Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson’s disease

Bénis D.1,2, David O.1,2, Lachaux J-P3, Seigneuret E., Krack P.1,2,4, Fraix V.1,2,4, Chabardès S.1,2,5 and Bastin J.1,2*

1 Fonctions Cérébrales et Neuromodulation, Université Joseph Fourier, 38042 Grenoble, France.
2 INSERM, U836, Grenoble Institut des Neurosciences, 38042 Grenoble, France.
3 INSERM, U1028, Centre de Recherche en Neurosciences de Lyon, Université Claude Bernard, Lyon, France.
4 University Hospital, Department of Neurology, Grenoble, 38042 Grenoble, France.
5 University Hospital, Department of Neurosurgery, Grenoble, 38042 Grenoble, France.

Models of action selection postulate the critical involvement of the subthalamic nucleus (STN), especially in reactive inhibition processes when inappropriate responses to a sudden stimulus must be overridden 1 2. The STN could also play a key role during proactive inhibition, when subjects prepare to potentially suppress their actions 3 4. Here, we hypothesized that STN responses to reactive and proactive inhibitory control might be driven by different underlying mechanisms with specific temporal profiles.

Deep Brain Stimulation of the STN, used as a symptomatic treatment of Parkinson disease, allows direct recording of Local Field Potentials (LFP) from STN stimulation electrodes with millisecond time precision.

Recordings in twelve Parkinson’s disease patients during a modified stop signal task (SST) revealed a decrease of beta band activity (BBA, 13-35 Hz) in the STN during reactive inhibition of smaller amplitude and shorter duration than during motor execution. Crucially, the onset latency of this relative increase of BBA took place before the stop signal reaction time, and could thus be thought of as a “stop” signal inhibiting thalamo-cortical activity that would have supported motor execution. Finally, results also revealed a higher level of BBA in the STN during proactive inhibition which correlated with patients’ inhibitory performances. We propose that BBA in the STN would here participate to the implementation of a “hold your horse” signal to slow down motor responses, thus prioritizing accuracy as compared to speed. Taken together, our results provide strong electrophysiological support for the hypothesized role of the STN during proactive inhibitory control and rapid motor inhibition.

References:
FC3_2. Reliability of Resting Brain Networks in BOLD and ASL FMRI across Time and Platforms

Jann K.¹, Gee D.², Kilroy E.¹, Cannon T.³, Wang DJ.¹
¹Department of Neurology, UCLA, Los Angeles, California, USA
²Department of Psychology, UCLA, Los Angeles, California, USA
³Department of Psychology, Yale University, New Haven, CT, USA

Since the seminal work by Biswal in 1995¹, the study of resting brain networks (RBN) based on functional connectivity (FC) in resting state fMRI (rs-fMRI) has experienced an upsurge from basic to clinical neuroscience. In addition to the widely used blood oxygen level dependent (BOLD) contrast, RBNs can be detected using arterial spin labeled (ASL) perfusion MRI which measures cerebral blood flow (CBF) using magnetically labeled blood water as an endogenous tracer. Compared to BOLD, perfusion based FC analysis provides quantitative and more direct measures of the physiology and metabolism of specific networks. To date, however, no studies have systematically addressed the test-retest (TRT) reliability of RBNs detected using BOLD and ASL rs-fMRI across time and/or sites.

In the present study, we performed repeated 2D-EPI BOLD and background suppressed 3D GRASE pCASL² rs-fMRI scans in the same 10 healthy young subjects (6F/4M; Age [mean±SD] = 22±3 years) – 2 times on each of the 2 MR scanners – to evaluate the reliability of RBNs detected using each technique. After preprocessing, functional connectivity was assessed by means of a temporally concatenated group Independent Component Analysis (ICA) approach that identified 5 common RBNs. Statistical analyses were performed on the network as well as on a voxel-wise level. Multivariate repeated-measures ANOVAs and post-hoc t-tests were computed to identify differences between modalities, scanners and sessions. TRT reliability of ASL and BOLD based RBNs was estimated using Intraclass Correlation Coefficients (ICCs).

We found that CBF based FC is feasible and yields a group RBNs similar to the BOLD-RBNs, but with significant differences in specific areas depending on the modality. Furthermore, TRT analysis indicates more reliable networks in BOLD (ICC=0.900/0.925) than ASL (ICC=0.625/0.550). However, while the spatial pattern of the DMN is more reliable using BOLD, ASL provides highly reproducible, network specific CBF measurements. Thus, the combination of ASL and BOLD rs-fMRI provides a powerful tool for characterizing RBNs.

FC3_3. Investigating the effect of functional connectivity definition on graph theoretical metrics

Hale J.R.¹, Mayhew S.D.¹, Przezdzieki J.¹, Arvanitis T. N.², Bagshaw A.P.¹
¹School of Psychology, University of Birmingham, Birmingham, B15 2TT, UK
²School of Electronic, Electrical and Computer Engineering, University of Birmingham, Birmingham, B15 2TT, UK

Brain function is thought to be mediated by integration of functionally specialised regions to form networks. Owing to their potential to characterise and summarise large-scale networks, graph theoretical methods are increasingly being applied to study the brain’s functional networks¹. Graphs are made by defining regions (nodes) and computing the functional connectivity (FC) strength between them (edges) to form an association matrix. While graph theory metrics are sensitive to several assumptions, to date there has been less consideration of the formation of the association matrix². We examine several factors: node and edge characterisation, connectivity threshold (CT) and timeseries length (TL).

Eight healthy subjects underwent a 15 min resting state fMRI scan. Standard preprocessing was performed³. Data from a separate cohort were used to define a functional parcellation scheme using resting state networks (RSNs) identified from fMRI data using MELODIC⁴. For each RSN, nodes were defined from 3x3x3 voxel cubes in each major functional region. FC was assessed between BOLD timecourses extracted from network nodes using Pearson correlation and partial correlation, computed for all pairs of nodes and averaged across subjects, forming association matrices. Matrices were constructed using the whole time-series and data averaged over 2 min and 30 s epochs. A range of thresholds were applied to binarise matrices and graph metrics computed as a function of CT using the Brain Connectivity Toolbox¹.

Pearson correlation FC analysis graph metrics displayed stability across TLs. With increased CT the number of modules identified increased, reaching the number of RSNs expected from the parcellation scheme when CT=0.2-0.3, becoming more variable thereafter. Clustering coefficient (C) and the characteristic path length (PL) of each RSN were also found to be stable up until CT=0.3. As expected, connection strength for partial correlation analysis was lower, but showed stability across TL. Modularity was more variable across thresholds, and C and PL were more sensitive to changes in CT.

The choice of CT and edge definition greatly influenced graph metrics, which will have a major impact on subsequent interpretation of brain networks. Graph metrics were stable across TLs which is noteworthy for applications such as sleep where data are epoched when classifying stages. The functional parcellation scheme allows some internal validation of graph theory quantities, e.g. a low CT that estimates a low number of modules can be identified as inappropriate; which is particularly useful when summarising changes in FC between sleep stages, or between patient and control subjects.

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FC3_4. Evaluating the physiological plausibility of time-varying connectivity methods using large-scale evoked potentials in an animal model

Plomp G.¹, Quairiaux C.², Astolfi L.²,³, Michel, C.M.¹,⁴

¹Department of Fundamental Neuroscience, University of Geneva, Geneva, Switzerland
²Department of Computer, Control, and Management Engineering, University of Rome “Sapienza”, Italy
³Santa Lucia Foundation IRCCS, Rome, Italy
⁴Neurology Clinic, University Hospital Geneva, Switzerland

Time-varying connectivity measures are increasingly used to study directed interactions between brain regions from electrophysiological signals. These methods may show good results in simulated data but it is unknown to what extent connectivity results obtained from real data are physiologically plausible. We here compare time-varying connectivity measures on a benchmark data set of multichannel somatosensory evoked responses (SEP) measured across rat cortex, where the structural and functional connectivity is relatively well-understood: Rat SEPs after whisker stimulation are exclusively initiated by contralateral primary sensory cortex (S1), at known latencies, and with known spread of activity from S1 to specific regions. This allows for a comparison of the physiological plausibility of time-varying connectivity measures according to fixed criteria. We evaluated the performance of four implementations of time-varying Partial Directed Coherence (PDC), comparing row- and column-wise normalization, and introducing a weighting by the spectral power. The different PDC approaches gave mostly converging results, but row-normalized, weighted PDC showed the largest effect sizes and best temporal resolution with results that were invariably physiologically plausible. The results provide a strong validation of information transfer methods in an animal model and suggest a driving role for ipsilateral S1 in the later part of the SEP. The benchmark SEP dataset will be made freely available so that the physiological plausibility of existing and future connectivity methods can be similarly evaluated.
Unilateral stimulation induces contralateral positive (PBR) and ipsilateral negative (NBR) BOLD responses in primary visual (V1), motor (M1) and somatosensory (S1) cortices [1,2,3]. NBR are thought to reflect neuronal inhibition required to optimise task performance [1,2,3]. However, the functional significance of NBR and its balance with PBR has not been studied at the single-trial level, where signal modulations most relevant to dynamic network processing occur [4]. We investigate the relationship between single-trial variability in PBR and NBR amplitude in V1, M1 and S1 for unilateral stimulation.

Three fMRI experiments were recorded in 14 subjects (age=28±5yrs). Visual: 80 trials of a 1s duration left-hemifield checkerboard presented at 100% or 25% contrast with inter-stimulus interval (ISI) = 16-21s. Motor: 5s duration isometric contraction of right-hand at 10% and 30% of maximum force. 40 trials of each force were recorded with ISI=5-9s. Somatosensory: 10s median nerve stimulation (MNS) was applied to the right wrist at 2Hz. Data were recorded over 40 trials with ISI=20s.

BOLD data were standardly preprocessed and GLM analyses performed using regressors of stimulus timings. Group-level ROIs were defined from a 3x3x3 voxel cube centered on the group peak voxel in contralateral (c) PBR and ipsilateral (i) NBR regions of V1, M1, and S1. Single-trial responses were extracted, baseline corrected and single-trial amplitudes were measured as the peak signal change within the time window: (mean response latency±TR*2). For each subject the linear correlation of single-trial PBR-NBR amplitudes was assessed between: cV1-iV1; cM1-iM1; cS1-iS1.

Significant contralateral PBR and ipsilateral NBR were observed in V1, M1 and S1. In all three sensory modalities we found that the average magnitude of cPBR and iNBR were negatively correlated, whilst the natural modulations of single-trial PBR and NBR were positively correlated. Further GLM analyses showed that single-trial cPBR amplitude was significantly positively correlated with the BOLD response to the stimulus in grey matter across widespread brain regions in all three datasets.

Single-trial PBR-NBR correlations form part of a global-brain positive correlation with the cPBR, that is strongest in stimulus-driven primary sensory cortex. This bilateral modulation may have neuronal origin, related to widespread, complex modulation of brain networks by simple sensory tasks [5]. Physiological confounds of breathing and heart-rate do not contribute. Additional work using resting-state fMRI data and also EEG-fMRI recordings is underway to quantify the potential contribution of vascular effects.

References
Coherence analysis is a popular tool in neuroscience to detect connectivity between spatially separated populations of neurons. The coherence indicates the linear relation between two signals as a function of frequency. By definition coherence varies between zero and one, where one indicates a perfect linear noise-free relation. Coherence is the magnitude squared of the (complex) coherency. Coherency phase describes the relative timing between the signals and is often used to estimate the time delay between the signals.

Cortimuscular coherence (CMC) in the beta band demonstrates connectivity between the cortex (recorded with EEG or MEG) and the spinal motoneurons (recorded muscle activity with EMG). Typically a linear phase-frequency relation is found, suggesting the presence of a time-delay. In literature three slopes of the phase-frequency relation are reported. Most studies report a negative slope (cortex leads muscle), which is often smaller than physiologically would be expected. A positive slope (muscle leads cortex) and a constant slope are also reported. Furthermore these slopes typically have a non-zero intercept, which is awkward and not well explained.

Traditionally CMC was considered a unidirectional coupling. With a unidirectionally coupled time-delay the phase-frequency relation would present as a straight slope with zero intercept. However the underlying system could include feedback loops and also sensory information could be present in the cortical signal. Here we analysed how this affects the coherency phase and the estimation of time delays. We considered four scenarios: 1. a unidirectional (efferent) system with a time-delay; 2. a system with a feedback loop with time delays in the forward (efferent) path and (afferent) feedback path; 3. a system without a feedback loop, but with additional sensory information in the cortical signal; and 4. the combination of 2 and 3. For the scenarios we derived the coherency phase and estimated the time-delay by fitting the slope of coherency phase in the beta band.

We found that both the presence of a feedback loop and the presence of afferent information in the cortical signal have a huge effect on the coherency phase, depending on the relative strength of the pathways and noise magnitudes. Within the beta band the slope of the phase-frequency relation is reduced and has a nonzero intersect. If the afferent pathways are stronger than the efferent pathways even a phase advance will result, i.e. the slope can become positive. In conclusion, the coherency phase depends on complex interactions within the sensorimotor loop, where the time delay cannot be simply estimated from the phase-frequency relationship.