

# DBS Technology



## Deep Brain Stimulation (DBS) 'at the right moment' An innovative protocol in Parkinson's disease

- Realistic conditions match with (theoretical) computer modeling and experimental (in-vitro preparation) studies
- A new power saving protocol

Research and Enabling technologies

2011

## Background

### Parkinson's disease

In our basic research work (Cagnan et al., Eur J. Neurosci, 2009), we investigated why typical stimulation at 120 Hz is effective and for the first time explained the frequency characteristics of STN-DBS for Parkinson's disease. Next, this theoretical concept was validated in in-vitro experiments where we used a slice preparation and recorded from thalamo-cortical (TC) neurons using the patch-clamp technique. These experiments confirmed the theoretical observations and reproduced the predicted frequency dependence of DBS in suppressing oscillations at Parkinsonian tremor frequencies (Cagnan et al., to be submitted).

This study also suggested that there is a much more efficient way of stimulation than the usually applied 120 Hz, namely stimulation with a short pulse applied at a critical phase of the ongoing tremor oscillation. Experiments in patch clamped neurons demonstrated validity of the concept and a rough estimate is that the power needed for this form of stimulation is a factor 10 lower than the usually applied continuous 120 Hz.

## The Technology

Deep Brain Stimulation (DBS) is a therapeutic option for several brain diseases. The therapy consists of implanting one or more stimulation electrodes in a deep brain structure and a battery driven stimulator device in the chest, quite comparable to pacemaker support for the heart. In Parkinson's disease, standard L-DOPA treatment fails once degeneration of the dopamine system has exceeded certain limits and for those patients DBS is the therapy of last resort. Approximately 50.000 Parkinson's disease patients have been implanted worldwide. Use of DBS for management of several other brain diseases (e.g. epilepsy, OCD, severe depression, anorexia) is currently under investigation. One of the major problems is that the basic mechanisms of action of DBS are poorly understood which hampers the search for optimal stimulation paradigms.

## The Project

In this study, we investigated whether stimulation applied at the right phase of ongoing tremor oscillation can be as effective as high frequency stimulation. To this end, we used in-vitro thalamic brain slices to patch-clamp TC neurons in current-clamp configuration and investigated TC neurons' response to oscillations at Parkinsonian tremor frequencies, induced by direct current injection, and to short pulse trains, applied at different phases of the induced oscillation at tremor frequencies. Short pulse trains were applied by activating afferent nerve fibers generating a physiologically realistic input model for capturing down-stream effects of DBS.

## Applications

We first investigated this stimulation paradigm for Parkinson's disease, but we do not exclude that similar strategies could be effective for epilepsy, OCD or depression (Nagel et al., Neuromodulation, 2009).

## R&D Status

After establishing that high frequency stimulation prevents TC spiking locked to oscillations at tremor frequencies and that efficacy (i.e. blockade of spike transfer by high frequency stimulation) is stimulation frequency dependent, we investigated whether a similar effect could be attained when using a stimulus pulse at the frequency of tremor oscillation. Results show that when stimulation is applied at the right time, similar effects to high frequency stimulation can be achieved using a stimulus train with stimulation frequencies an order of magnitude less than high frequency stimulation.

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## Key publications

1. Buzsaki, G., A. Smith, et al. (1990). PETIT-MAL EPILEPSY AND PARKINSONIAN TREMOR - HYPOTHESIS OF A COMMON PACEMAKER. *Neuroscience* 36(1): 1-14.
2. Cagnan, H., H. G. E. Meijer, et al. (2009). Frequency-selectivity of a thalamocortical relay neuron during Parkinson's disease and deep brain stimulation: a computational study. *European Journal of Neuroscience* 30(7): 1306-1317.
3. Llinas, R. R., U. Ribary, et al. (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences of the United States of America* 96(26): 15222-15227.
4. Nagel SJ, and Najm IM. Deep Brain Stimulation for Epilepsy. *Neuromodulation* 12: 270-280, 2009