**The problem:** Inferring neuronal population activity from non-invasive measurements of human brain activity is the holy grail of modern neuroscience. Our technical abilities for measuring human brain activity non-invasively have exploded in recent years, and today the vast majority of our measurements are carried out using two modalities. The first is blood oxygen level dependent functional magnetic resonance imaging (BOLD FMRI or BOLD), which is a hemodynamic measure with high spatial resolution (~1mm precision, full brain coverage) but limited temporal resolution (~1 sample/second). The second is electroencephalography (EEG), an electrophysiological measure with high temporal resolution (500+ samples/second) but relatively limited spatial resolution (~1cm precision, limited to cortical surface). Both BOLD and EEG have yielded significant insights into the workings of the human brain in health and disease over the past decades. However, our interpretation of the signals measured using these modalities leaves much to be desired: detailed inferences about specific neuronal population activity driving signal changes in BOLD and MEG/EEG are lacking. In other words, while thousands of papers are published monthly using BOLD and EEG, we know relatively little about how the measurements acquired with BOLD and EEG relate to activity in the underlying neuronal populations, such as spike rate or synchrony. Hence, while we are able to measure human brain activity with great temporal precision (EEG) and spatial resolution (BOLD), we are unable to infer specific neuronal activity in space and time from these measurements, limiting our ability to link differences in EEG/ BOLD signals across health and disease to differences in neuronal activity. The problem is that our understanding of brain signals acquired non-invasively remains largely at the measurement level, instead of the deeper level of underlying neuronal population activity.

**The theoretical approach**: To achieve a deeper level of understanding we need to develop a model to bridge the gap between non-invasive signals measured using EEG/BOLD, and the neuronal population activity driving these signals. Typically, population receptive field (pRF) models are used to predict the output of a certain instrument to a given stimulus or task. The pRF model is often employed on BOLD data, and constructed in single voxels by estimating that voxel’s stimulus preferences through the magnitude of the BOLD response to a wide range of different stimuli. In this way, the BOLD response to any arbitrary stimulus can be predicted. We propose that, rather than using pRFs to model the output of a certain instrument such as EEG or BOLD, we instead model the signals in a neuronal population, and from this population activity, predict the electrophysiological/hemodynamic responses measured by the instrument using a forward model. However, to model the signals generated by a neuronal population, one requires knowledge of the time varying set of synaptic inputs to said neuronal population, which depends on measures such as coherence and spike rate, measures which are unattainable in humans. Instead, we must estimate these synaptic inputs by assuming that neuronal population activity is composed of the summed activity of several separate circuits, which can be measured using invasive high-density electrocorticography (micro ECOG or ECOG).

These circuits are as follows: 1) a circuit time locked to the stimulus, 2) an asynchronous circuit, 3) a narrowband high frequency circuit, and 4) a narrowband low frequency circuit. The model linking stimulus to synaptic inputs can be developed by developing each component circuit separately. For example, the rate of spike arrival to neuronal population (asynchronous circuit) can be inferred using the magnitude of the ECOG broadband signal. Another component, (synaptic coherence) can be inferred using the narrowband high frequency content of the ECOG signal, which has very different stimulus preferences from the asynchronous circuit (based on neurophysiological literature). Additional circuit models will be developed to account for low frequency oscillations and stimulus locked signals. In this way, the time varying synaptic inputs to a neuronal population can be estimated using empirical signals measured using ECOG; the model is developed by using pRFs to predict features of the electrophysiological measurement (broadband ECOG, or narrowband high frequency) and these measurements are then translated into synaptic inputs of a neuronal population. Once the neuronal population inputs have been estimated, neuronal dendritic potentials will be inferred using a variant of a leaky integrator model, whose time scale parameters will be fit based on the shape of the ECOG power spectrum. Finally, the electrode time series will be approximated by linearly summing dendritic potentials in the local neuronal population, completing the forward model from stimulus → synaptic input → dendritic potentials → electrode time series.

Once a model linking features of the non-invasive neurophysiological signal to neuronal population activity is established, neuronal population activity must be linked to the BOLD signal, to determine which features of the neuronal circuitry responses effectively drive BOLD. To do so, we must first distinguish between BOLD effects due to microvasculature, which directly interfaces with neuronal populations, and BOLD effects due to macrovasculature, which reflect passive draining of downstream veins. This can be accomplished by linking high field gradient echo and spin echo BOLD signals to invasive optical imaging signals in rodents. A bridging model will then be constructed, with neuronal population activity time series as the input, and vascular drive as output. This bridging model, in combination with micro/macrovasculature modeling of BOLD, will allow neuronal population activity to be inferred from changes in non-invasively measured BOLD.

**The objectives:** The objective is to build a model that will allow us to infer neuronal population activity from commonly used non-invasive measurements such as EEG and FMRI. This will allow us to estimate specific features of neuronal activity such as synaptic coherence or neuronal firing rate from EEG/FMRI, deepening our understanding of human brain activity in health and disease. For instance, at the moment if we wish to compare the EEG response in autism vs healthy controls to an image of a face (ref), we can only speculate about the differences in brain activity between the two populations, as we are restricted to the measurement level. By constructing a model that can infer neuronal population activity from non-invasive measurements, we will be able to speak about differences in neuronal firing rate, or synaptic coherence, deepening our understanding of the effects these disorders have on the brain.

**The methodology:** Using custom MRI hardware developed for high spatiotemporal resolution BOLD, and high density intracranial human electrocorticography (micro ECOG), a unique set of measurements will be obtained at the level of neuronal population activity in humans. Pre-operative functional MRI will be carried out at 7Tesla (Utrecht) or 3Tesla (NYU), as well as pre-operative EEG and MEG recordings, all using the same stimulus set. The same subjects (12 at Utrecht, 12 at NYU) will then undergo surgery, and micro ECOG will be implanted, to record neural activity directly from the cortical surface in response to the same stimuli. The same experiments, with the exception of micro ECOG, will be carried out in control subjects. Leaky membrane integrator models of neural activity will be used to translate synaptic inputs to dendritic potenials.