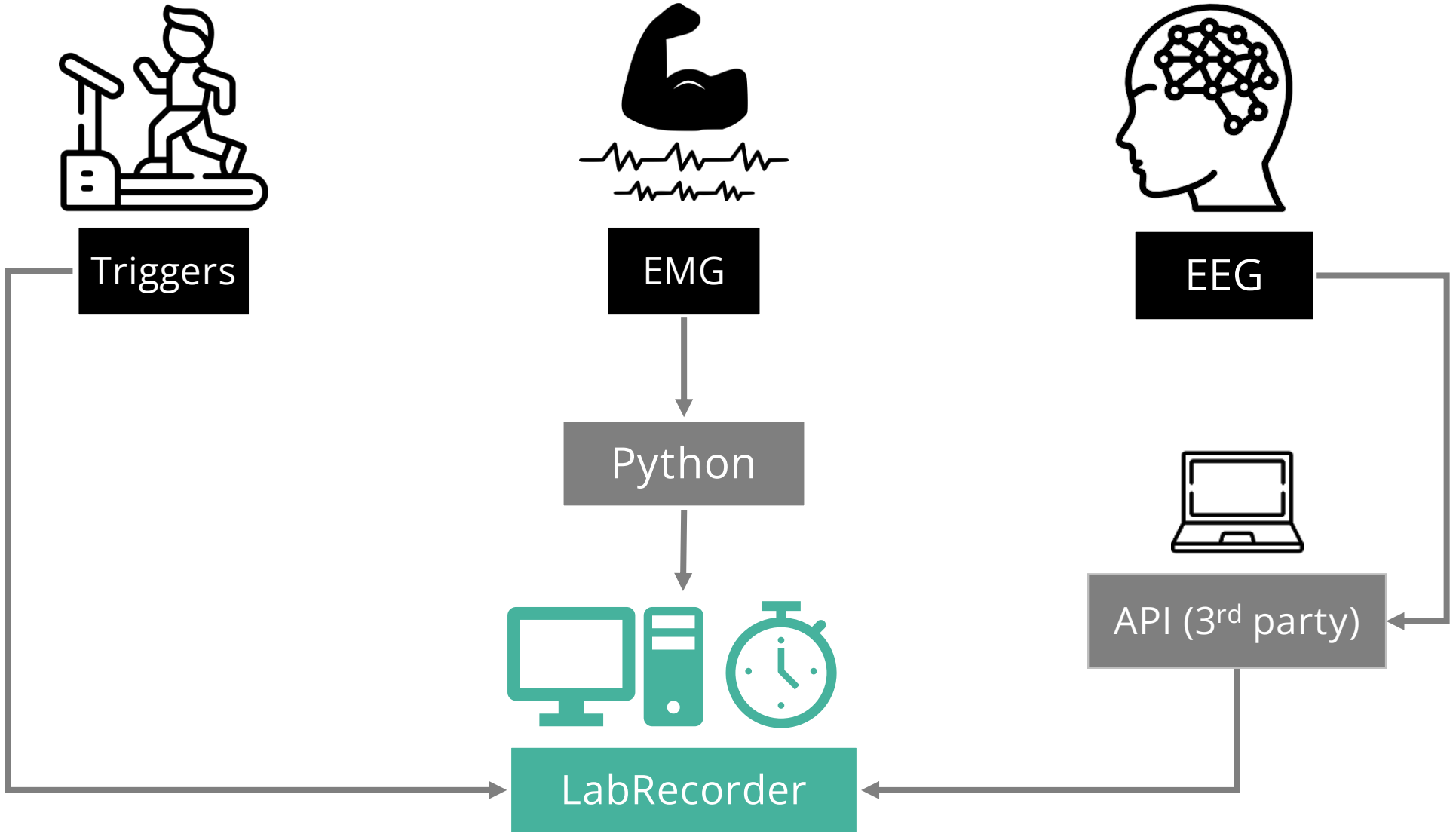
Building a sustainable lab environment



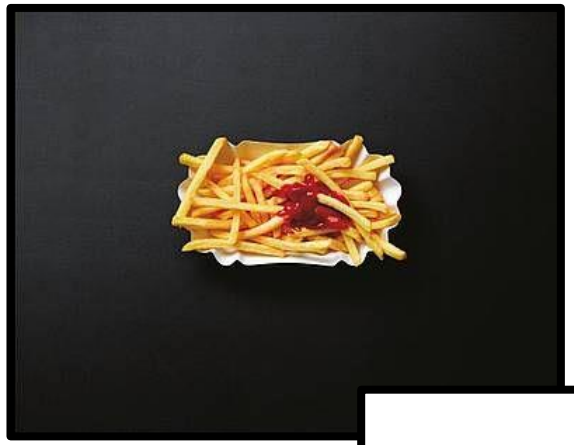
Open science

- Open software (Lab streaming layer architecture)
- Open data (BIDS)
- Open source (GitHub)

Open software | Lab streaming layer



Open data | BIDS



BIDS
BRAIN IMAGING DATA STRUCTURE

Example1/
- sub-001/[ses-01/]
  - eeg/
  - ...
  - **motion/**
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    - **sub-001[_ses-01]_task-<label>_tracksys-<label>_motion.json**
    - **sub-001[_ses-01]_task-<label>_tracksys-<label>_channels.tsv**
    - sub-001[_ses-01]_task-<label>_tracksys-<label>_events.tsv
    - sub-001[_ses-01]_task-<label>_tracksys-<label>_events.json

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0,694520294	0,191824943	0,843726573	0,397571025	0,88542996	0,895276224
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0,577995093	0,045616941	0,04903375	0,940889749	0,153318421	0,668360752
0,054555716	0,791513927	0,587116733	0,466957774	0,975446368	0,048053341
0,966026984	0,196283834	0,711044406	0,338944328	0,719445195	0,438488392
0,98417512	0,507944361	0,1180168	0,796692478	0,175376468	0,488659533
0,98839607	0,155737146	0,800206213	0,633481382	0,752698206	0,852943441
...	...	...	...	...	...


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    "MAGNChannelCount": 6,
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    "ManufacturersModelName": "BW-imu600",
}
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name	type	units	srate	tracked_point	component	placement
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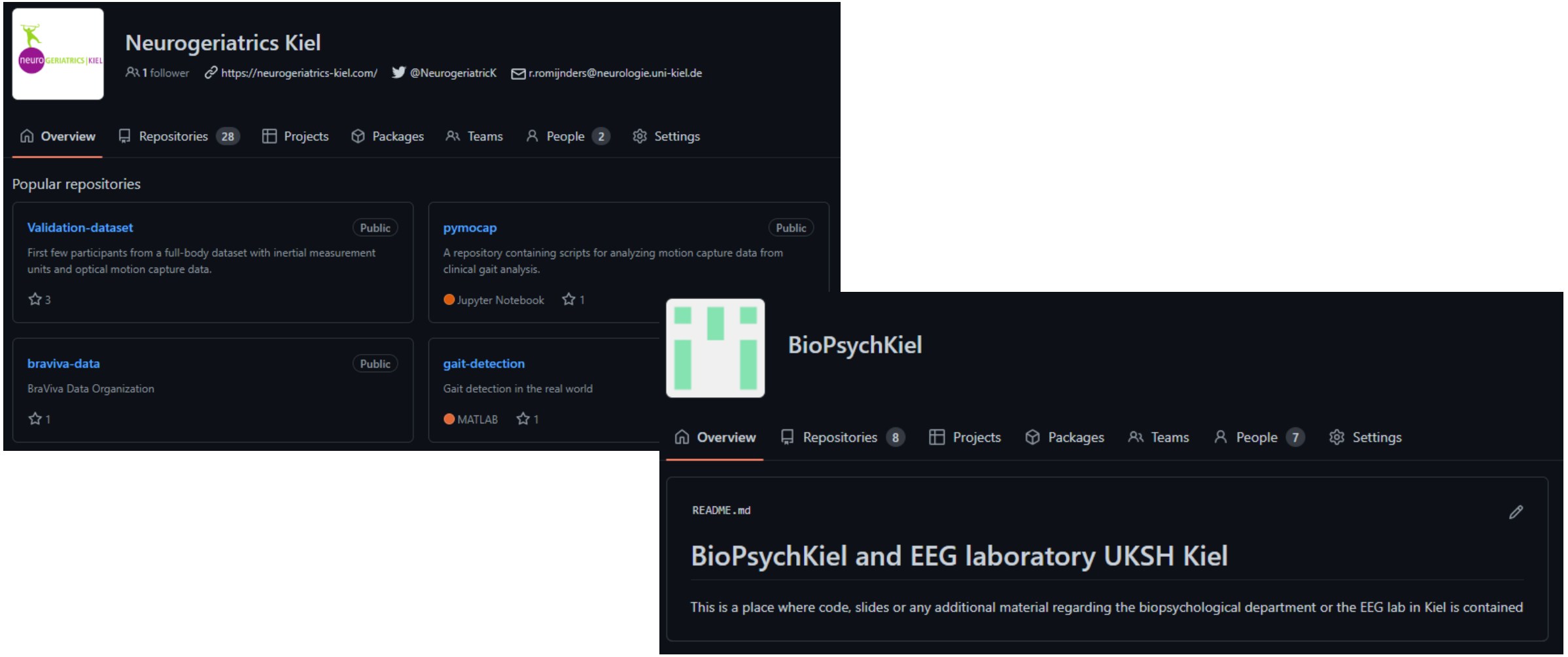
imu1_lf_acc_y	ACCEL	m/s^2	222	lf	y	left_foot
imu1_lf_acc_z	ACCEL	m/s^2	222	lf	z	left_foot
imu1_lf_gyro_x	GYRO	rad/s	222	lf	x	left_foot
imu1_lf_gyro_y	GYRO	rad/s	222	lf	y	left_foot
imu1_lf_gyro_z	GYRO	rad/s	222	lf	z	left_foot

Open source | GitHub



Thanks to all ☺

Kiel: Neuro-Klinik, Walter, Hanna, Jenni, Markus, Clint, Prof. Berg, Prof. Deuschl, Jos

StepuP partners

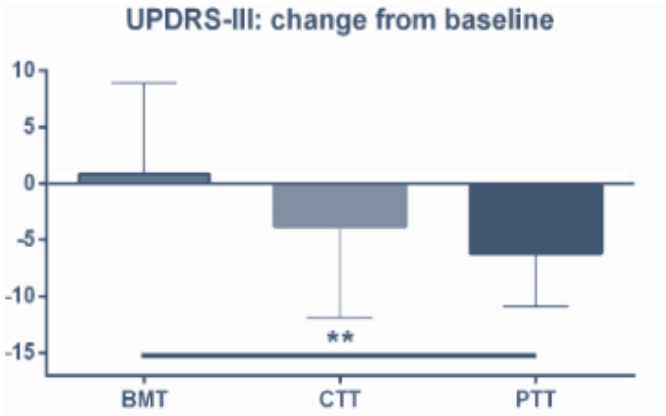
- **Amsterdam** team: Prof. Jaap van Dieën (coordinator), Dr Bernadette van Wijk and Dr Sjoerd Bruijn
- **Sydney** team: Dr Matthew Brodie, Prof. Nigel Lovell, Dr Martin Ostrowski, Prof. Daniel Chan
- **Tel Aviv** team: Prof. Jeff Hausdorff, Prof. Nir Giladi, Dr Talia Herman
- **Bologna** team: Dr Fabio La Porta, Prof. Pietro Cortelli, Prof. Giovanna Calandra Buonaura, Prof. Lorenzo Chiari and Dr Luca Palmerini
- **Zürich** team: Dr Navrag Singh and Dr Deepak Ravi

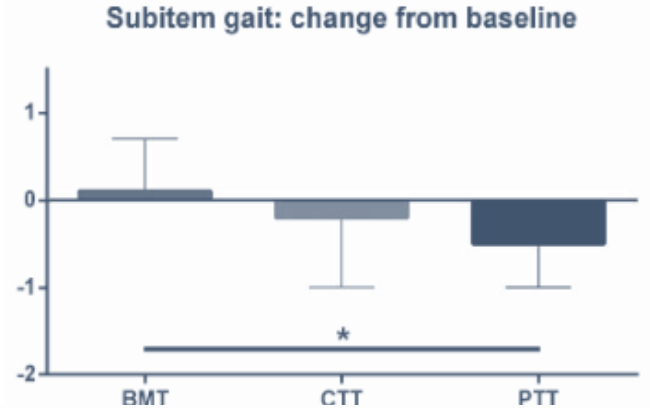
Additional slides

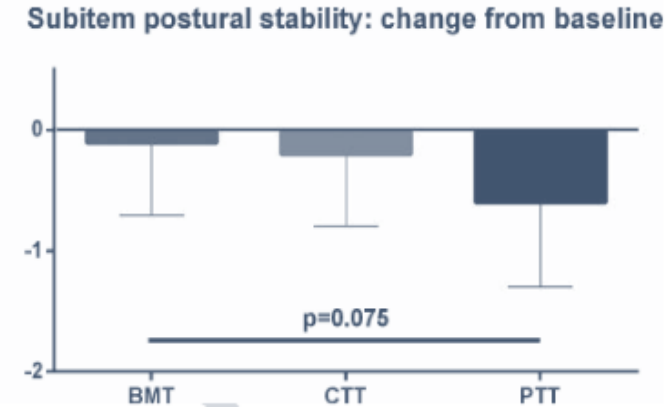
Perturbation Treadmill Training Improves Clinical Characteristics of Gait and Balance in Parkinson's Disease | Gaßner ea., Journal of Parkinson's Disease, 2019

- Significant overall symptom improvement
- Gait and Balance might be different training

→ Translation to everyday life







Studies on treadmill training (with perturbations)

- Mak MK, Wong-Yu IS, Shen X, Chung CL. **Long-term effects of exercise and physical therapy in people with Parkinson disease**. Nat Rev Neurol 2017
- Shen X, Wong-Yu IS, Mak MK. **Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis**. Neurorehabil Neural Repair 2016
- Gassner H, Steib S, Klamroth S, Pasluosta CF, Adler W, Eskofier BM, Pfeifer K, Winkler J, Klucken J. **Perturbation Treadmill Training Improves Clinical Characteristics of Gait and Balance in Parkinson's Disease**. J Parkinsons Dis 2019

Studies on cortical oscillations (during walking)

- Link between sensorimotor integration during gait and cortical activity in the sensorimotor and pre-motor areas

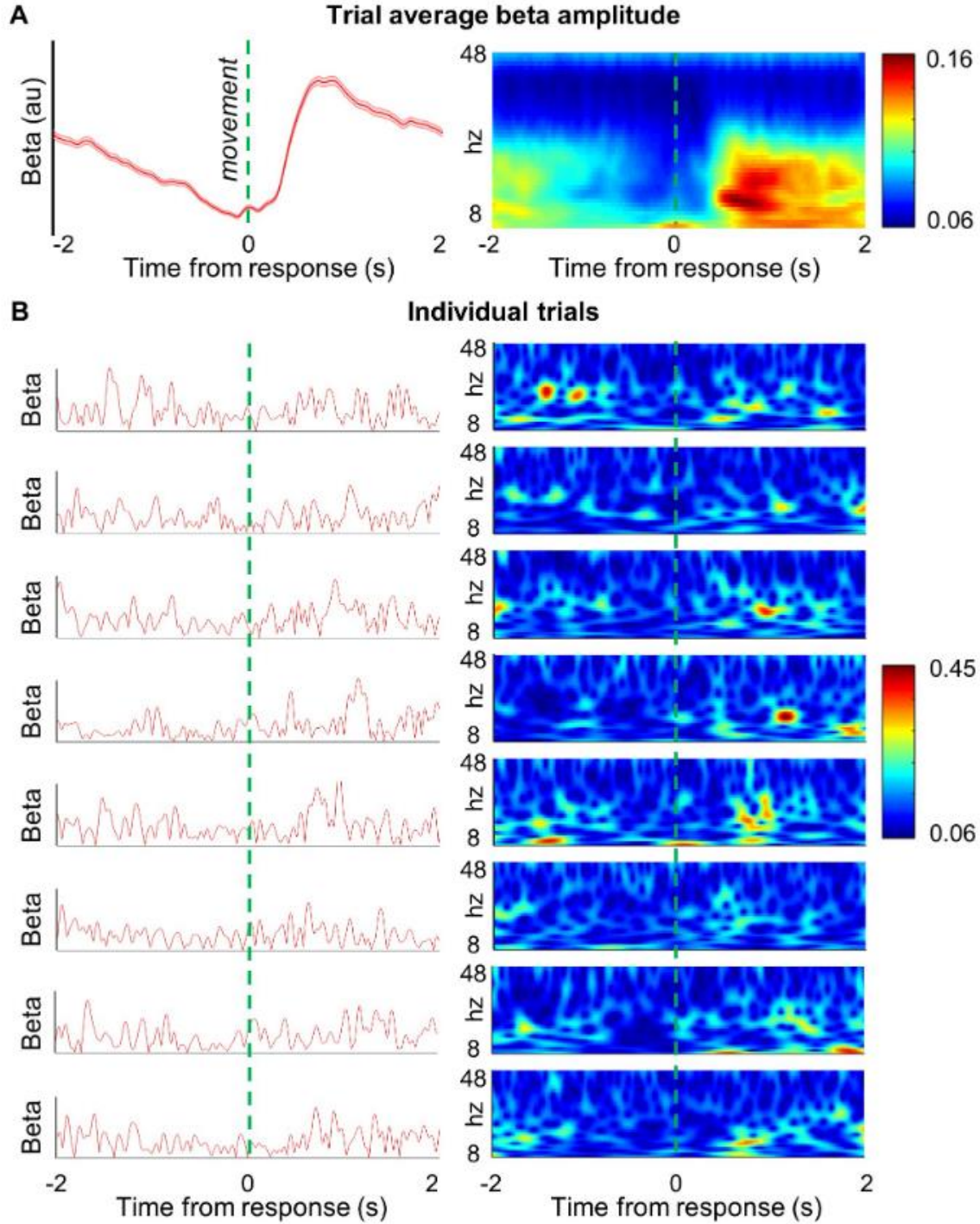
→ (Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., & Müller-Putz, G. R. **EEG beta suppression and low gamma modulation are different elements of human upright walking**. Front Hum Neurosci 2014.

- Motor cortex plays a key role in feedback control of gait

→ (Bruijn SM, van Dieën JH, Daffertshofer A. **Beta activity in the premotor cortex is increased during stabilized as compared to normal walking**. Front Hum Neurosci 2015)

- Increased beta band activity during gait in people with PD suggests compromised cortical control of gait

→ (Allali G, Blumen HM, Devanne H, Pirondini E, Delval A, Van De Ville D. **Brain imaging of locomotion in neurological conditions**. Neurophysiol Clin 2018) & (Tosserams A, Weerdesteyn V, Bal T, Bloem BR, Solis-Escalante T, Nonnekes J. **Cortical Correlates of Gait Compensation Strategies in Parkinson Disease**. Ann Neurol 2022)


A
Trial average beta amplitude
Beta (au)
movement
-2
0
2
Time from response (s)
48
hz
8
0.16
0.06
B
Individual trials
Beta
0.45
0.06