

Training course:

Real-time fMRI: Fundamental Principles for Clinical Applications

Clinical applications of real-time fMRI neurofeedback – in 6 steps

David Linden

Cardiff University

1) What is your clinical question (and patient group)?

A few examples

Psychiatry: Depression

- Improve symptoms of depression (in those who have insufficient response to antidepressants/ psychotherapy) – but what aspect of the clinical syndrome and over what timescale?
- Anhedonia – inability to experience joy, lack of motivation
- Might benefit from both the physiological and psychological mechanisms involved in neurofeedback with focus on experience and regulation of emotions

Psychiatry: Alcohol dependence

- Help patients maintain abstinence after detoxification – but through what mechanism?
- Craving is a key factor in relapse risk - and is associated with increased responsiveness of motivation circuits to alcohol cues
- Use neurofeedback to teach patients downregulation of this cue reactivity

Neurology: Parkinson's disease

- Improve hypokinetic symptoms in PD – and possibly reduce dosage of dopaminergic drugs
- Imagery of gait initiation is used in physiotherapy approaches, but effects might be improved by providing feedback about “successful” imagery
- Use neurofeedback of higher motor areas in combination with imagery to improve motor symptoms of PD

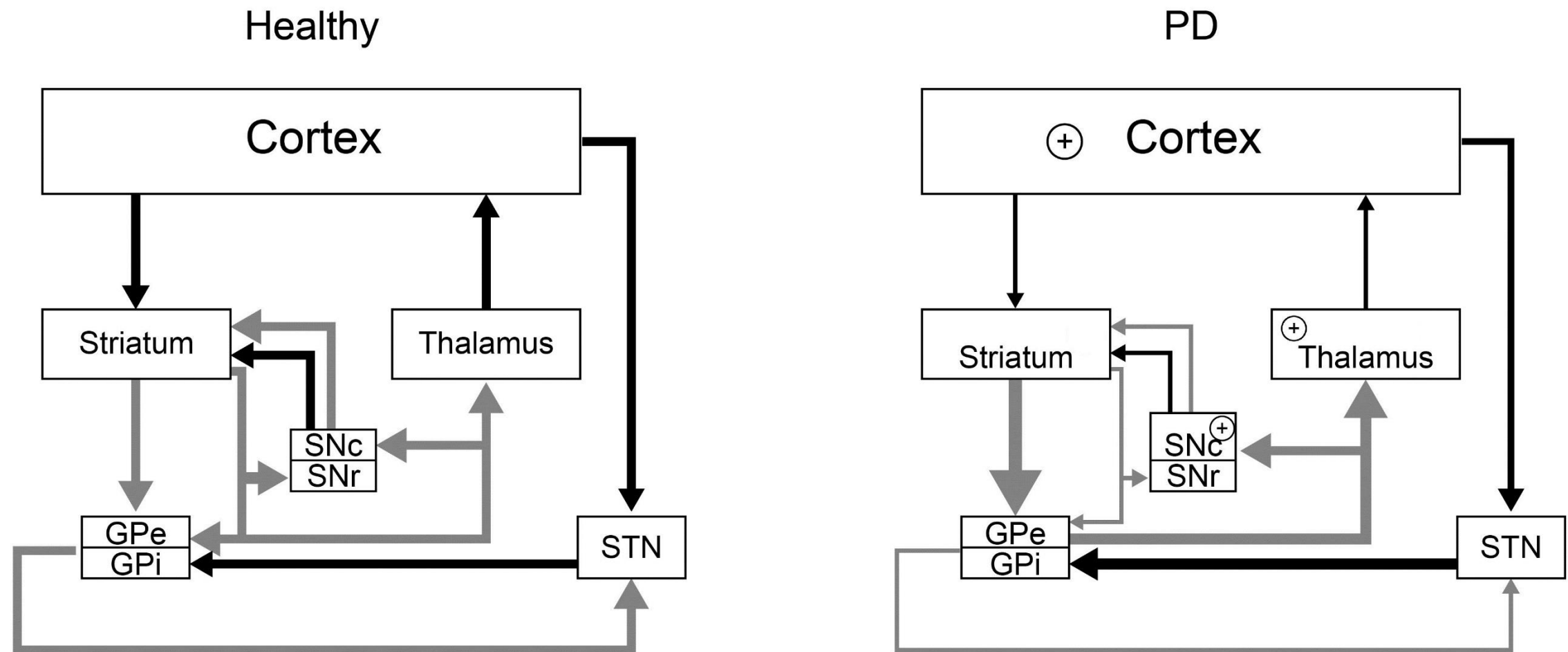
General medicine: Chronic pain

- Chronic pain often not responsive to analgesic treatment – psychological mechanisms (e.g., dysfunctional learning) have been implicated
- Focus on patients with medically unexplained pain syndromes
- Map out aberrant response to nociceptive stimuli and
- Train self-regulation of this response to reduce chronic pain

2) What is your mechanistic model for the intervention?

Possible contributions of neurofeedback I

- (Self-)modulation of dysfunctional neural circuits (endogenous “DBS”)?
- Activation of compensatory circuits
- Based on pathophysiological models
- See example from PD:



Simplified circuit Schema of PD pathophysiology and expected changes through neurofeedback. The left panel summarises the canonical excitatory (black arrows) and inhibitory (grey arrows) connections between cortex and basal ganglia (GPe/i: Globus pallidus externus/ internus; SNc/r: Substantia nigra pars compacta/ reticulata). According to pathophysiological models of PD, inputs from SNc and cortex to the striatum and from thalamus to cortex decrease, and inhibitory inputs to the thalamus increase (thinner and thicker arrows compared to left panel) through the complex effects of reduced dopaminergic activity in the “direct” and “indirect” pathways.

The “+” symbol denote areas that could be upregulated by fMRI-NF to redress that balance and improve cortical motor control.

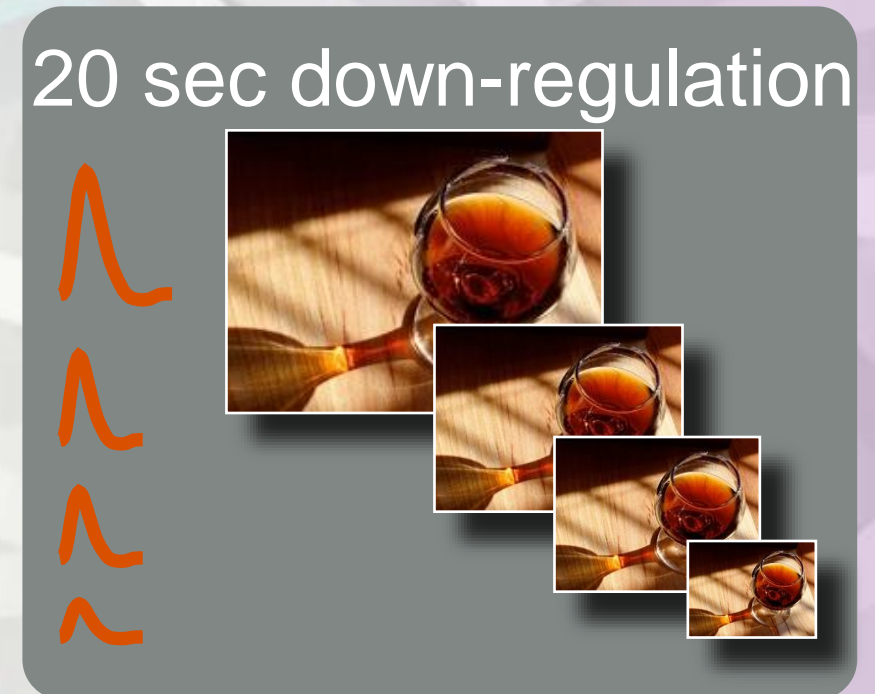
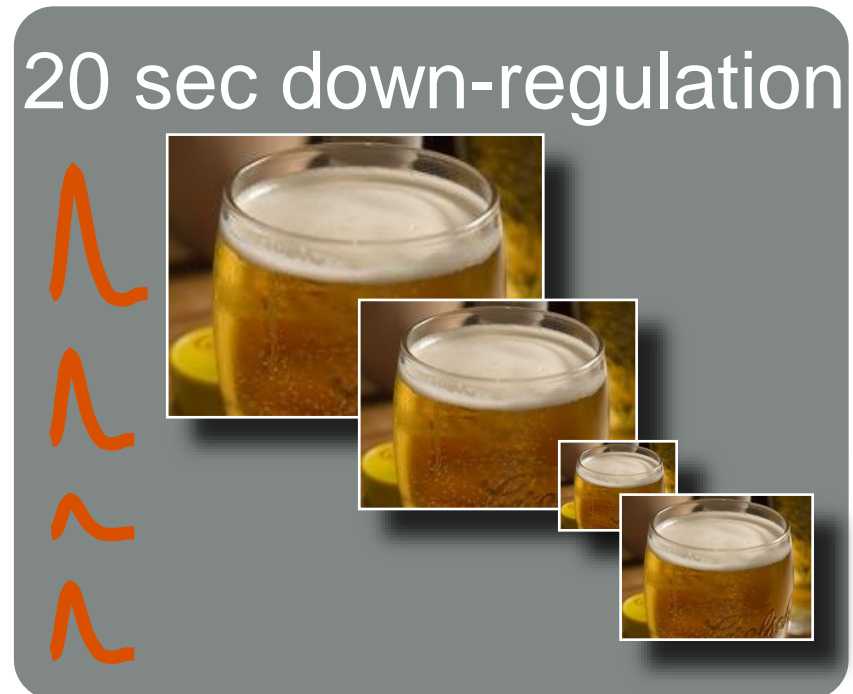
Possible contributions of neurofeedback II

- Motivational factor in psychological interventions, exercise programmes
- Re-learning of stimulus-(physiological) response associations
- See example from alcohol use disorder:



A New Approach - 'Motivational Neurofeedback'

Neurofeedback using picture size variations contingent on target area activation



Repeated size sequence as perceptual control ("mirror run")

Sokunbi, Linden, Habes,
Johnston, & Ihssen (2014).
Frontiers in BN.

→ Task provides real motivational consequences (approach and avoidance)

3) What are your target areas/ networks?

Key questions:

Anatomical vs. functional target selection

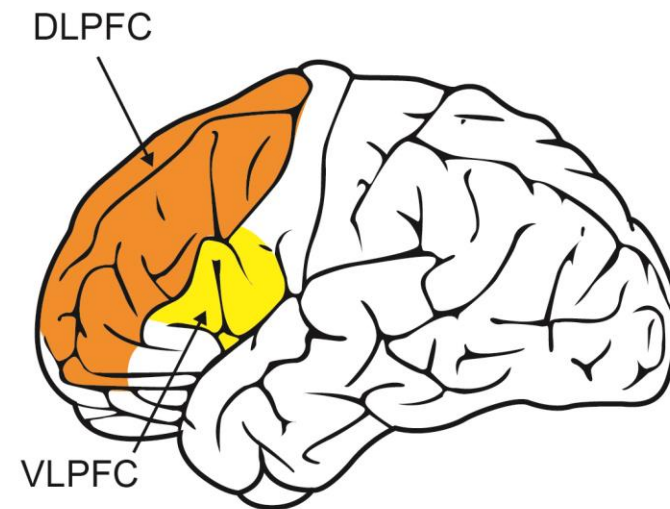
Dysfunction vs. compensation

Down vs. upregulation

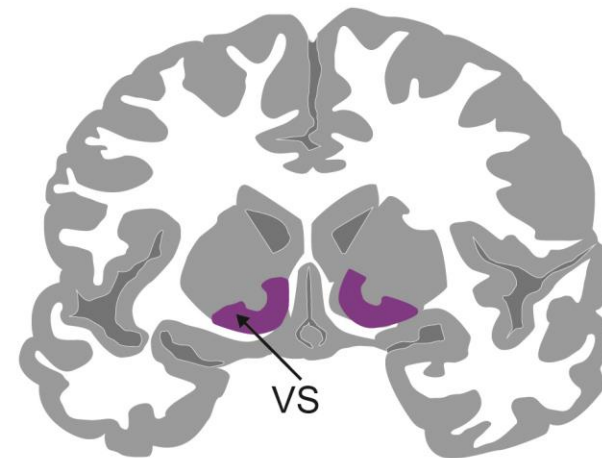
Criteria for selection of brain targets I

- Direct evidence for lesion/ dysfunction, e.g. stroke
- Network imbalance arising from primary lesion, e.g. PD
- Neuropsychological models of mental disorders, e.g. depression

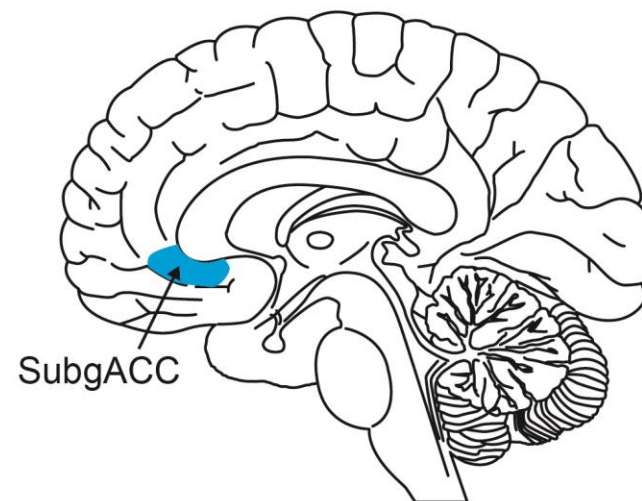
Neurofeedback in depression: attractive neural targets



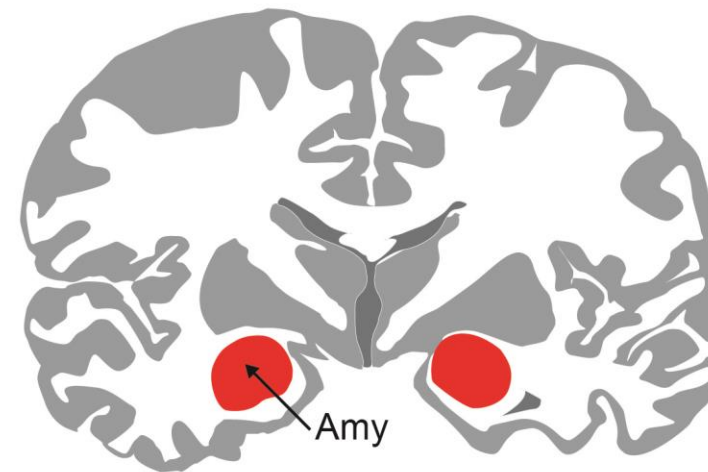
Cognitive control/
emotion regulation circuitry
(lateral PFC)



Reward circuitry
(ventral striatum)



Cortical limbic circuitry
(subgenual ACC)



Subcortical limbic circuitry
(amygdala)

Criteria for selection of brain targets II

- Enhancing compensatory mechanisms or
- Suppressing hyperactivity
- Example: design of NF intervention for alcohol use disorder



Dysfunctional Brain Responses to Visual Alcohol Cues

Task: Passive viewing of alcohol pictures in the MRI scanner

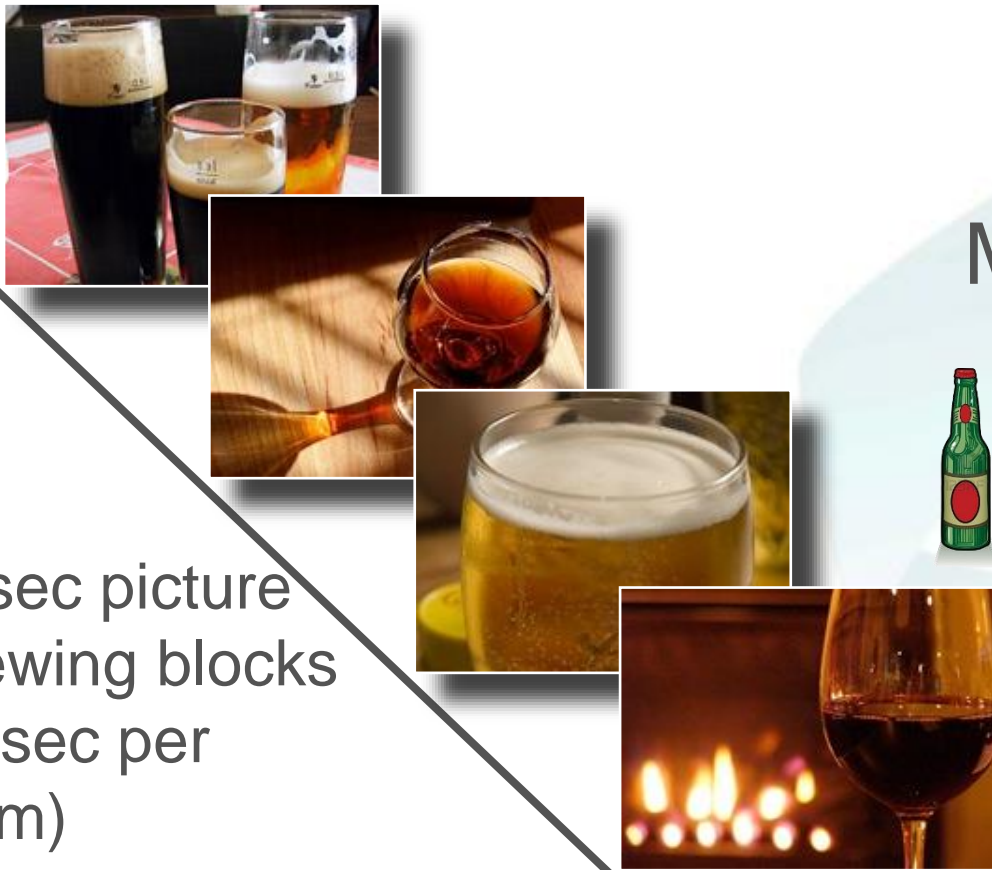
Participants: 23 student participants who were either “heavy” or “light” drinkers

What is “heavy drinking” in the UK?

Men: more than 21 alcohol units/week



8-sec picture viewing blocks (2 sec per item)

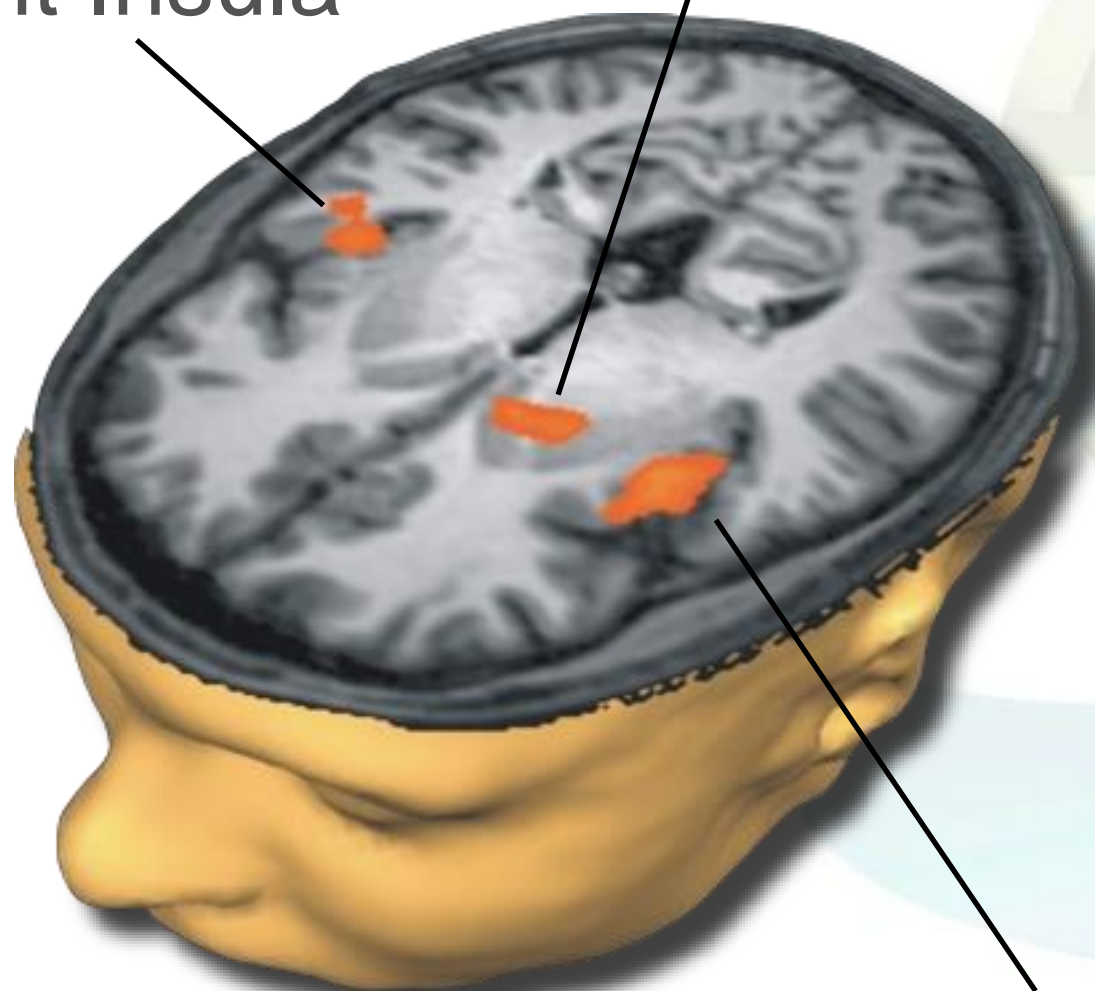




Alcohol Cue Reactivity in the Brain

Ventral Striatum

Right Insula



Heavy versus light drinkers showed **increased** brain responses to alcohol pictures in the Insula and Ventral Striatum.

→ Areas involved in **reward** processing and **craving**

→ Similar responses can be seen in alcohol dependence.

→ Here: May index addictive dispositions in preclinical stages

Left Insula



Reactivity to Other Cues

Alcohol dependence is not only characterised

- by increased responsiveness to alcohol cues
 - but also by reduced responsiveness to OTHER, healthy, non-chemical incentives or life goals
- **Lack of current concerns** (Cox & Klinger, 1988)

Examples of current concerns (identified in rating studies)



Family & Relationship



Finance & Employment



Education



Heavy Drinkers - Reduced Responsiveness to Other (Healthy) Life Goals

Inferior frontal gyrus
(BA9)



8-sec picture
viewing blocks
(2 sec per
item)



- IFG involved in action planning & representation of action goals
- Healthy goals positioned lower in the motivational hierarchy

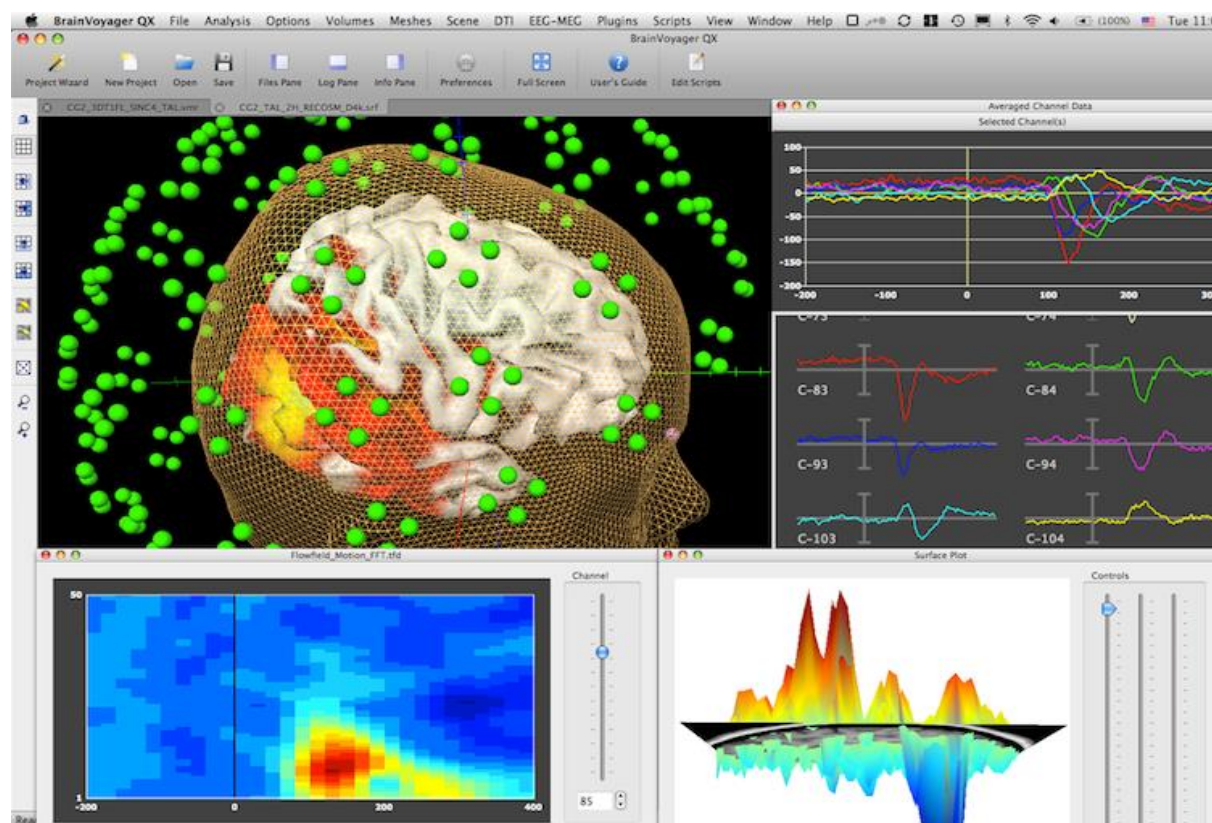
4) What procedures can you use to maintain effects?

Maintenance and transfer procedures

- Imagery homework
- Diaries
- Training DVDs
- Smartphone apps
- Exercise equipment (e.g. based on gaming consoles)
- Physiological and psychological transfer technologies



Transfer technology: EEG and serious games



- EEG informed by fMRI can combine spatial and temporal information and serve as ambulatory neurofeedback device

- Gaming scenarios can combine social and neural training components



www.braintrainproject.eu

If you haven't done it up to now

- involve patient and carer groups in discussions on the final protocol
- assess practicability with them
- and revise based on their comments

5) What are the best outcome measures?

Outcome measures

- Often dictated by conventions of clinical trials
- But what is most appropriate for drug trials may not work for complex interventions
- Consider symptom clusters likely to improve
- Consider timescales
- Consider patient target group (e.g. motivational state)
- Find outcomes mechanistically related to your model of neurofeedback response

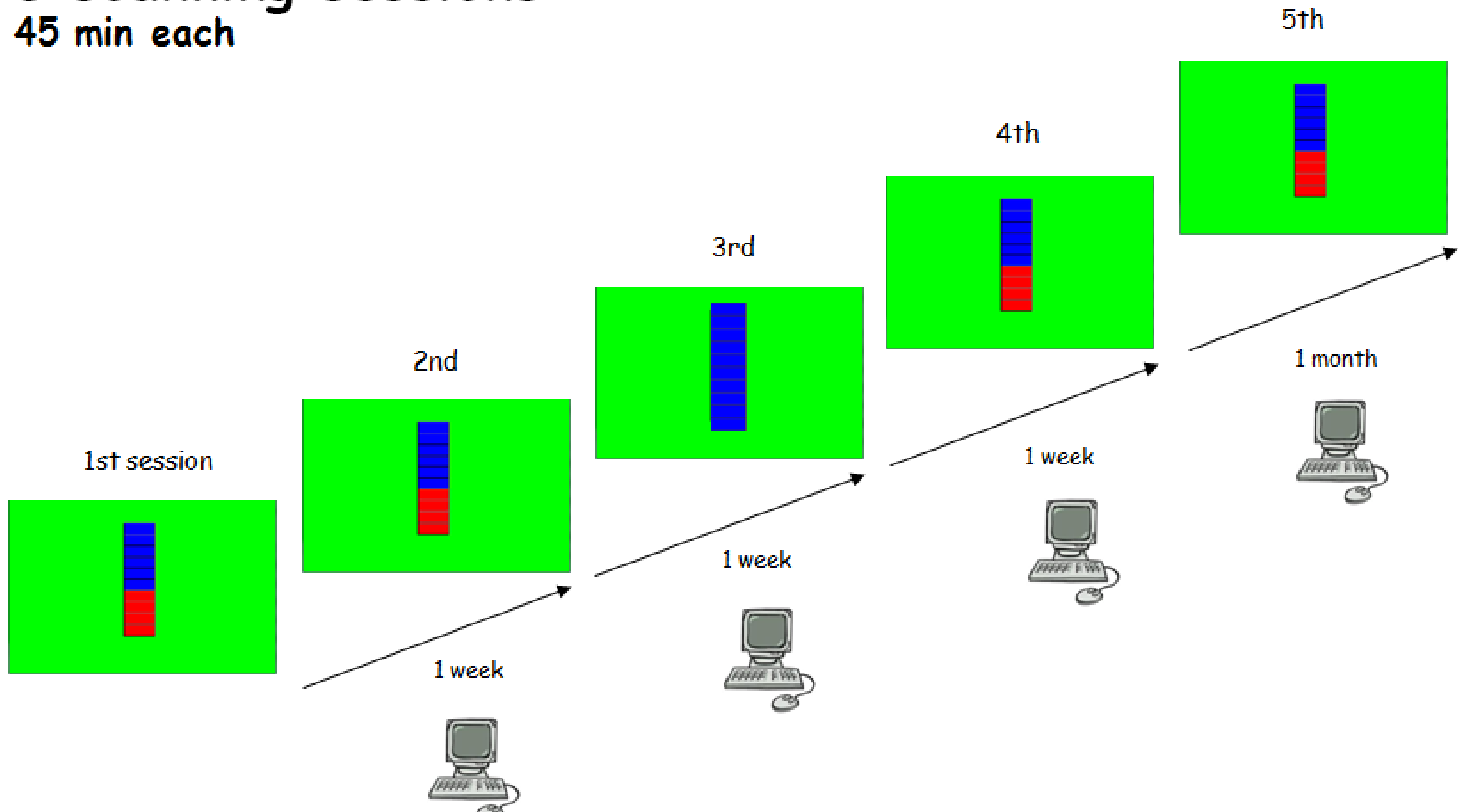
6) What is the best study design?

Study design – many options

- Pilot trial of feasibility in healthy individuals – is your NF target realistic?
- Pilot trial in patients – can they achieve self-regulation as well?
- Single group feasibility study – compliance, attrition, initial clinical outcome data, neural outcome data
- Randomised designs – vs. treatment-as-usual, comparator intervention, sham NF, other active NF
- ...

RCT: Neurofeedback in Depression (2 groups: upregulation of limbic areas vs. PPA)

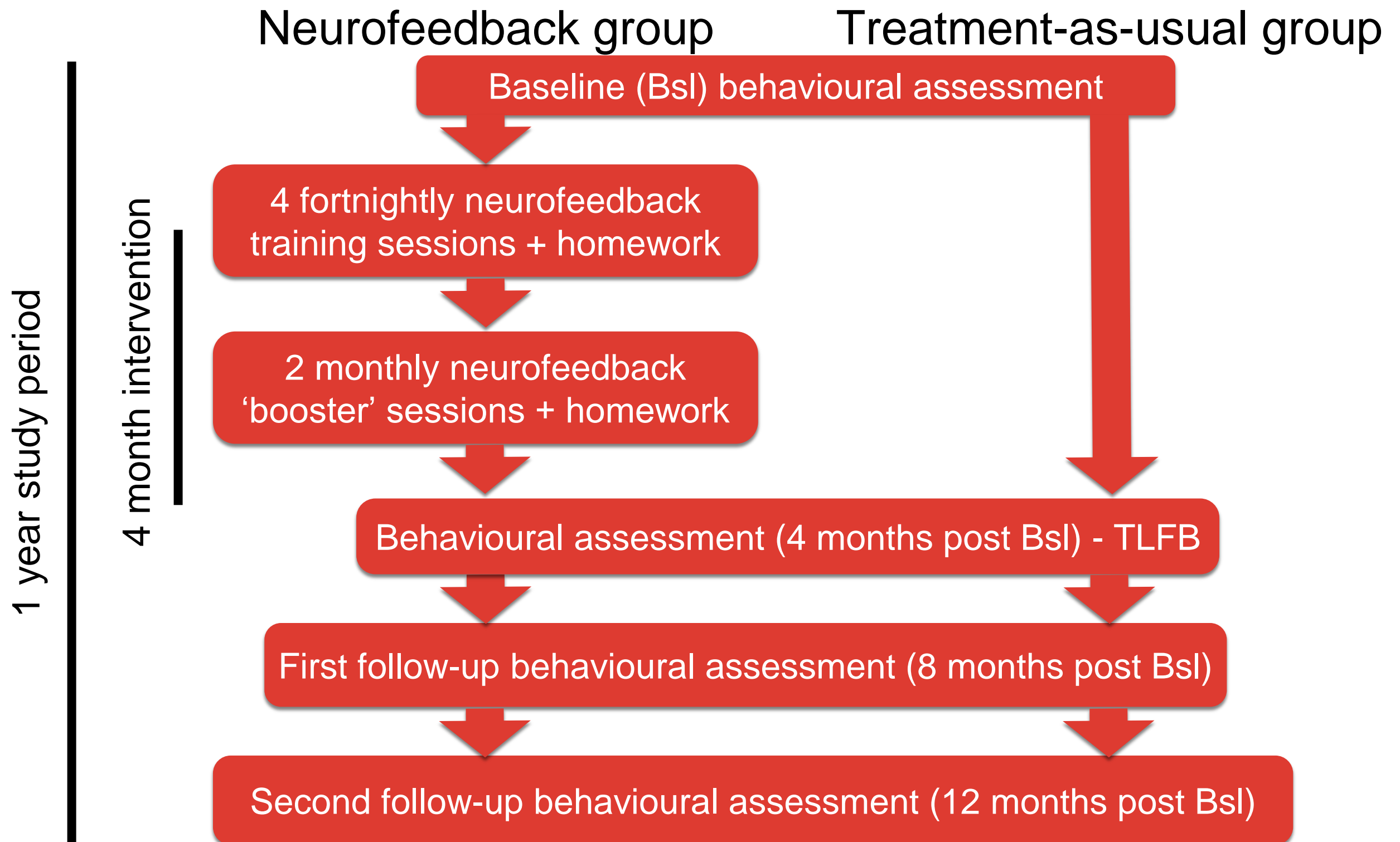
5 scanning sessions
45 min each



Medical Research Council Developmental Clinical Study
“Neurofeedback in Depression”

(David Mehler, Moses Sokunbi, Isabelle Habes, Kali Barawi, Leena Subramanian et al.)

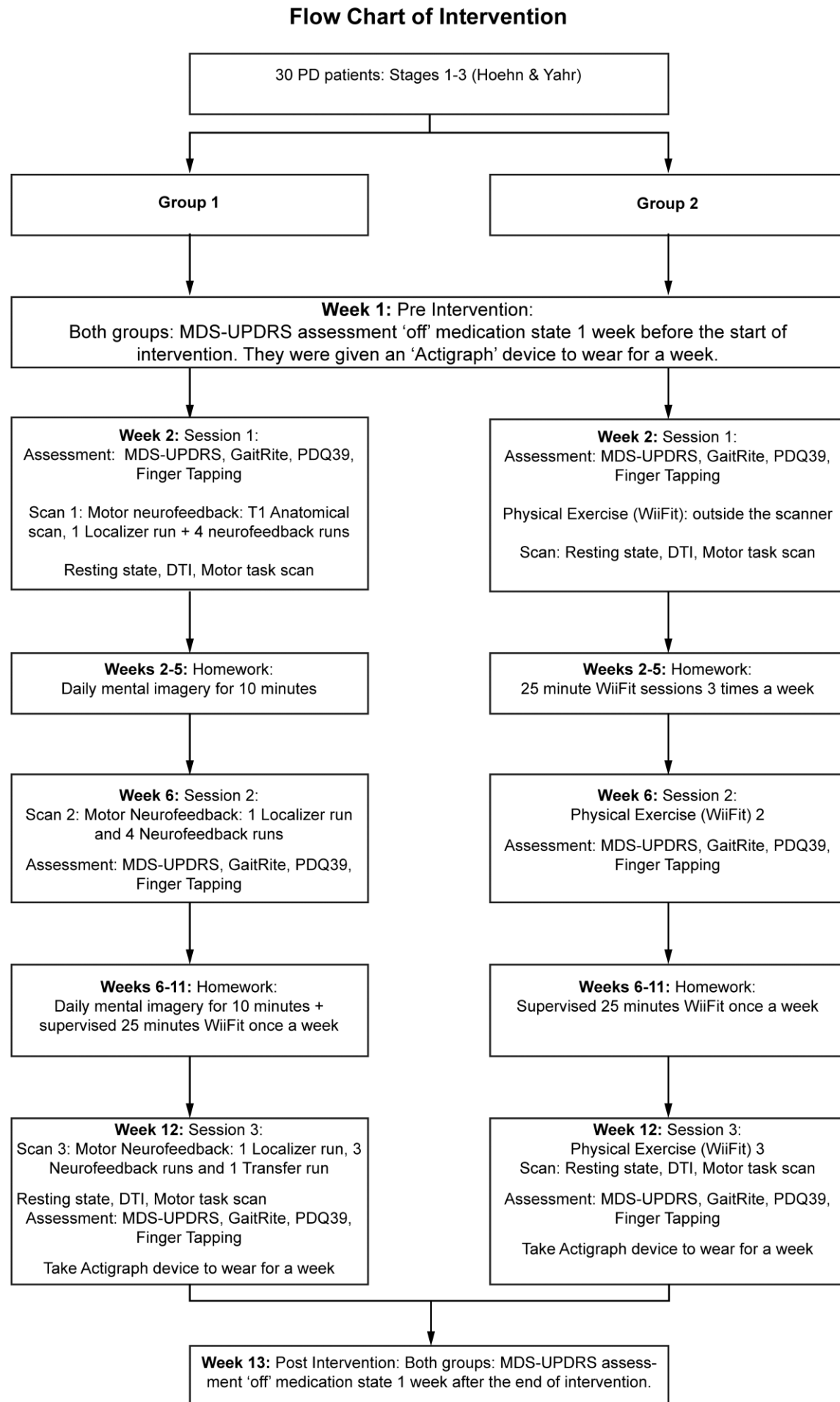
NF for alcohol dependence



www.braintrainproject.eu

Joe Whittaker, Angharad Williams, Leena Subramanian, Niklas Ihssen, Miles Cox et al.

Trial design in PD: NF with transfer technology (TT) vs. TT alone



(Subramanian et al., under review)

Summary – (at least) 6 steps from the clinical idea to the first NF study

- Identify the right clinical question and patient group
- Think about the potential therapeutic mechanisms of neurofeedback for this disease
- Select promising target areas/ networks and neurofeedback designs (up/ downregulation; activation level vs. functional connectivity or other multivariate measures; coupling with stimuli vs. blank screen)
- Do you need maintenance/ transfer procedures?
- Select suitable outcome measures
- Select trial design