Deep brain stimulation
Mechanisms of action, Cortex-Basal Ganglia-Physiology and Therapy Optimization

To move or not to move –
neural correlates in the Parkinsonian and healthy motor system

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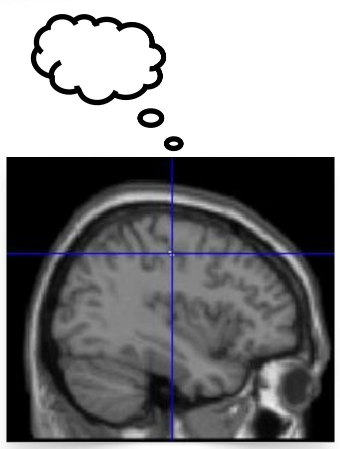
complexity in the movement chain

"What is left over if I subtract the fact that my arm goes up from the fact that I raise my arm?"

L. Wittgenstein (1953)

I choose / prepare / imagine / quasi… to move.*



rest	pre	post

- optimal neural prerequisites for motor performance?
- neural pathology in patients with movement disorders
- therapy, brain-computer interfaces

*talk by Prof M. Hallett (ICCN Berlin, March 21, 2014)

quote: http://philosophy.uchicago.edu/faculty/files/ford/Ford[Action&Generality].pdf
image credit: http://images.fineartamerica.com/images-medium-large/detail-from-the-creation-of-adam-michelangelo.jpg | http://www.clipartbest.com/cliparts/LcK/qkx/LcKqkxpca.png
http://upload.wikimedia.org/wikipedia/commons/thumb/d/de/Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg/512px-Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg.png

I .... to move.*

spatio-temporal dynamics (variability)

Bak et al. (1988); Chialvo (2010); Kelso (1995); Kelso et al. (2013); Palva et al. (2013); Shew and Plenz (2012); Tognoli and Kelso (2009)…

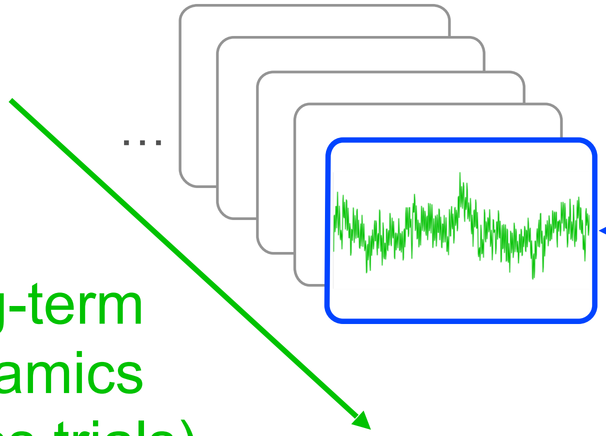
neural dynamics:

healthy and disease

temporal dynamics

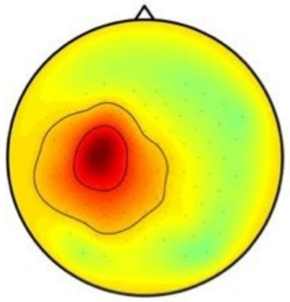
meta-stability

spatial dynamics



long-term dynamics (across trials)

short-term dynamics (single trials)



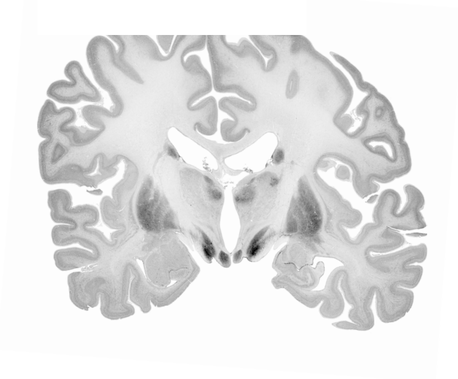


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image credit: http://www.neurosupply.com/images/dispEEG.jpg | http://www.clipartbest.com/cliparts/LcK/qkx/LcKqkxpca.png | https://bigbrain.loris.ca/main.php
http://upload.wikimedia.org/wikipedia/commons/thumb/d/de/Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg/512px-Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg.png

movement-related neural dynamics

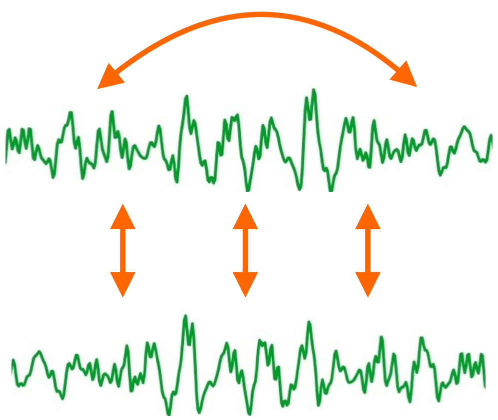
SIGNALS

1) in time (LRTC)
2) in space (connectivity)

prerequisites

PARADIGM

3) quasi-movements



1) time: fractal dynamics (LRTC) in neural oscillations from Parkinsonian basal ganglia

2) space: connectivity in Parkinsonian basal ganglia and the relation to motor symptoms

3) paradigm: quasi-movements (EEG, brain-computer interfacing)

Can you do a movement without doing it?

image credit: http://fc01.deviantart.net/fs70/f/2013/267/5/6/dmc_delorean_by_conman17-d6nny97.jpg
http://upload.wikimedia.org/wikipedia/commons/thumb/d/de/Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg/512px-Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg.png

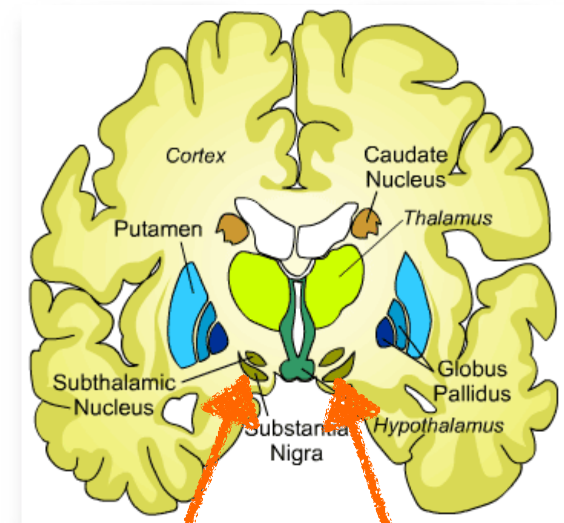
levodopa
(dopamine precursor)

Parkinson’s disease
- approx. 4 million worldwide
- approx. 1 million US

cardinal symptoms
- bradykinesia/akinesia
- rigor
- tremor

PD treatment
- dopaminergic medication
- deep brain stimulation

Benabid et al. (2009; Brown and Williams (2005); DeLong and Wichmann (2007); Kremens et al. (2014); Tanner et al. (2008)



degeneration of dopaminergic neurons in basal ganglia (SN_{pc})

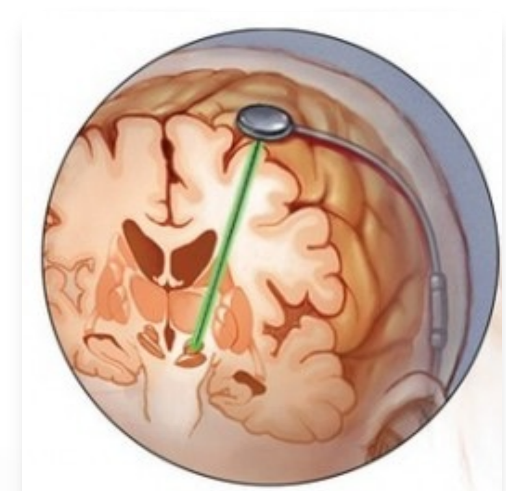
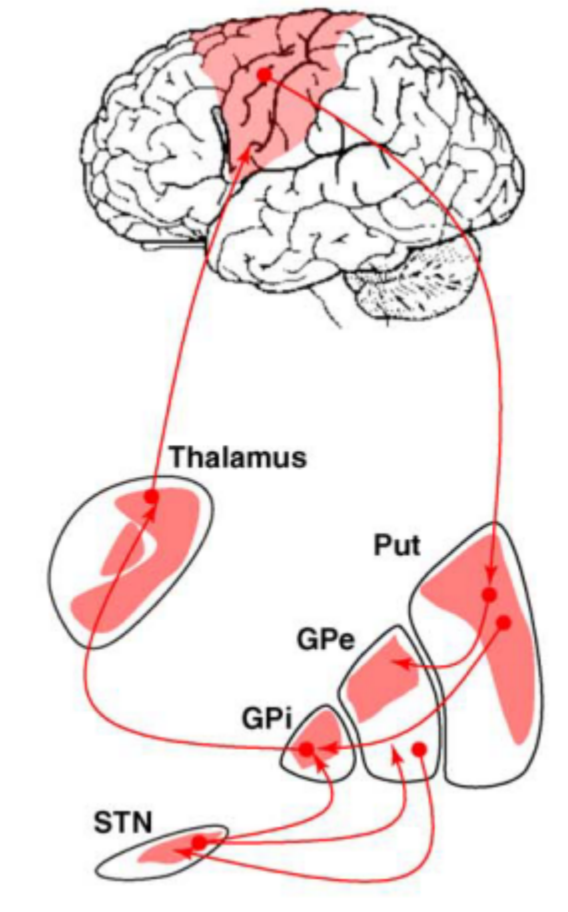


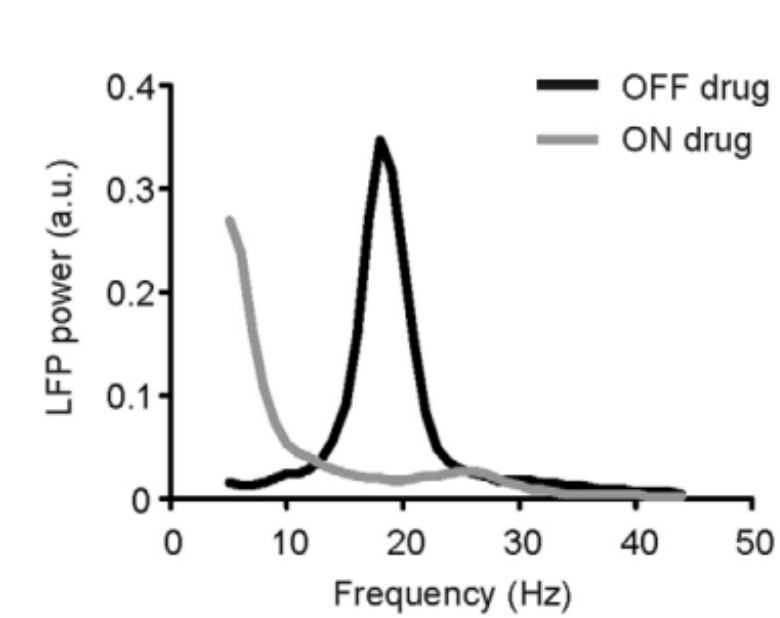
image credit:http://media.web.britannica.com/eb-media/09/82609-004-7ECF9841.jpg | http://scienceblogs.com/purepedantry/wp-content/blogs.dir/454/files/2012/04/i-05b9f20e65a3464654059e6249f4e016-basal-ganglia.jpg
https://www.mims.com/resources/drugs/Thailand/pic/Madopar%20250%20tab00f8110e-92ac-49d7-b945-9fab001e4a7d.GIF | http://www.extremetech.com/wp-content/uploads/2013/07/Deep-brain-stimulation-640x353.jpg
http://upload.wikimedia.org/wikipedia/commons/thumb/d/de/Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg/512px-Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886_2.svg.png

PD is associated with excessive neural synchronization of beta oscillations (10–30 Hz) in the basal ganglia (subthalamic nucleus, STN)

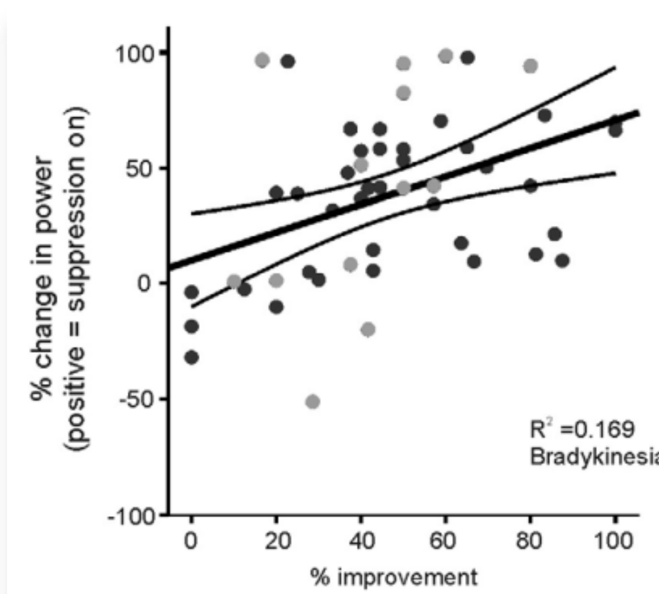
Brown and Williams (2005)



Krack et al. (Trends Neurosci, 2010)

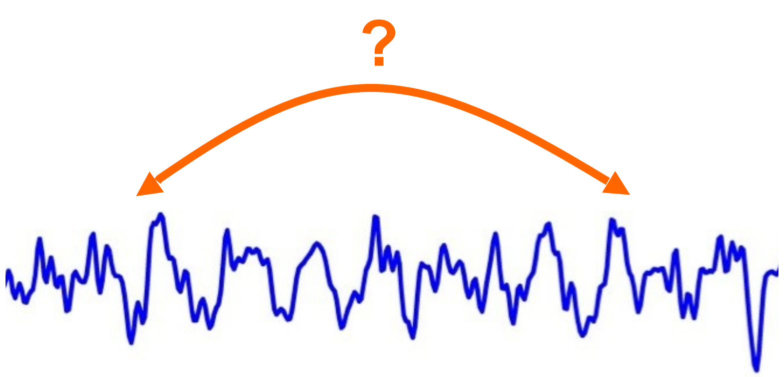


Kühn et al. (Exp Neurol, 2009)



Kühn et al. (Exp Neurol, 2009)

- power does not contain temporal information (momentary fluctuations)
- not sensitive to segment permutation
- power is sensitive to non-neural factors (eg, impedance)



temporal correlations?

long-range temporal correlations in EEG

- amplitude fluctuations in spontaneous neural oscillations: slowly decaying autocorrelations (power-law; self-similarity, fractal) Linkenkaer-Hansen et al. (2001); Nikulin and Brismar (2004); Palva et al. (2013)
- indicate a complex system in a meta-stable state Bak et al. (1987); Bressler and Tognoli (2006); Kello et al., (2010); Kelso (1995); Kelso et al. (2013); Poil et al. (2012); Shew et al. (2011)

unstable ←——————→ **stable**

meta-stability

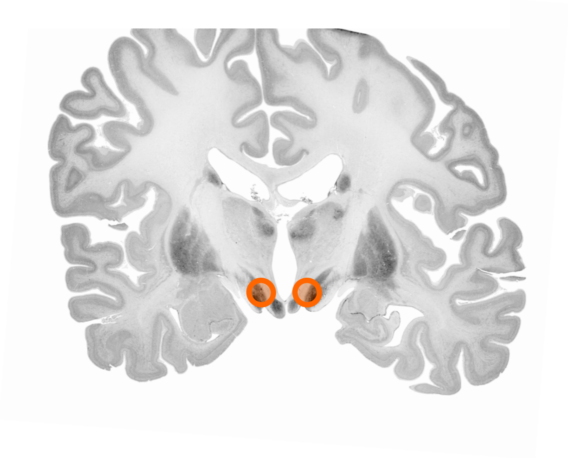
“healthy” network

- memory Beggs and Plenz (2004)
- flexibility and adaptation Chialvo (2010)
- excitation-inhibition balance Poil et al. (2012)

previous findings in human EEG (MEG, ECoG)

- temporal correlations up to 200 sec in spontaneous α and ß oscillations
  Linkenkaer-Hansen et al. (2001)

- decrease of LRTC in disease (vs. healthy controls):
  major depression Linkenkaer-Hansen et al. (2005)
  Alzheimer disease Montez et al. (2009)
  schizophrenia Nikulin et al. (2012)



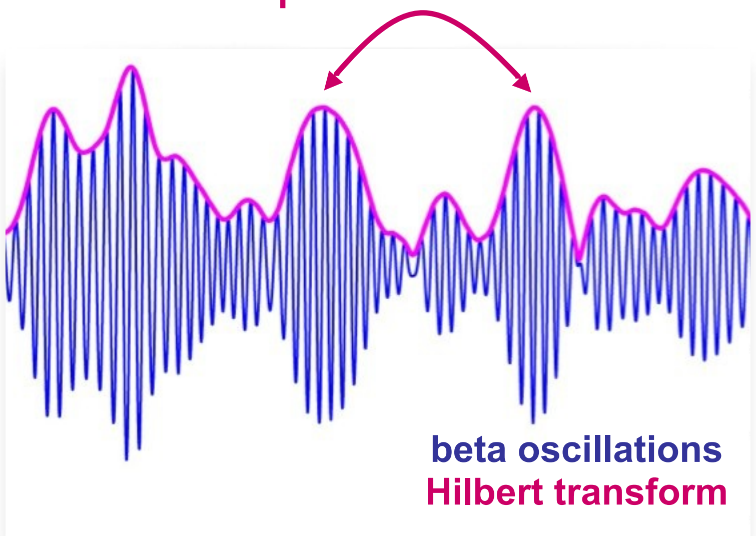
→ LRTC in subcortical regions?

→ modulation by medication?

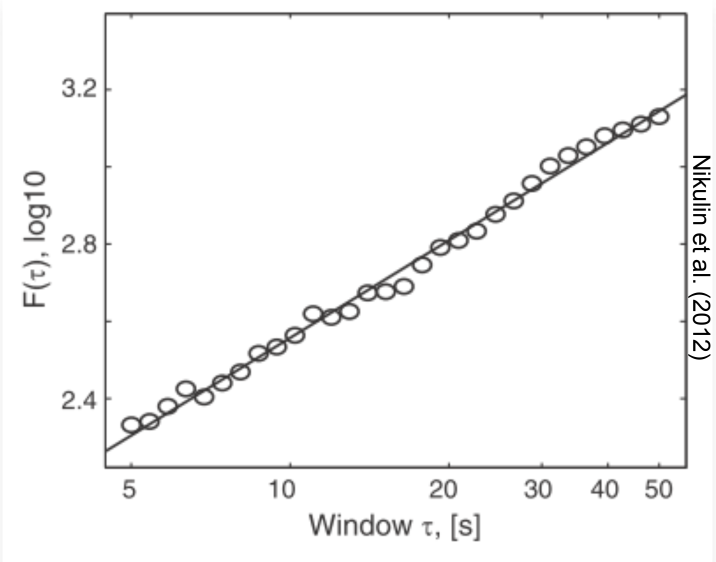
image credit: https://bigbrain.loris.ca/main.php

1) extract amplitude envelope of neural oscillations (Hilbert transformation)

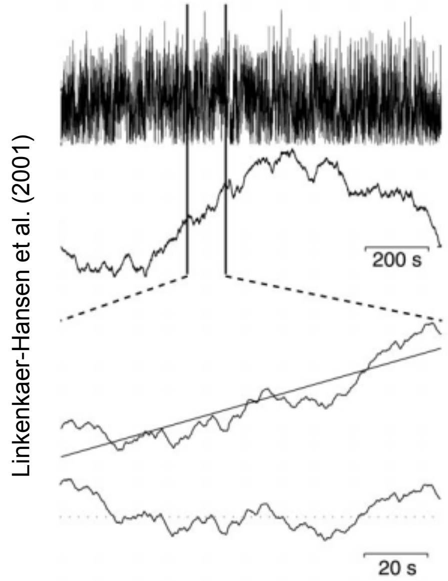
temporal correlations?



3) Do the average amplitude fluctuations scale with the window size in form of a power-law?



2) Detrended Fluctuation Analysis



- integrate
- windowing, detrending
- average SD
- repeat for different windows
  present study: up to **50 sec**

4) scaling exponent (slope)

exponent = 0.5
→ uncorrelated (white noise)

0.5 < exponent ≤ 1
→ long-range temporal correlations ("meta-stability")

Peng et al., Nature 1992; Kantelhardt et al., Physica A 2001; Linkenkaer-Hansen et al., J Neurosci 2001; Nikulin and Brismar, Clin Neurophysiol 2004; Kello et al., Trends Cogn Sci 2010

…up to 50 sec in subcortical rest recordings

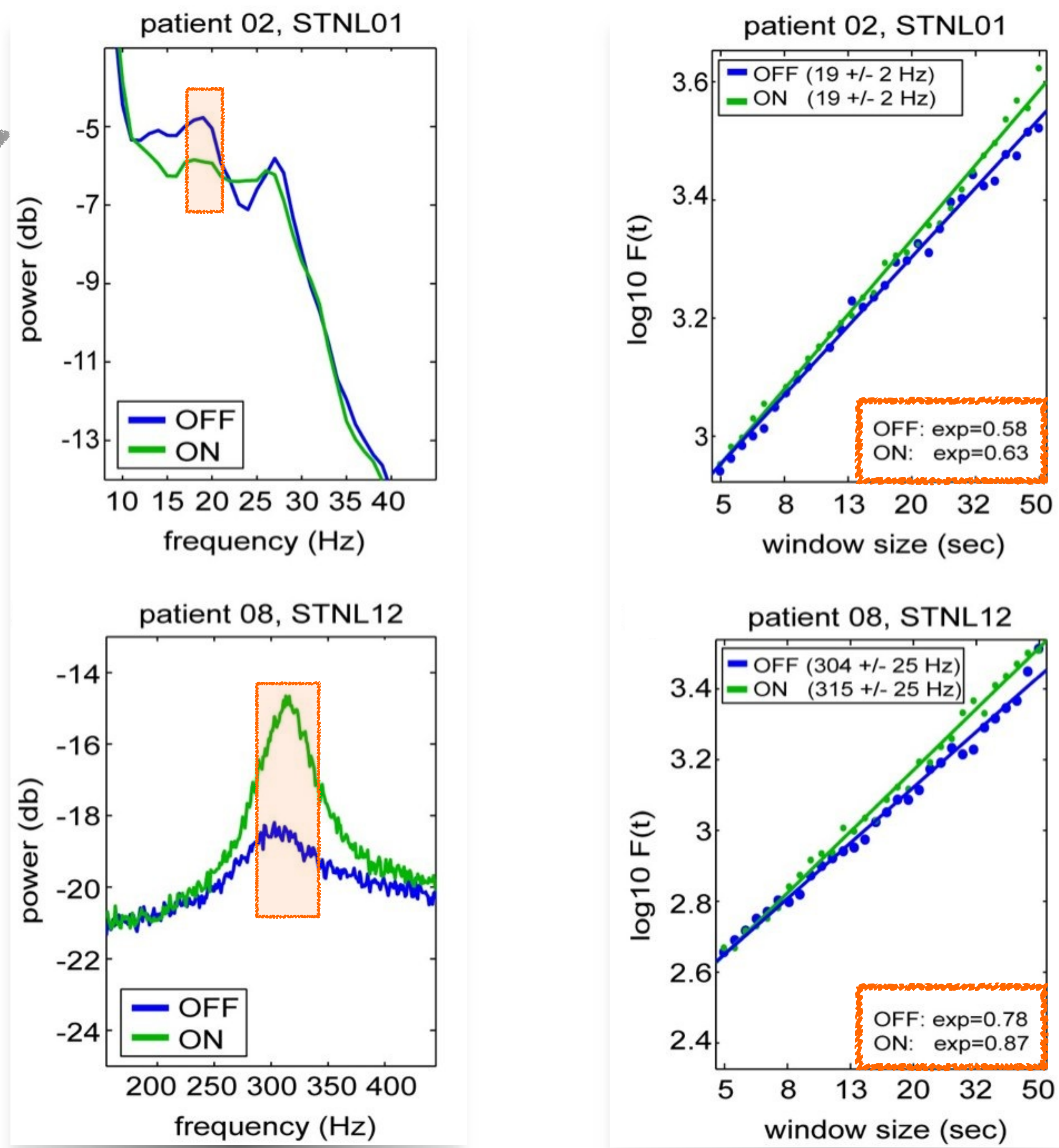
ON drug
OFF drug

2 exemplary patients

power **LRTC**

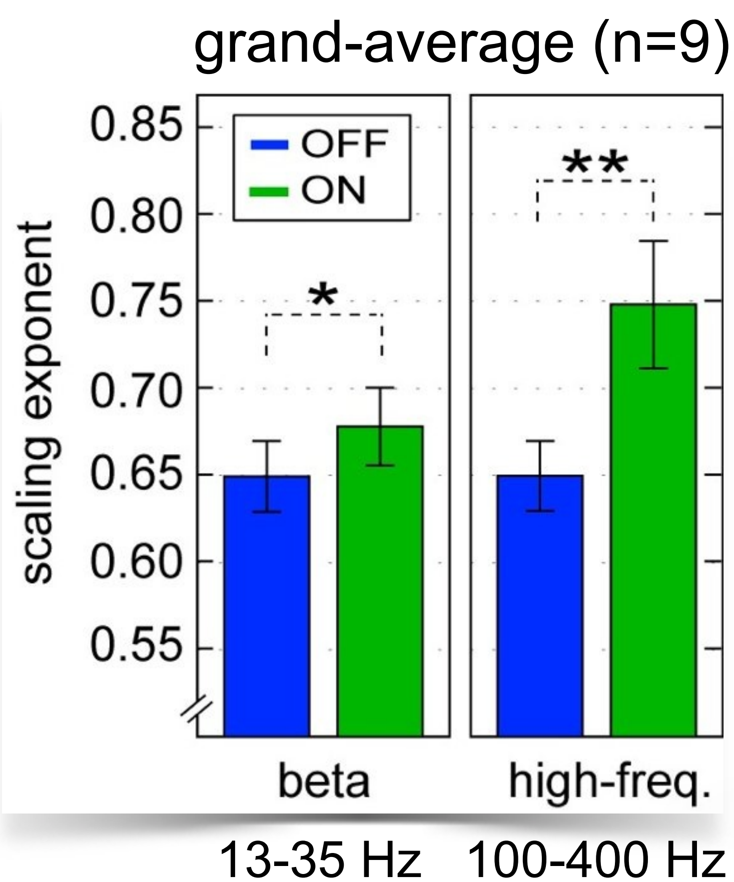
beta

high-frequency



Hohlefeld et al. (2012). Long-range temporal correlations in the subthalamic nucleus of patients with Parkinson's Disease. *European Journal of Neuroscience 36*(6), 2812–2821.

LRTC up to 50 sec in subcortical rest recordings



- increased LRTC in levodopa ON
- increased memory, more efficient signal processing in basal ganglia
- different profile compared to spectral power
- variability of spectral power (impedance, stun effects…)

Hohlefeld et al. (2012). Long-range temporal correlations in the subthalamic nucleus of patients with Parkinson's Disease. *European Journal of Neuroscience 36*(6), 2812–2821.

image credit: https://bigbrain.loris.ca/main.php

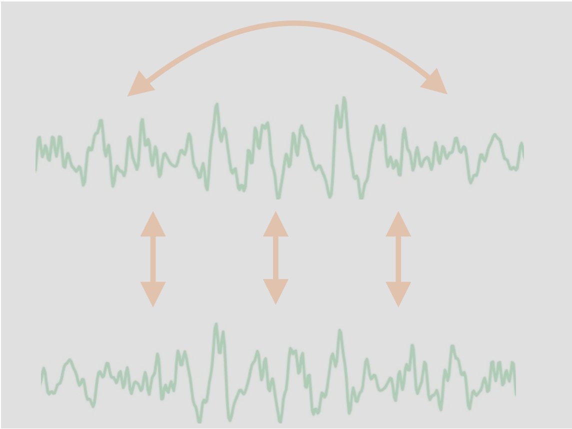
movement-related neural dynamics

SIGNALS

1) in time (LRTC)
2) in space (connectivity)

PARADIGM

3) quasi-movements



1) time: fractal dynamics (LRTC) in neural oscillations from Parkinsonian basal ganglia

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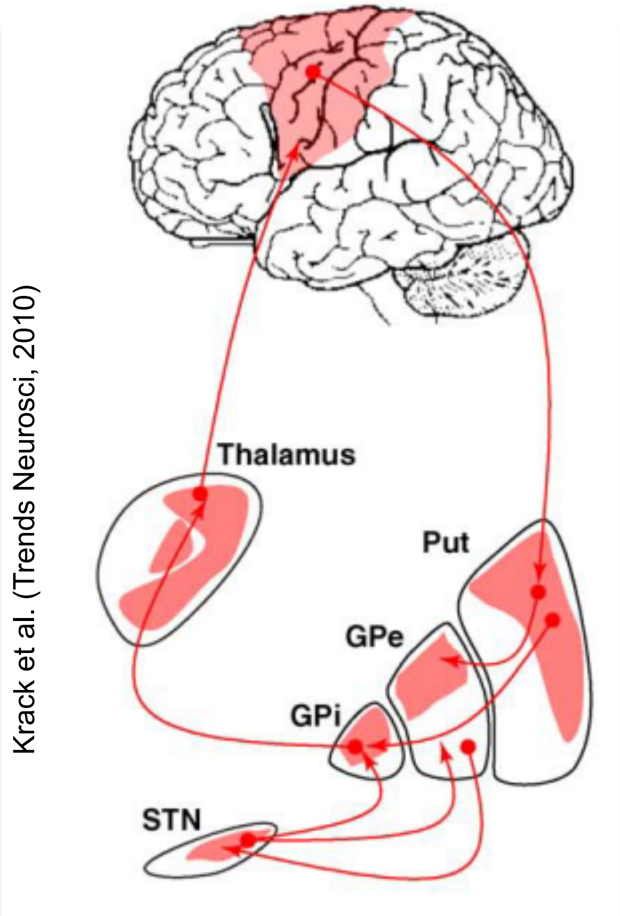
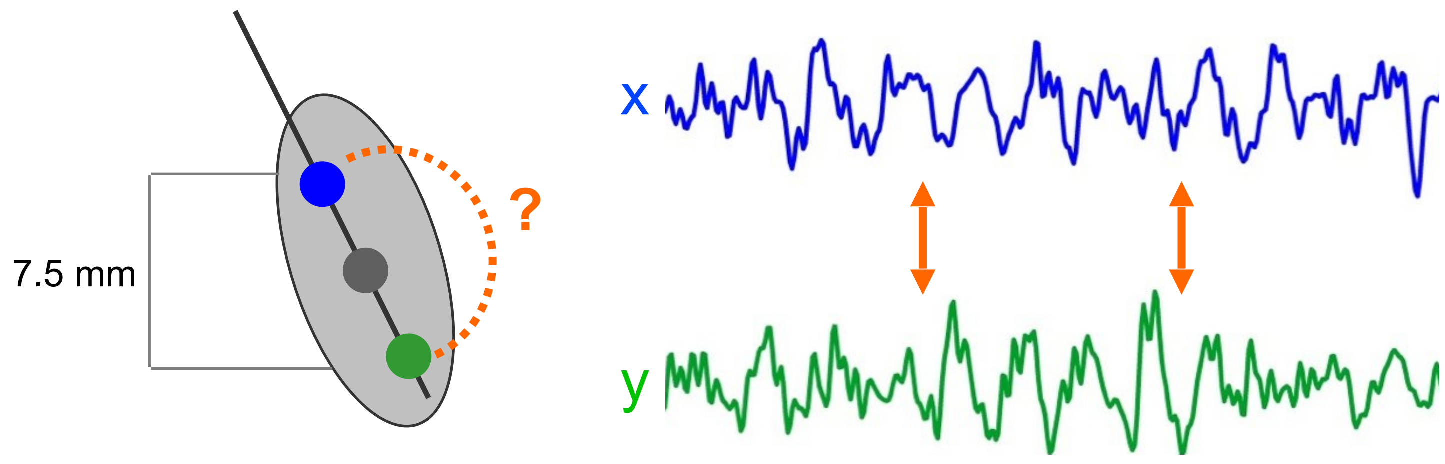
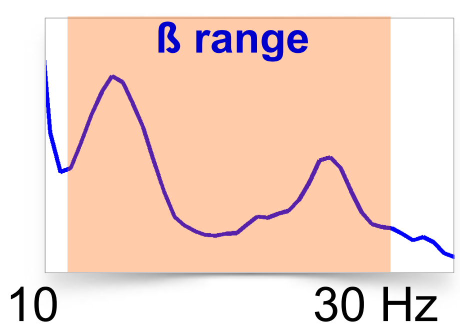
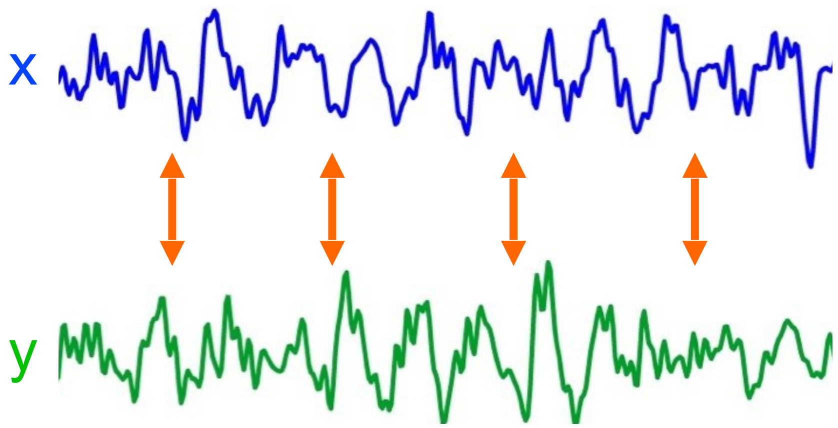


subthalamic nucleus (STN): local field potentials





- presence of genuine neural interactions and directionality of information flow?
- ≠ volume conduction
- differences between medication states?
- relation to clinical motor scores?



cross-spectrum (FT)

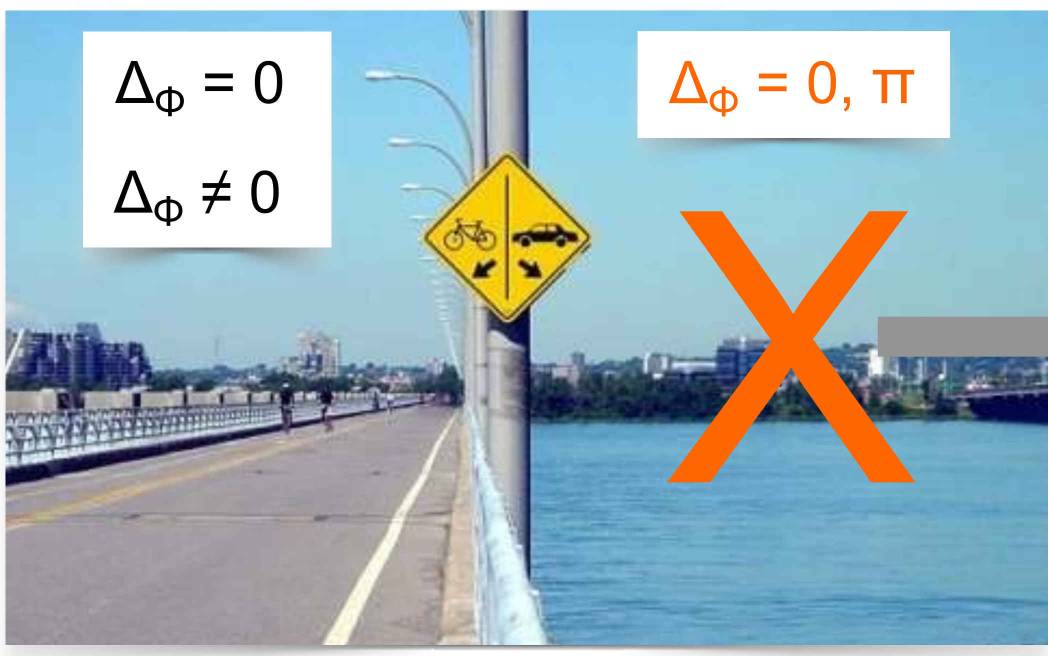
$$S_{ij}(f) \equiv \langle x_i(f) x_j^*(f) \rangle$$

coherency

$$\boxed{C_{ij}(f)} \equiv \frac{S_{ij}(f)}{(S_{ii}(f) S_{jj}(f))^{1/2}}$$

<u>cross-spectrum</u>
normalized

true interaction | volume conduction



*Friston (1994)

functional connectivity*

imaginary part of coherency (iCOH) Nolte et al. (2004)
out of phase part ≠ volume conduction

effective connectivity*

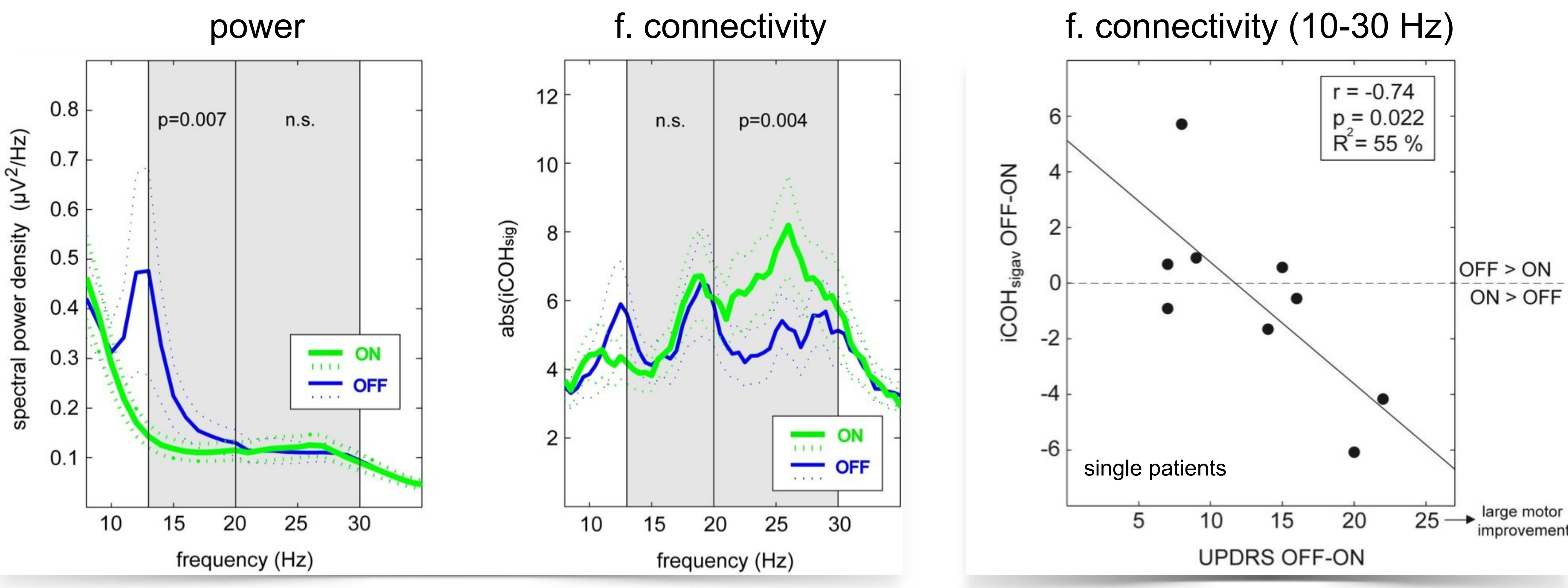
phase-slope index (PSI) Nolte et al. (2008)
(based on the imaginary part of coherency)

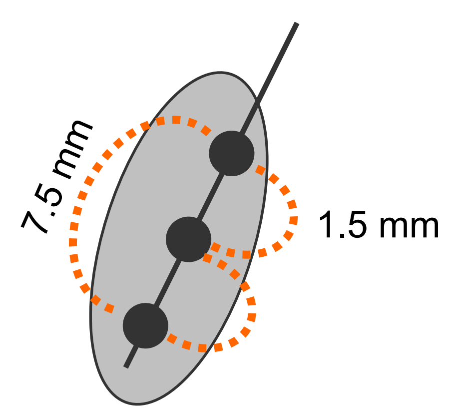
estimation of "detectability"
jackknife normalization Nolte et al. (2008)

$$iCOH_d = |iCOH/STD(iCOH\_jn)|$$
$$iCOH_d > 2.58 = p < 0.01$$

image credit: http://www.boredpanda.com | Nolte et al. (2004)

connectivity in basal ganglia (subthalamic nucleus)





- increase of functional/effective connectivity after levodopa administration
- increased fC relates to motor improvement (ON state)
- preserved patterns of information flow after levodopa administration

Hohlefeld et al. (2013). Functional and effective connectivity in subthalamic local field potential recordings of patients with Parkinson's Disease. *Neuroscience 250*, 320–332.

long-range temporal correlations (“fractals”) in basal ganglia

- further evidence for the omnipresence of LRTC
- novel biomarker for disease state in PD
- medication improves temporal stability (“memory”) of neural oscillations in PD

functional and effective connectivity in basal ganglia

- genuine neural interactions (time-lagged ≠ volume conduction)
- increased after medication in PD
- relation to motor symptoms

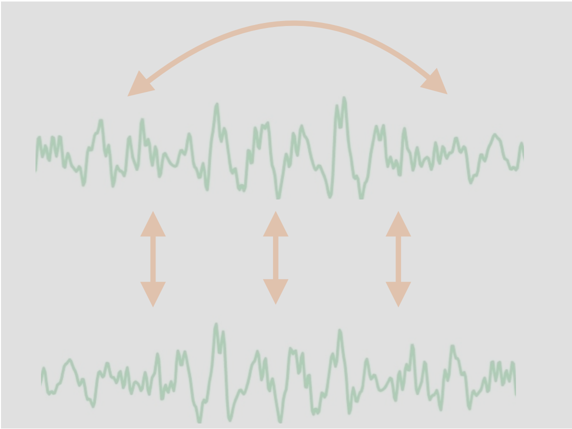
movement-related neural dynamics

SIGNALS

1) in time (LRTC)
2) in space (connectivity)

PARADIGM

3) quasi-movements



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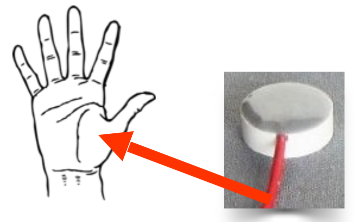
Can you do a movement…

…without doing it?

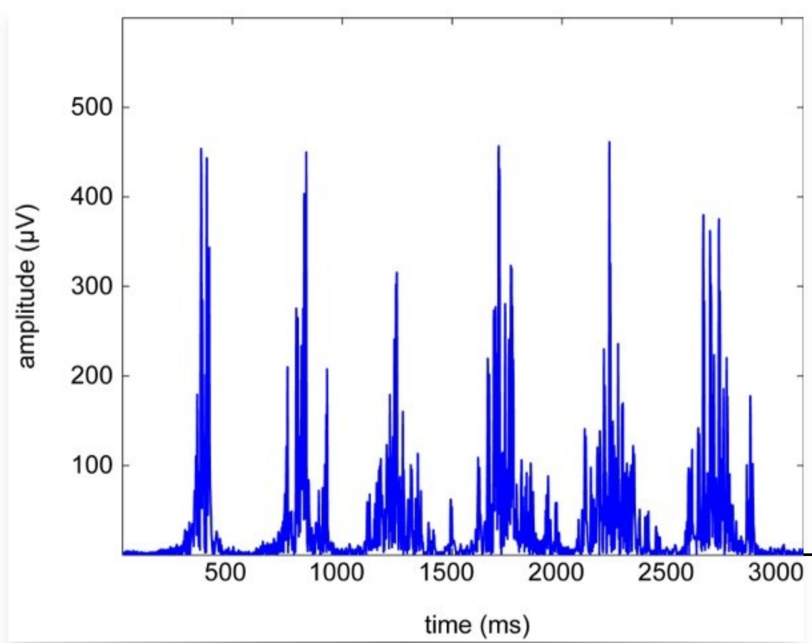


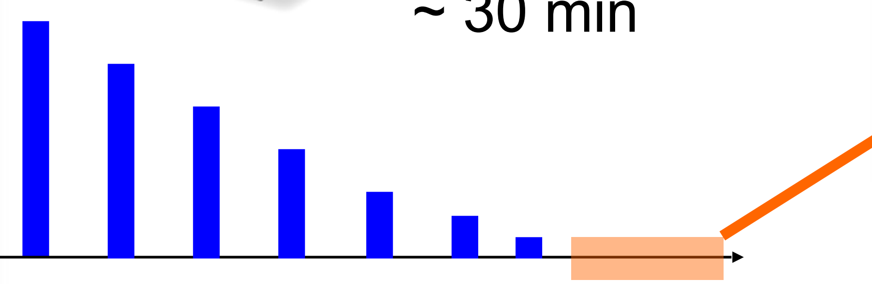
abductor pollicis brevis

"Perform a weak movement with your thumb.
Now minimize this movement even further
and make it as small as possible."

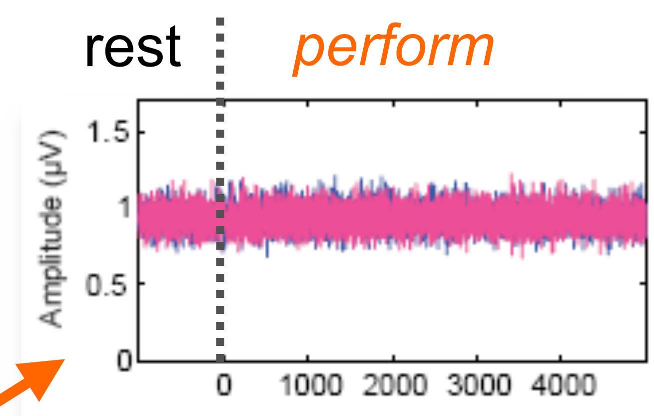
normal thumb movement

EMG neurofeedback





~ 30 min



quasi-movements:

Hohlefeld et al. (NeuroReport, 2011); Hohlefeld et al. (Brain Res, 2011);
Hohlefeld (Free University, 2011); Nikulin*, Hohlefeld* et al. (Neuropsychologia, 2008)

"volitional movements with zero muscle output"

undetectable by objective measures of muscle activity (e.g., EMG)

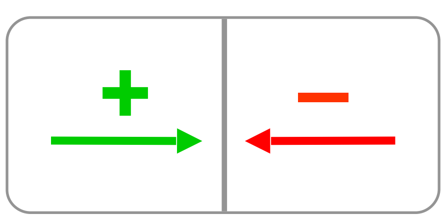
image credit: http://www.clipartsfree.net/svg/20845-hand-palm-facing-out-vector.html | http://www.wpclipart.com/computer/laptop/laptop_grayscale.png.html
http://static.freepik.com/free-photo/alarm-clock-clip-art_427965.jpg | http://www.easycap.de/easycap/e/products/products.htm#13

movement performance:

sequence of neural activations,
related to carrying out a motor intention,
culminating in muscle contraction

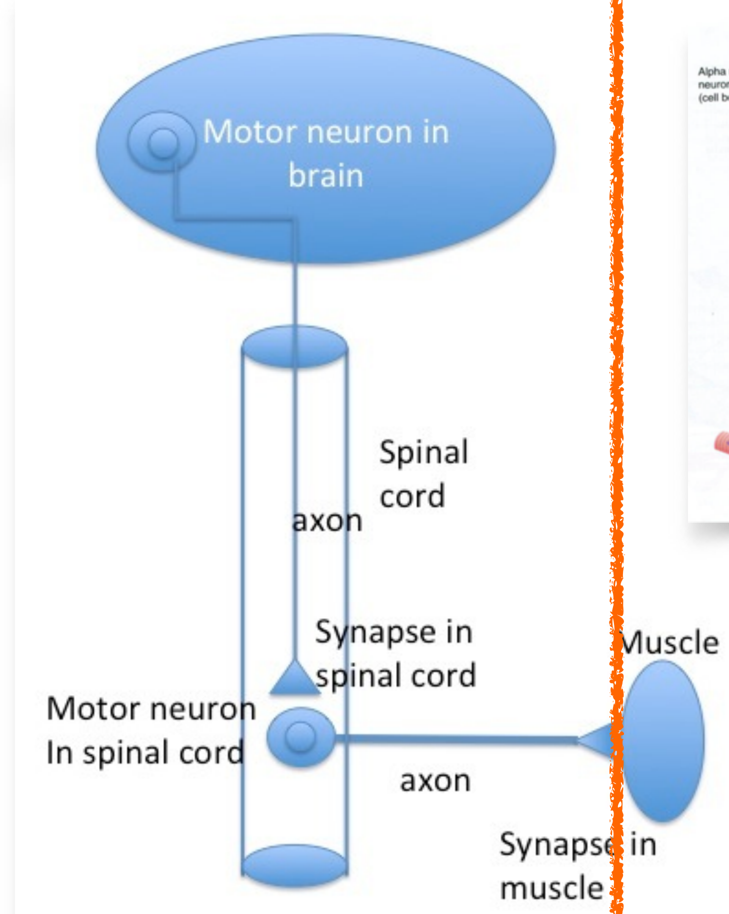
covert stages

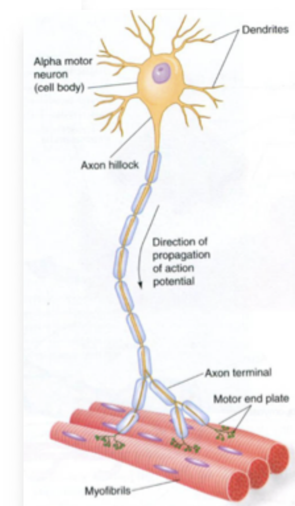
overt movement

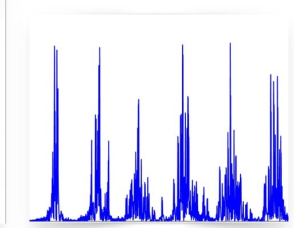


equilibrium
“meta-stable“

either/and:
gas too weak
break too strong







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http://us.cdn3.123rf.com/168nwm/cd123/cd1231111/cd123111100014/11141445-silhouette-american-football-quarterback-aiming-to-throw-ball.jpg | http://s1251.photobucket.com/user/vladimirzec/media/Fiziologija/img280.jpg.html

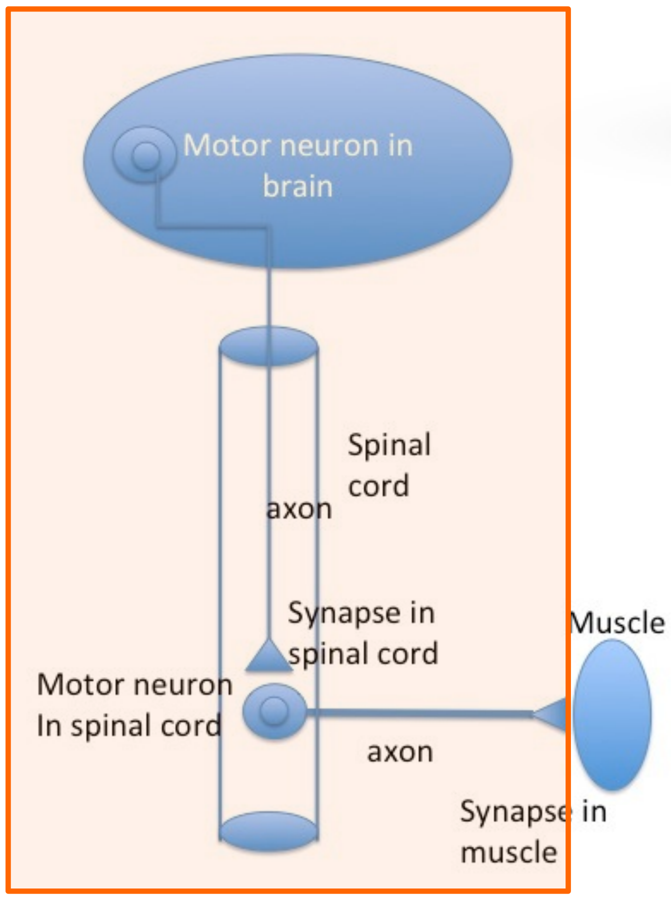
quasi-movements:

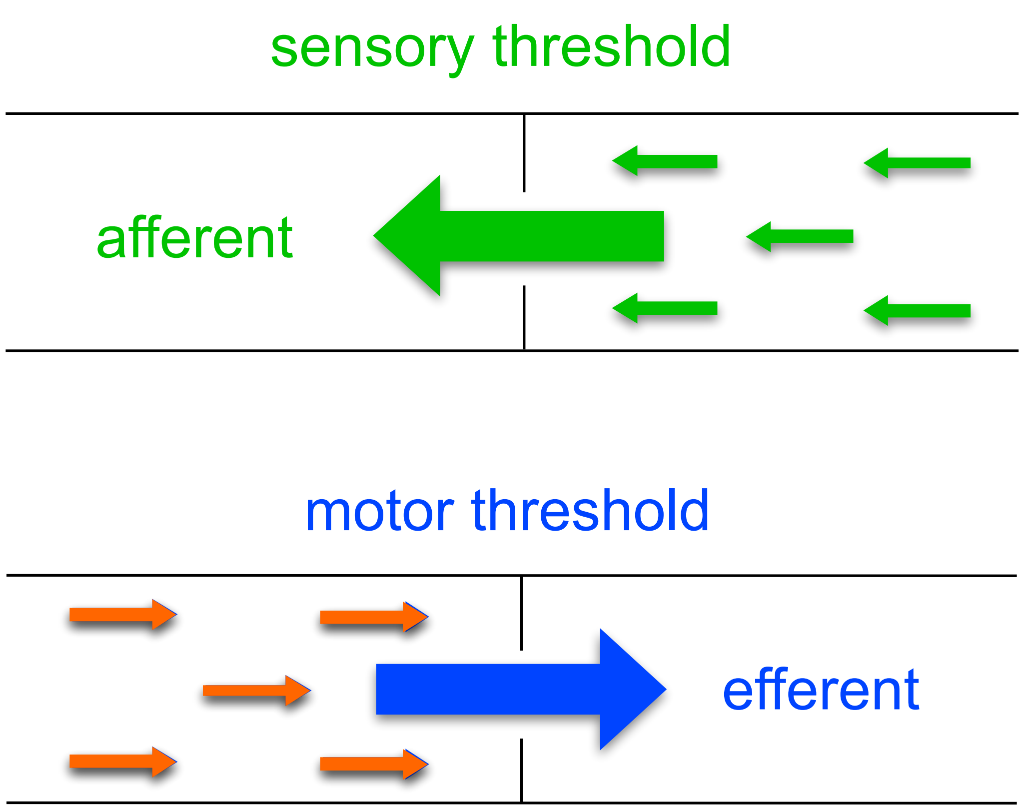
volitional movements with zero muscle output*

*as determined by objective measures

Hohlefeld et al., NeuroReport 2011; Hohlefeld et al., Brain Res 2011; Hohlefeld FU 2011; Nikulin*, Hohlefeld* et al., Neuropsychologia 2008

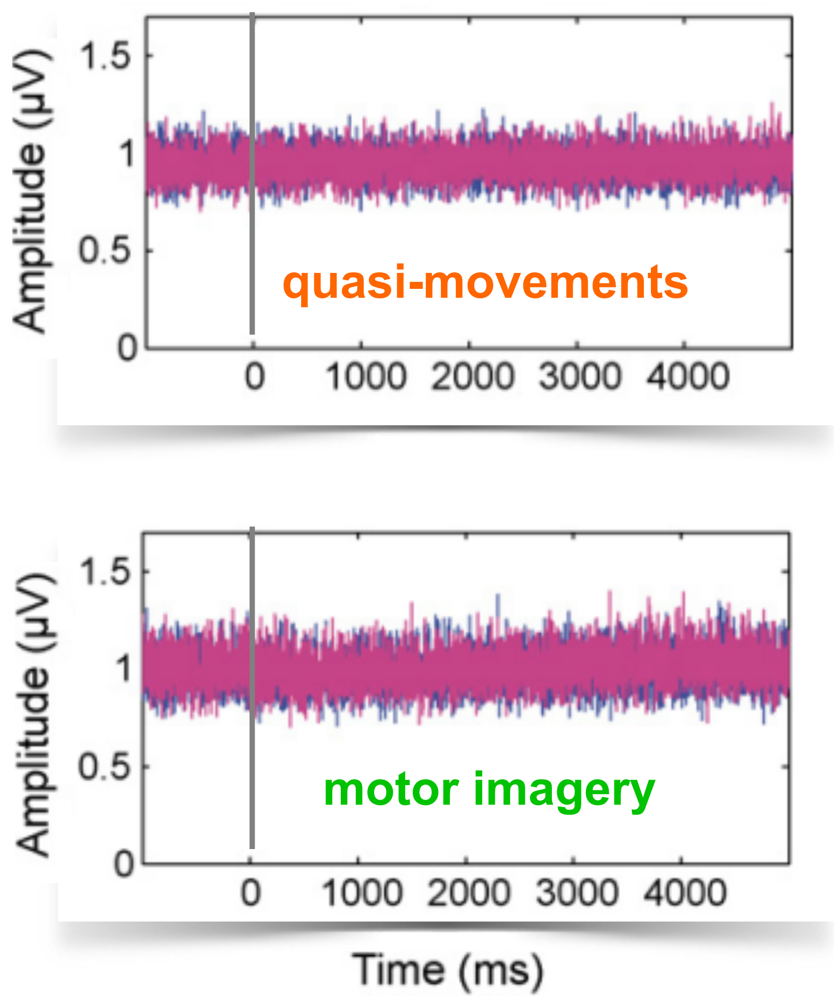
covert



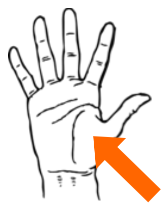


quasi-movements…a fine-graded motor skill

image credit: http://www.brc.cam.ac.uk/wp-content/uploads/2010/04/Slide12.jpg | http://fc01.deviantart.net/fs70/f/2013/267/5/6/dmc_delorean_by_conman17-d6nny97.jpg averaged EMG (single subject)

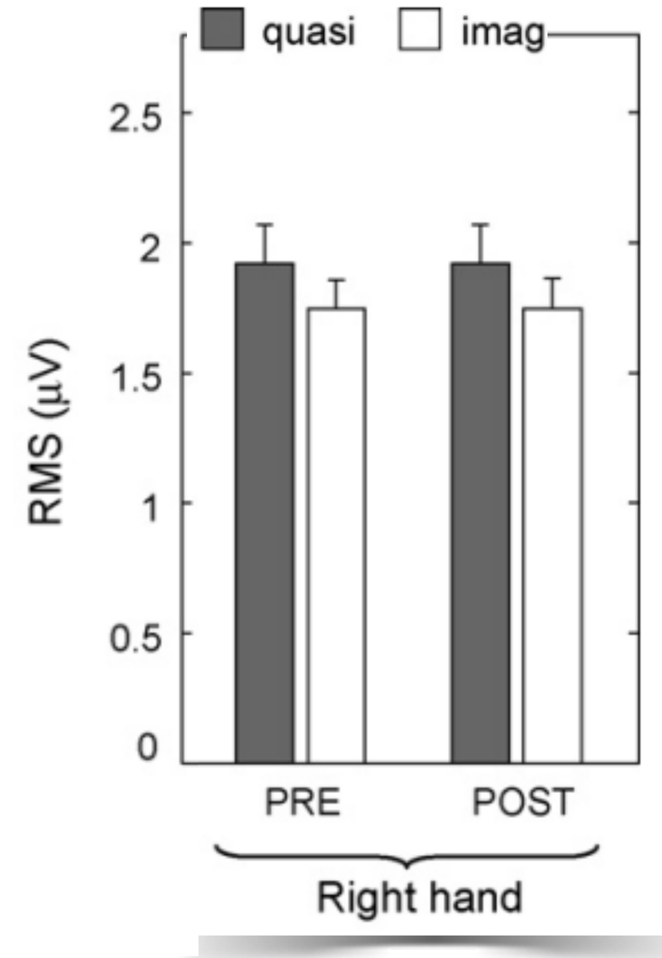


right APB



similar results
for left APB

grand-average EMG

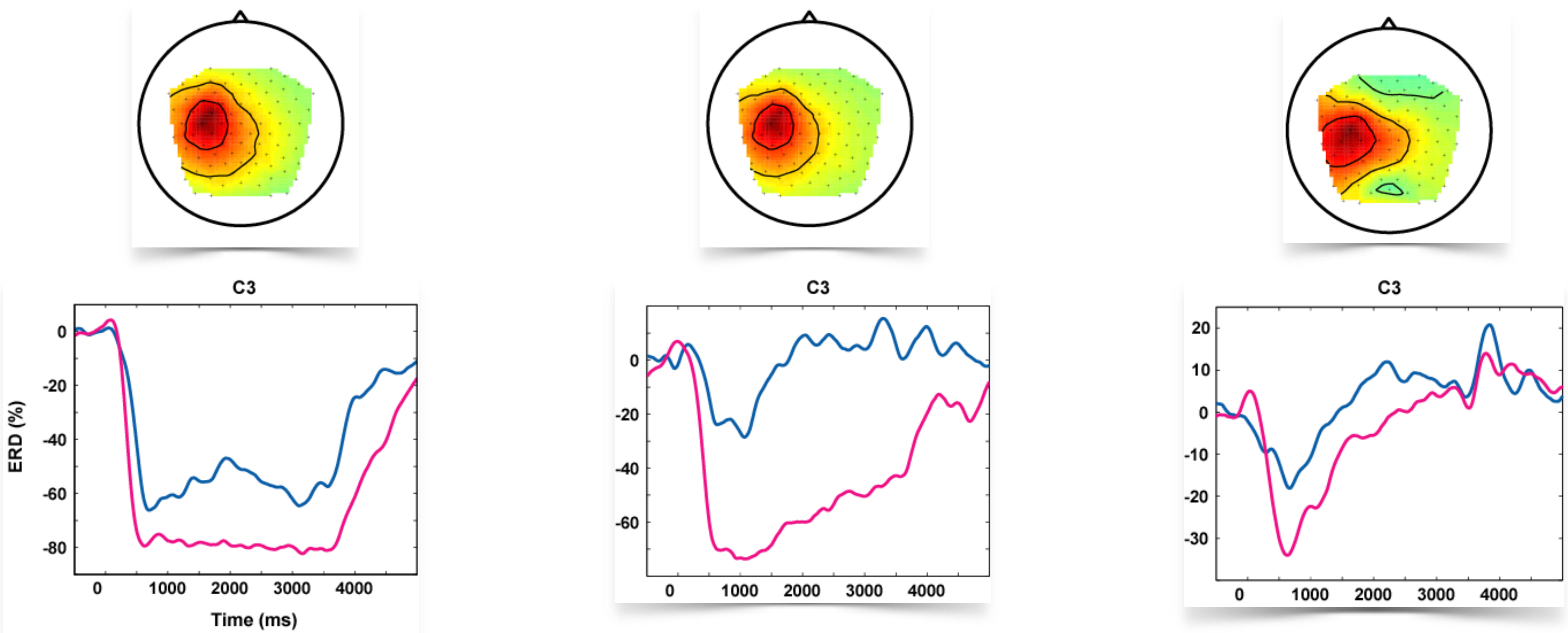


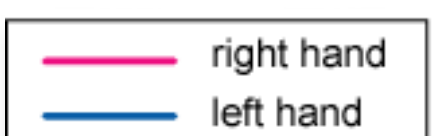
- no significant differences between pre- and post-stimulus EMG
- no differences between QM and imagery (based on EMG activity)

Nikulin*, Hohlefeld* et al. (2008). Quasi-movements: A novel motor-cognitive phenomenon. Neuropsychologia 46(2), 727–742. *equally contributed.

spatial topography of neural activation and event-related desynchronization (8–13 Hz)

overt movement | quasi-movements | motor imagery

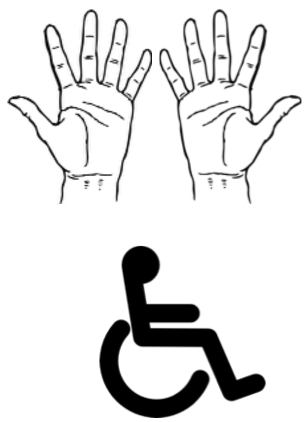


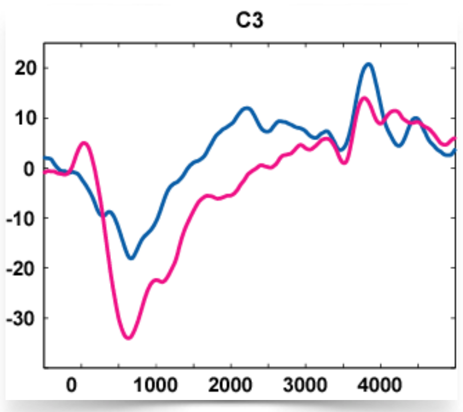


ERD in contralateral hemisphere:
movement > quasi > imagery

image credit: http://www.clipartsfree.net/svg/20845-hand-palm-facing-out-vector.html

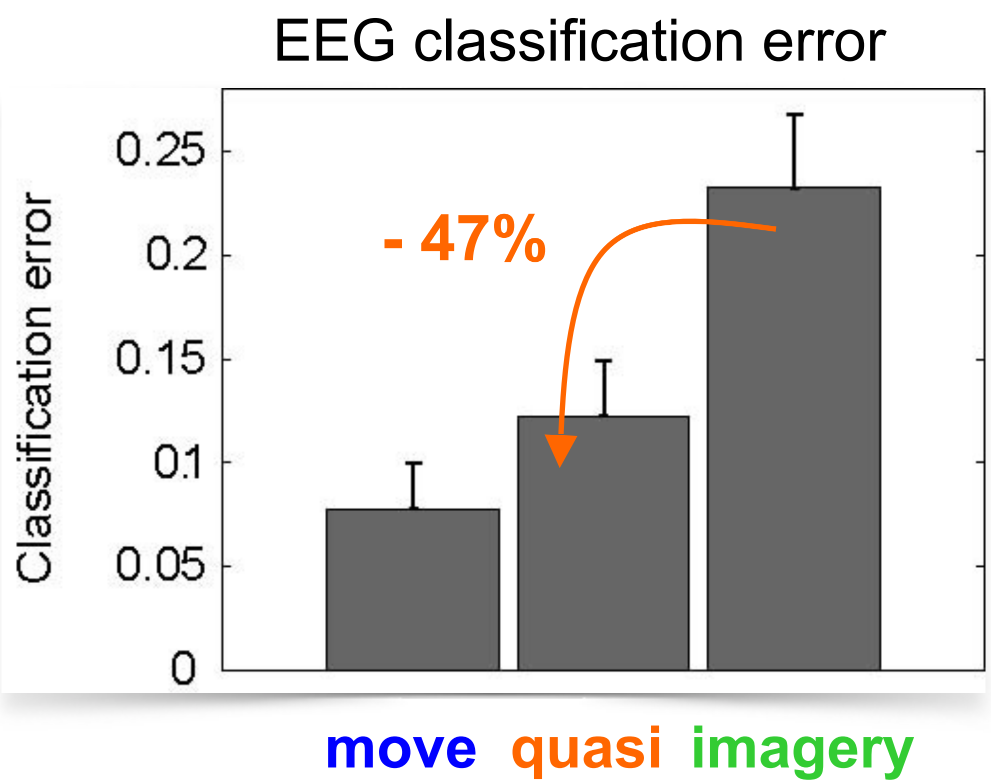
Nikulin*, Hohlefeld* et al. (2008). Quasi-movements: A novel motor-cognitive phenomenon. Neuropsychologia 46(2), 727–742. *equally contributed.





brain-computer interface (BCI)

- discriminate brain states related to motor cognition, e.g., imagine left vs. right hand movement
- for patients (paralysis, amputation, coma…)
- algorithms/mental strategies tested in healthy subjects
- illiteracy problem!



Nikulin*, Hohlefeld* et al. (2008)

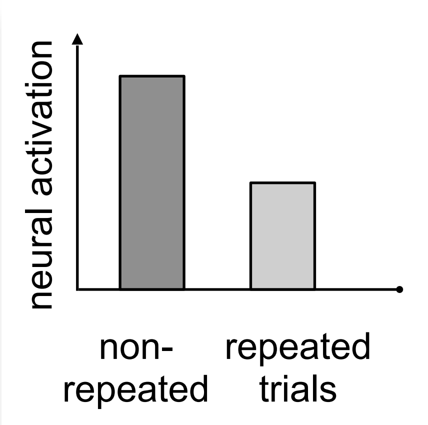
quasi-movements

- increased classification accuracy ~ 47% (up to 86 %) compared to standard imagery
- not related to occasional EMG responses
- effective for BCI (illiterate problem)
- healthy subjects ⇔ patients

image credit: http://www.clipartsfree.net/svg/20845-hand-palm-facing-out-vector.html | http://www.clker.com/clipart-10835.html

Nikulin*, Hohlefeld* et al. (2008). Quasi-movements: A novel motor-cognitive phenomenon. Neuropsychologia 46(2), 727–742. *equally contributed.

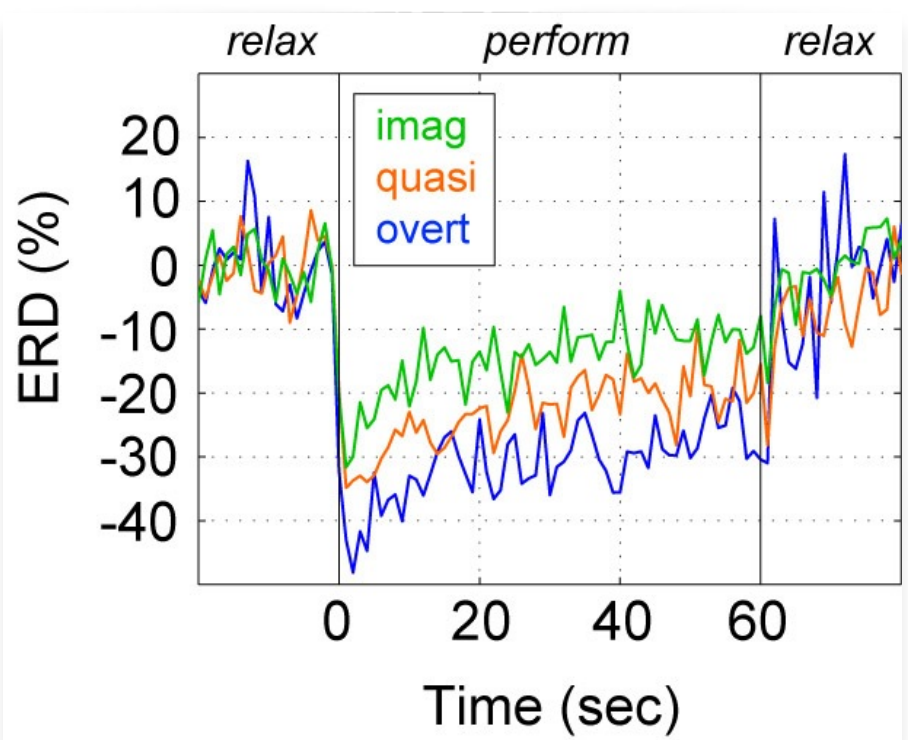
repetition suppression



repetition suppression (RS) is found with…

- afferent: stimulation Grill-Spector et al. (2001)
- efferent: movement Wu et al. (2008)
- open question: internally (central) triggered RS?

Laplacian ERD, C3 contra,
grand-average (n=13), 9–12 Hz



RS in covert movements (EEG)

- motor RS primarily due to central activation
- quasi-movements: α-ERD ~10 sec longer sustained than motor imagery

Hohlefeld et al. (2011). Covert movements trigger repetition suppression of electroencephalography in sensorimotor cortex. NeuroReport 22(3), 141–145.

image credit: http://www.clipartsfree.net/svg/20845-hand-palm-facing-out-vector.html | http://www.clker.com/clipart-candle-11.html

- long-range temporal correlations (“fractals”) in basal ganglia
- functional/effective connectivity in/between basal ganglia

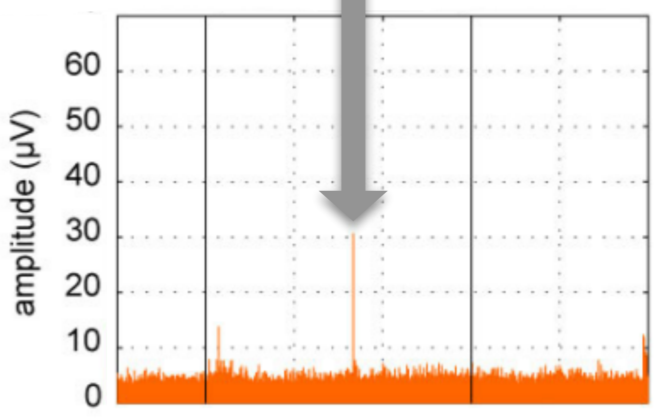
covert vs. overt movement stages

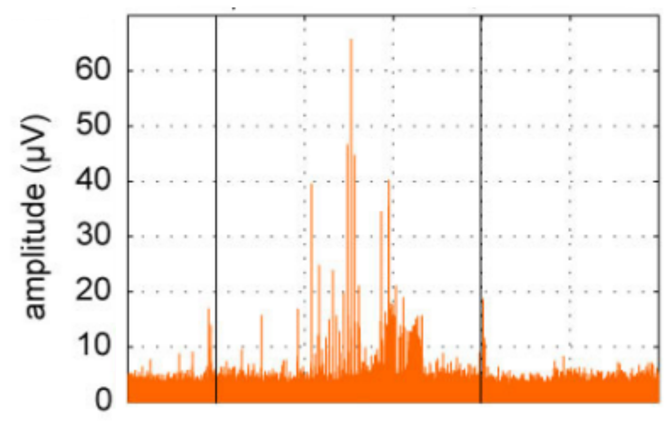
- muscle contraction is just the end stage
- brain activity during covert stages: intention matters!
- different intentions: brings the motor system closer to motor threshold

EEG correlates of quasi-movements

- quasi-movements: volitional movements with zero motor output
  … subjective reports: “I am doing a movement” , “I feel the movement”
  … silent EMG in the majority of trials (comparable to motor imagery)
  … strong EEG activity over sensorimotor cortices
- effectiveness for BCI
- overcome the mixture challenge of efferent vs. reafferent signals
- covert stages: internal repetition suppression

~1% maximum
voluntary contraction





EMG detection rate
during quasi-movements:
~20 %

Nikulin*, Hohlefeld*
et al. (2008)

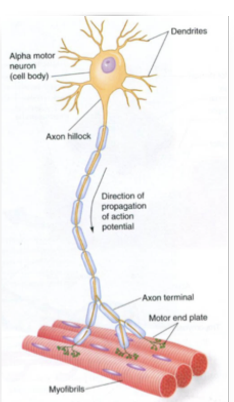
more
training?

occasional mini “motor slips“
during quasi-movements:

a window into "phase transitions“ in the motor system
between rest and movement?

quantum of action — 1 motor unit
subquantum — quasi-movements

Prof. G. Curio (personal communication, 2014)



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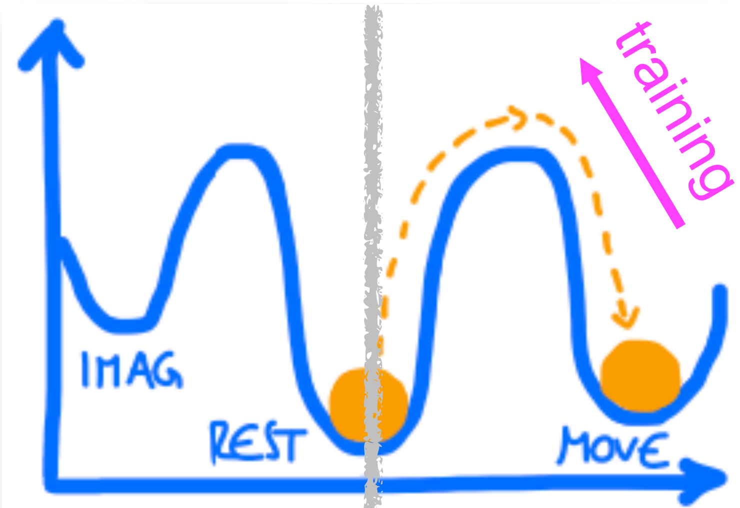
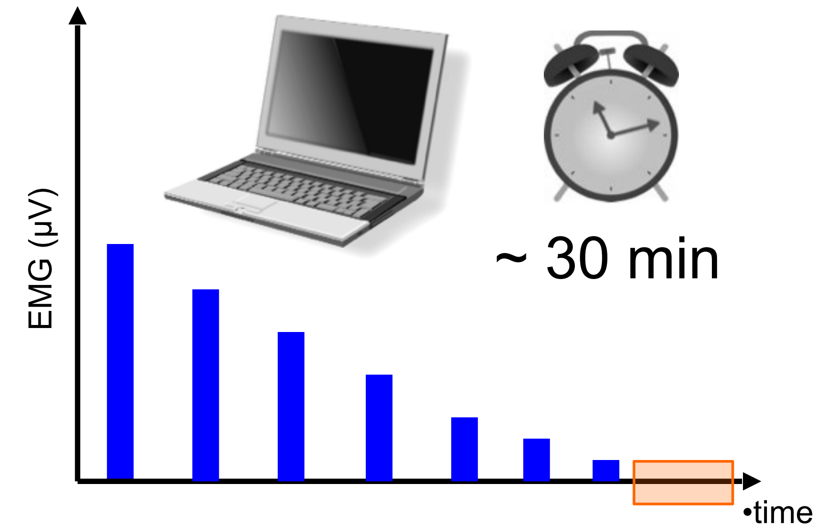
before training

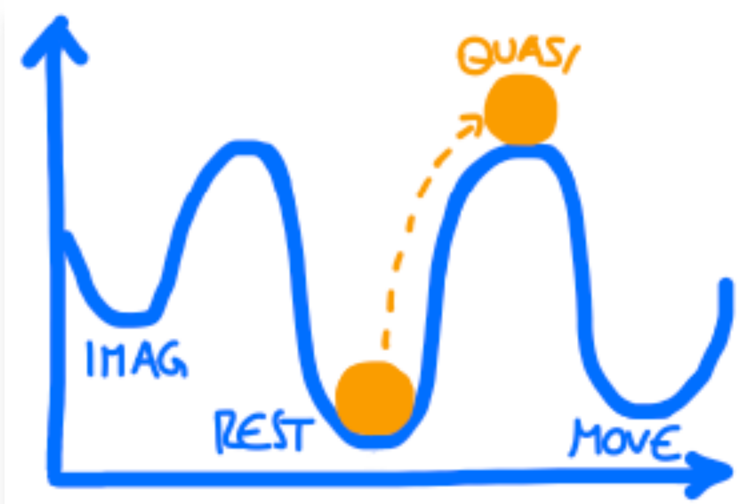


movement **simulation** movement **intention**

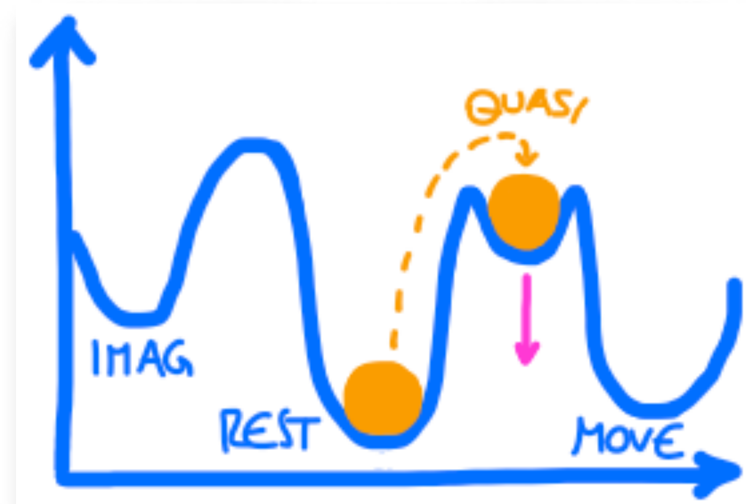
EMG neurofeedback



training



after training



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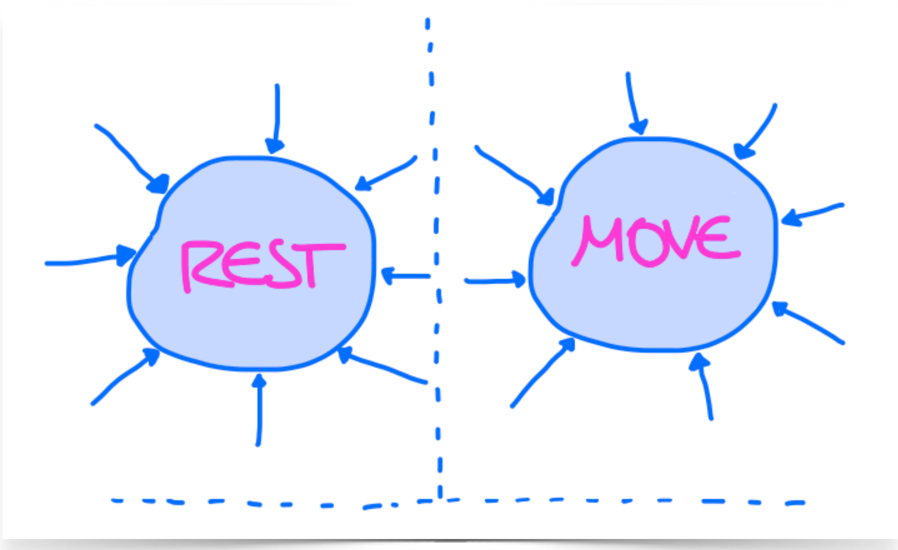
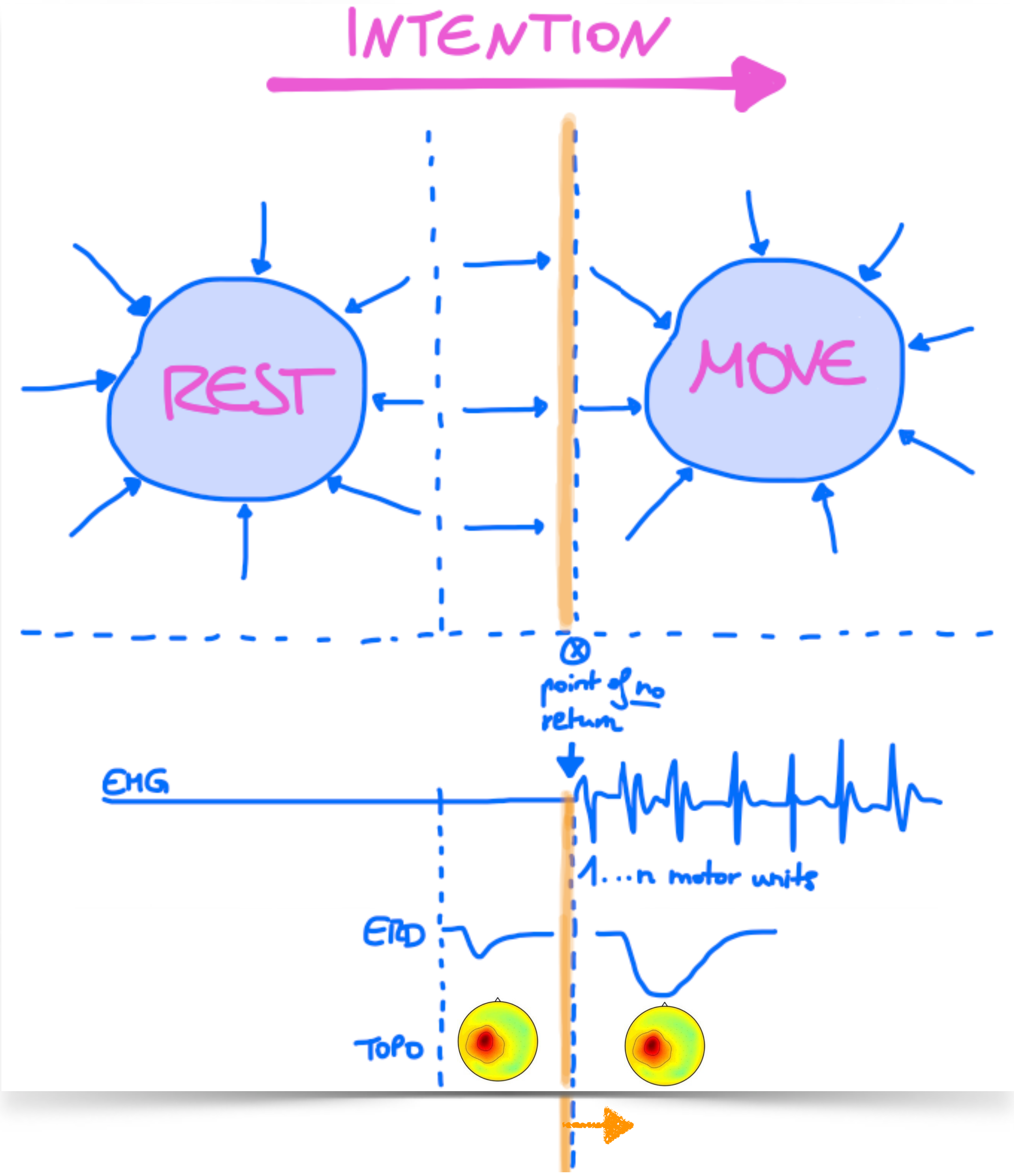
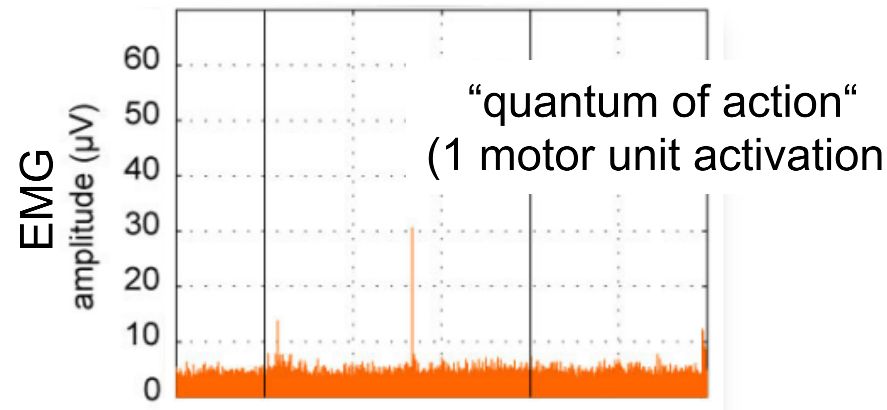
attractor landscapes in the motor system





spontaneous fluctuations
- neural noise
- attention, drowsiness, motivation…

might determine occurrence of motor slips
…“transition“ rest—movement?



methods (Parkinson patients)

- long-range temporal correlations
- connectivity (≠ volume conduction)

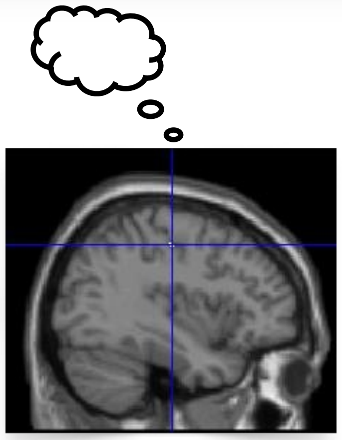
paradigm

- quasi-movements: "subquantum" of action

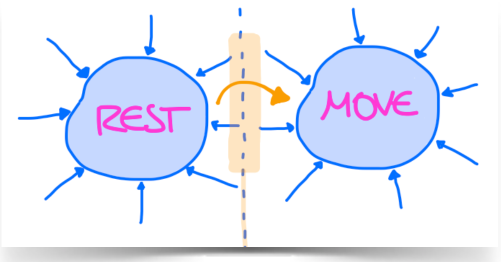
applications (QM)

- brain-computer interface
- intention
- repetition suppression
- movement dynamics ("phase transitions")

I choose / imagine / quasi .... to move.



…to move **AND** not to move



"What is left over if I subtract the fact that ~~my arm goes up~~ from the fact that I raise my arm?"

L. Wittgenstein (1953)

acknowledgements

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