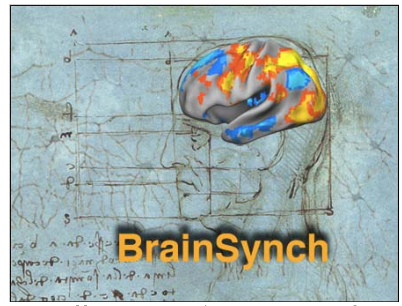
Publishable summary

The goal of *BrainSynch* is to understand how neuronal assemblies exchange information (functional neuronal communication), and how variability in neuronal communication explains variability in behavioural performance, both in the intact and injured brain. While we know a lot about neural signals at the local level (single neurons and individual areas), and how they encode information about objects in the environment, motor actions, and even cognitive functions, almost nothing is known on how ensembles of areas exchange information and communicate to mediate complex behaviour. Neural communication involves temporal interactions between neuronal assemblies, not only locally within an area but also on a larger-scale between brain areas. We focus on large-scale interactions that arise at two distinct but potentially related temporal scales: 'slow' (~0.1 Hz) fluctuations of the blood oxygen level dependent (BOLD) signal, as readily measured with functional magnetic resonance imaging (fMRI); and 'fast' (1-150 Hz) neuronal oscillations, as can be measured at various spatial scales (e.g. multi-unit activity (MUA) and local field potentials (LFP) at fine spatial scale; electroencephalography (EEG); magneto encephalography (MEG) at intermediate scale. We will explore how the different temporal and spatial scales relate mechanistically, and how variability in ongoing spontaneous or task-induced neuronal interactions relates to cognition and behaviour. Understanding the relationship between spontaneous and task-induced activity is a fundamental goal for modern neuroscience as it is becoming increasingly clear that the majority of the brain's energetic budget is spent on spontaneous activity (about 95%) and that only a small fraction (~5%) is actually used to drive the brain. There are also potentially helpful clinical applications as many neurological and psychiatric diseases including stroke, head injury, multiple sclerosis, and Alzheimer's disease, may be characterized by abnormal neural communication.



http://www.brainsynch.org/

The second year of the project has been characterized by a strong acceleration in the development of novel methods for recording, analyzing, and modelling neural signals from human and non-human primates. The consortium as a whole has developed ex-novo or optimized at least 8 novel techniques that will be hereafter briefly described. As coordinator of *BrainSync*, I am especially proud of these achievements as science typically advances in leaps and bounds mostly and foremost based on the development of novel technologies or analyses.

Novel methods

- Two different pipelines of MEG data have been developed to look at interactions across brain regions in the resting state. One pipeline from UdA Chieti focuses on both band-limited power fluctuations and imaginary coherence of the signal. The first method was used to describe for the first time MEG brain networks of spontaneous correlation at rest (de Pasquale et al. 2010 Proc Natl Acad Sci U S A. 2010 Mar 30;107(13):6040-5). The second method is able to pick consistent lagged signal interactions between regions. The second pipeline from UKE Hamburg employs phase delays of the envelope of the power fluctuations to extract maps of orthogonalized phase correlation that solve the problem of local leakage between neighbouring voxels (Jorge Hipp, David J Hawellek, Andreas K Engel 2010 Society for Neuroscience, 2009: 381.24).
- KU Leuven in collaboration with UdA has developed a novel method to compare patterns of temporal correlation in the fMRI signal between monkeys and humans. The method is based on the cross-correlation and feature specificity of time series in one species onto time series from the other species (D.Mantini, M.Corbetta, S.Kolster, GL.Romani, G.Orban, V.Wanduffel Society for Neuroscience, 2009: 13.7).
- RU has continued to optimize the subdural grids for the recordings of local field potential

activity from large swaths of the neocortex in monkeys (Rubehn B, Bosman C, Oostenveld R, Fries P, Stieglitz T. J Neural Eng. 2009 Jun;6(3):036003).

- RU and KU Leuven have combined MR-compatible subdural grids of electrodes with fMRI recordings in the monkey.
- KU Leuven and UCL have combined TMS with fMRI recordings in monkeys following the initial development of combined electrical microstimulation and fMRI as published in *Science (*Ekstrom LB, Roelfsema PR, Arsenault JT, Bonmassar G, Vanduffel W. Science. 2008 Jul 18;321(5887):414-7).
- UCL has pioneered in humans the combination of TMS with fMRI. In a recent study they extended this approach to the study of interactions during active behavior (Blankenburg F, Ruff CC, Bestmann S, Bjoertomt O, Josephs O, Deichmann R, Driver J. Cereb Cortex. 2010 Feb 22)
- ICS Prague has developed a novel clustering algorithm for RSN's identification based on average association criterion which divides input elements (fMRI voxels) into disjoint clusters and a residual set.

Another important development in the second year was the convergence of results across a number of work packages on the presence of strong feedback interactions between regions in higher order parietal and frontal regions and visual cortex.

Interactions between dorsal fronto-parietal and visual cortex
MEG analysis of lagged signal interaction show a rich communication at non-zero lag between dorsal fronto-parietal regions and visual regions in the alpha band in humans at rest, even though relatively weak or no across-network interactions are present at lag 0 (Marzetti et al in preparation). These interactions can be flexibly modified by spatial attention and lead to a strengthening of the sensory modulation in visual cortex, as measured with BOLD fMRI, during stimulus processing (Blankenburg et al Cerebral Cortex 2010). In monkeys performing a similar paradigm, parietal regions directionally synchronize visual cortex in the beta-1 band (14-18 Hz)(Fries, WP4). Finally, inactivation of lateral intraparietal area leads to abnormally increased fMRI activation of visual areas during spatial attention tasks (Vanduffel, WP6). Although incomplete these findings lend strong support to the idea that frontoparietal regions are the source of attentional modulations onto visual cortex.

Finally, a number of important developments have occurred in each of the work packages as research in the consortium has steadily progressed.

- De Pasquale and colleagues have provided evidence that the topography of MEG power fluctuations at rest in human subjects resembles that of fMRI networks. However, in contrast to fMRI, MEG networks are highly non-stationary with intra-hemispheric connections being more consistently synchronized that inter-hemispheric ones. Marzetti et al showed this year, through analysis of time signal coherence, that while intra-hemispheric connections are characterized by zero lag signal interaction, inter-hemispheric functional interactions are lagged in time as captured by a measure of imaginary signal coherence. This result further characterizes the dynamics of spontaneous activity networks, which will be further analyzed next year under different conditions of visual sensory stimulation.
- Lachaux and colleagues have refined the temporal analysis of gamma band deactivation during visual search, and showed that ventral prefrontal cortex leads to the deactivation of other cortical regions. Next year they will complete the analysis of iEEG and fMRI patterns at rest to be compared with the fMRI/MEG analysis already performed.
- Vanduffel and colleagues discovered that spontaneous activity network in monkeys become highly synchronized across subjects (humans and monkeys) during natural vision. Furthermore, the large-scale structure of these networks breaks down in smaller clusters while other networks emerge. These changes may indicate a change from low to higher frequencies induced by the stimulation and task demands. This is now being investigated with MEG in human subjects.

- The consortium optimized attention paradigms that will be run at different sites. These paradigms emphasize the sustained maintenance of attention and sensory modulation, on one hand, and the dynamic shifts of attention and routing of information, on the other. MEG, iEEG, monkey fMRI, monkey LFP, monkey and humans TMS-fMRI studies are planned.
- Fries and colleagues provided direct evidence for inter-regional synchronization during spatial attention. Interestingly, different functional networks seem to synchronize at different frequencies. For example, while gamma synchrony is strong between visual areas (V1-V4), beta synchrony is stronger between parietal and visual areas. This may depend on the relative distance between areas, or the content of different computations.
- Driver and colleagues showed that parietal-to-visual cortex interaction can occur on a number of different attention paradigms and may involve both intra- and inter-hemispheric functional relationships.
- Engel and colleagues are making progress in characterizing anomalies of functional connectivity in multiple sclerosis (MS) and schizophrenia. In MS strong associations were detected between structural measures of gray and white matter atrophy, and factor scores of behavioural performance. This is an important finding to take under consideration when evaluating potential changes in functional connectivity with fMRI or MEG. An important question is whether these structural abnormalities have a topography that resembles functional connectivity networks as suggested by a recent study in neurodegenerative conditions (Seeley et al 2009 Neuron).
- Palus et al. have developed a new clustering method that optimizes community independently of whether interactions are linear or non-linear; broad- or narrow band; based on dependence/coherence/phase synchronization. When tested in fMRI data sets, it was found that linear interactions account for the majority of variability, and the application of the algorithm has led to clusters that are being compared to other methods (seed-based or ICA). The application to MEG, iEEG, and LFP data sets is planned.
- Deco and colleagues have extended the analysis of inter-regional interaction from Wilson-Cowan units to a Kuramoto model in which nodes are modelled as phase oscillators. By applying these models to a realistic neuroanatomical matrix based on diffusional spectral imaging data, they have been able to replicate the spatial-temporal structure of real fMRI correlation data. Extension of this analysis to LFP, iEEG, and MEG is underway. The ultimate goal of this modelling work is the development of a forward model that can relate fast (LFP, iEEG, MEG) to slow (fMRI) oscillations.