Real-time fMRI Neurofeedback: bench to bedside

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Overview

Real-time fmri neurofeedback allows to endogenously manipulate activity and connectivity of specific brain regions as well as neural networks, at rest or during a task, with predictable effects on behaviour. Therefore, this flexible technique is particularly well suited to investigate causal relationships between network-level activity and human cognition, the role of spontaneous neural activity, to identify neural targets for interventions and as a potential clinical intervention tool. While more emphasis has been put on the latter, results of randomised controlled trials have so far been mixed. The aim of this symposium is to showcase the latest developments and findings of fMRI neurofeedback as both a basic science tool and potential clinical intervention.

In this symposium we will discuss how real-time fmri neurofeedback can be a useful perturbation tool with particular advantages over stimulation techniques for network control. We will also present recent evidence of effects on behaviour, clinical measures and brain structure. We will highlight and address crucial challenges in regards to study design, timeline of behavioural or clinical assessments and discuss issues for clinical translation.

Lecture 1: *The untapped potential of neurofeedback for basic science research*

Dr. Michal Ramot Presenter

Interest in closed loop applications based on the use of the real-time signal from the brain has steadily increased over the past two decades. This interest has mostly been funneled in the clinical direction however, based on a view of closed loop neuromodulation as an interventionist tool which can be used to teach subjects to directly control their own brain activity. I will discuss an alternative view of closed loop neuromodulation, as an underused neural perturbation tool uniquely well suited to basic science research, and particularly to the study of causality and the function of spontaneous activity.
Spontaneous activity remains poorly understood, despite its predictive links to behavior, perhaps in part because it is so difficult to manipulate directly through traditional neural perturbation techniques. Closed loop neuromodulation is based on the real-time monitoring of signals from the brain, which allows us to directly reinforce desired brain states as they spontaneously occur. Under such an operant conditioning model, the likelihood of rewarded brain states increases, making closed loop neuromodulation a tool capable of direct manipulation of spontaneous activity, as several recent studies have demonstrated.
I will explore the advantages closed loop neuromodulation has as a neural perturbation tool – in terms of its flexibility, its dependence on endogenous activity such that intrinsic activation patterns are never violated, and its ability to target networks at different spatial and temporal scales. I consider the conditions necessary for it to truly advance our understanding of the function of spontaneous activity, while avoiding confounds. The differences between oft-confounded concepts such as brain-computer interface (BCI) and neurofeedback will also be described, distinguishing between them according to their intended goal – harnessing the brain to control an external device, vs. changing brain activity. Finally, I will discuss the role of volitional control in neurofeedback, the conceptual differences between explicit (overt) and implicit (covert) neurofeedback, and how these different approaches interact with

the different aims of clinically oriented vs. basic science oriented research. This is a crucial debate, as these differences drive critical study design decisions, which in turn limit the interpretability of the results.
The clinical focus of closed loop neuromodulation historically, has largely resulted in the neglect of this tool for basic science research, which persists to this day. Yet its potential as a flexible, non-invasive, network-oriented perturbation tool is tremendous, and deserves greater attention. Moreover, given the well described links between spontaneous activity and a large variety of neurological and mental health conditions, understanding the causal nature of the relationship between the two will be instrumental in developing better neural markers and clinical interventions, neurofeedback based interventions among them.

Lecture 2: *Time course of clinical change following neurofeedback*
Dr. Michelle Hampson Presenter

The changes in participants that are induced by real-time fMRI neurofeedback, in terms of both behavior and neural function, have been found weeks to months after the neurofeedback training has completed. However, the development of these changes over time has not typically been monitored. Interestingly, one study reported that changes in functional connectivity patterns induced by neurofeedback were greater a day after training than immediately after. Unfortunately, the subjects in that study were not followed longer, so it is unclear how their changes in brain function may have unfolded over the weeks after training.

Here we describe an unexpected temporal pattern of symptom changes we found in our neurofeedback studies. In a double-blind randomized clinical trial that included clinical follow-up for a month after neurofeedback, we saw a qualitative pattern of symptom improvement in the experimental group that grew over the weeks after the neurofeedback was completed. Examination of another clinical trial we were running, on a different clinical population, targeting a different brain area, and monitoring different clinical symptoms, showed a surprisingly similar pattern. Furthermore, examination of the literature suggests this pattern has also been present in the data from other neurofeedback studies. Therefore, we suggest it may be a relatively common pattern for fMRI neurofeedback.

The possibility that neurofeedback induces effects that tend to grow over time for weeks after training is exciting from a clinical perspective, as it suggests the power of neurofeedback for inducing substantial long-term effects. It also has important implications for the design of neurofeedback studies. The most salient implication is that following up participants for weeks to months after training is critical to ensuring that the time point of greatest effect of the intervention is sampled. In addition, researchers should be aware that interleaving assessments with neurofeedback sessions and identifying how many sessions were conducted before symptoms stabilized is a potentially flawed approach to identifying the optimal number of sessions. Specifically, if symptoms continue to grow after training, this approach will tend to substantially overestimate the optimal number of sessions. Finally, cross-over designs are likely to suffer from carry-over effects.

It is important for neurofeedback researchers to be aware that neurofeedback may induce changes in symptoms and brain patterns that continue to grow during the weeks after training and to design their studies, and interpret their data, accordingly.

Lecture 3: *Neurofeedback in chronic stroke patients to drive behavioural and structural brain change*

Dr. Zeena-Britt Sanders Presenter

Real-time fMRI neurofeedback has been suggested as a potentially useful tool in clinical disorders associated with aberrant brain activity patterns. For example, motor impairments after a stroke have previously been associated with decreased laterality of motor cortex activity. Additionally, motor impairment after stroke has also been shown to be strongly related to the structural integrity of the corticospinal tracts, the major motor output pathway in the brain. Especially, asymmetry of the two corticospinal tracts is correlated with motor impairment, with more asymmetry being related to worse motor functioning. Interestingly, neurofeedback training has also recently been shown to be associated with structural brain changes, in particular in white matter regions connecting target areas. These structural white matter changes appear to occur in a directionally specific manner in relation to the brain activity targeted with neurofeedback. This is a promising indication that as well as altering brain activity, neurofeedback may also potentially be a useful tool to target and alter brain structure.

We carried out a registered randomized, double-blind, sham-controlled trial in chronic stroke patients with mild to moderate upper limb motor impairment to explore whether patients were able to use neurofeedback to increase laterality of motor cortex activity, and whether this was associated with any improvements in behaviour or changes in brain structure. I will present the results of this trial which showed that the group receiving real neurofeedback improved in gross motor performance on the Jebsen Taylor Test, however there were no improvements on clinical measures of upper limb functioning. Interestingly, we found that one-week after neurofeedback training, asymmetry of white matter in the corticospinal tracts was reduced in the real group compared to the sham group. Additionally, increased white matter integrity in the stroke-affected corticospinal tract was associated with better neurofeedback performance.

I will discuss the opportunities and challenges that this work highlights in relation to the translation of fMRI neurofeedback to clinical settings. In particular, with respect to heterogeneity of patient populations and variability in individuals ability to use neurofeedback.