Supplemental Digital Content 1

Phase lag index (PLI)

The instantaneous phase difference for each time sample is computed using the analytical signal concept and the Hilbert transform. The PLI characterizes the asymmetry in the distribution of instantaneous phase differences between two signals. The reason for using the asymmetry of this distribution as a measure of functional interaction, is that a nonzero phase lag between these signals cannot be explained by volume conduction. The PLI ranges between 0 (no phase locking) and 1 (total synchronization). An index of the asymmetry of the phase distribution can be obtained from a time series of phase differences $\Delta\varphi(t_k)$, k = 1 … N_s in the following way:

$$\text{PLI} = \left|\left\langle sign\left[\sin\left(\Delta\varphi\left(t_k\right)\right)\right]\right\rangle\right|,$$

where the phase difference is defined in the interval [-π,π], <> denotes the mean value, N_s is the number of samples. For each subject, the PLI was calculated for all possible pairs.

Graph theoretical analysis

The unweighted clustering coefficient describes the likelihood that neighbors of a vertex are also connected, and it quantifies the tendency of network elements to form local clusters. We used the weighted equivalent of this measure to characterize local clustering.

For each vertex i, it is defined as:

$$C_{w,i} = \frac{\sum_{k\neq i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}w_{il}w_{kl}}{\sum_{k\neq i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}w_{il}}$$

where w_{ik} and w_{il} are the weights between vertex i and vertices k and l, respectively, and w_{kl} is the weight between vertices k and l. The average weighted clustering coefficient is computed by averaging $C_{w,i}$ over all vertices.

The average (weighted) shortest path length indicates the level of global integration of the network. In unweighted networks, it depends on the average number of edges used to connect any two vertices in the network (1). The average weighted shortest path length (L_w) is defined as the harmonic mean of shortest paths between all possible vertex pairs in the network, where the shortest path L_{ij} between vertices i and j is defined as the path with the largest total weight (2).

$$L_w = \frac{1}{(1/N(N-1))\sum_{i=1}^{N}\sum_{j \neq i}^{N}(1/L_{ij})},$$

with N the number of vertices.

Network properties are determined not only by edge weights and network topology, but also by network size. In order to facilitate comparison of results with other studies, we compared the calculated C_w and L_w values to a reference, C_{ws} and L_{ws}, derived from 500 surrogate networks of the same size. The surrogate networks were constructed by randomly shuffling the edge weights over the network. The resulting C_w/C_{ws} (gamma) and L_w/L_{ws} (lambda) are thus the normalized average weighted clustering coefficient and normalized average weighted shortest path length of the network.

PLI stability

Before we started our analysis, we studied the first 7 non-delirious patients and evaluated the length and number of epochs needed to reach stable PLI values (see Figure 1 and 2 below).

Epochs of 8 s resulted in stable PLI values, as can be see figure 1 for alpha band PLI. Elongation of the epoch length resulted in a decrease of PLI, as the PLI characterizes asymmetry in distribution of a consistent phase lag. The direction of this phase lag, however, may fluctuate over time. We therefore consider the epoch length of 8 s sufficient to obtain stable PLI values. With this epoch length of 8 s, 4 epochs were needed to obtain stable PLI values, as shown in Figure 2. The use of more epochs may increase the stability of the results, since connectivity values were averaged over multiple epochs. However, a trade-off must be made between epochs that meet the conditions of a consistent resting-state, eyes-closed recording versus using as much epochs possible Using more epochs will inevitably lead to analysis of epochs of less quality in terms of artifacts, eyes-closed and awake state.

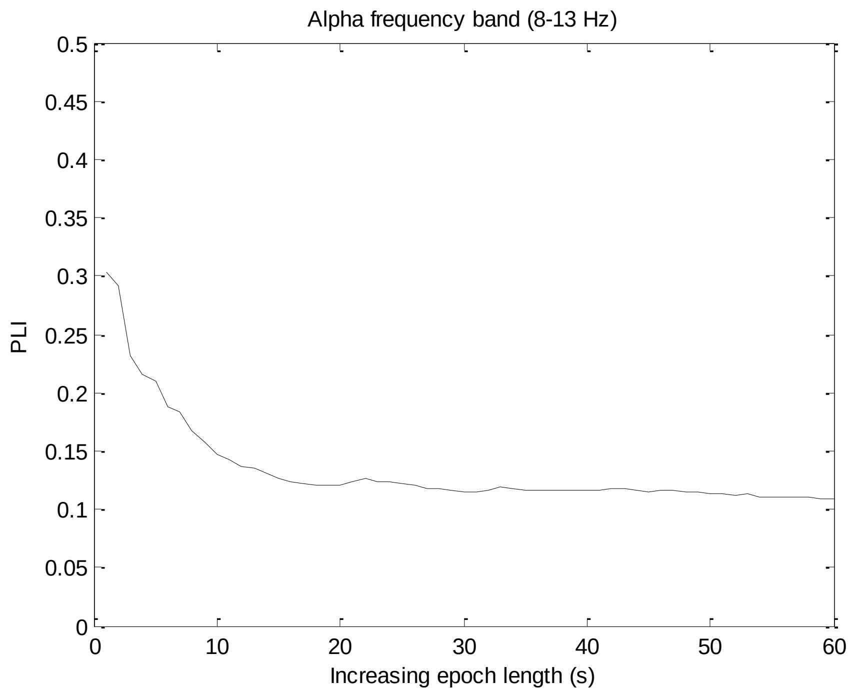

Figure 1: Effect of increasing epoch length on PLI for alpha frequency band.

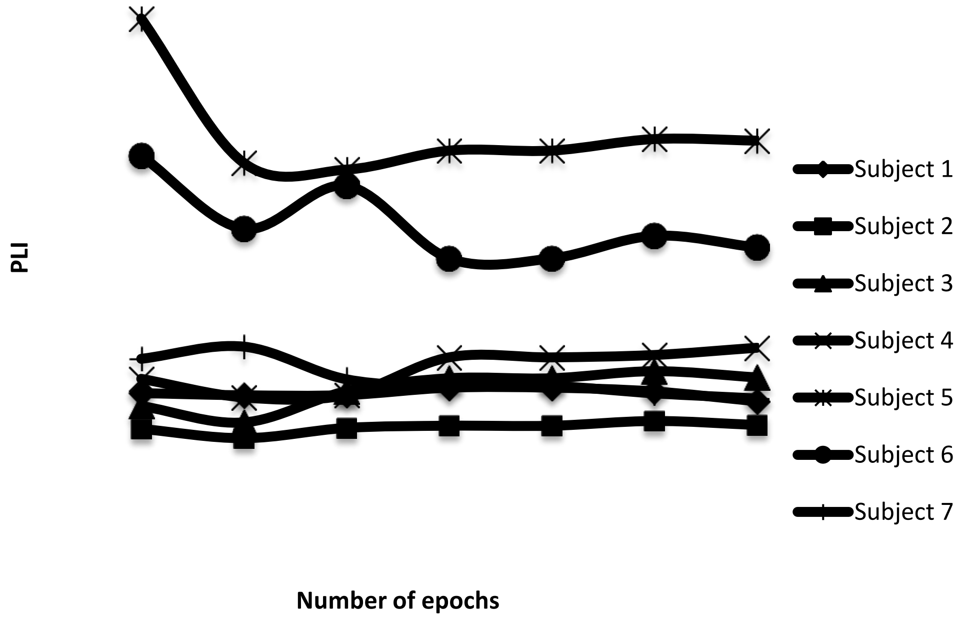

Figure 2: Effect of averaging increasing number of epochs in 7 non-delirious patients

Electroencephalography power spectra

For both delirious and non-delirious patients an average power spectrum is shown in figure 3. Delirious patients show increased slowing of background activity compared to non-delirious patients.

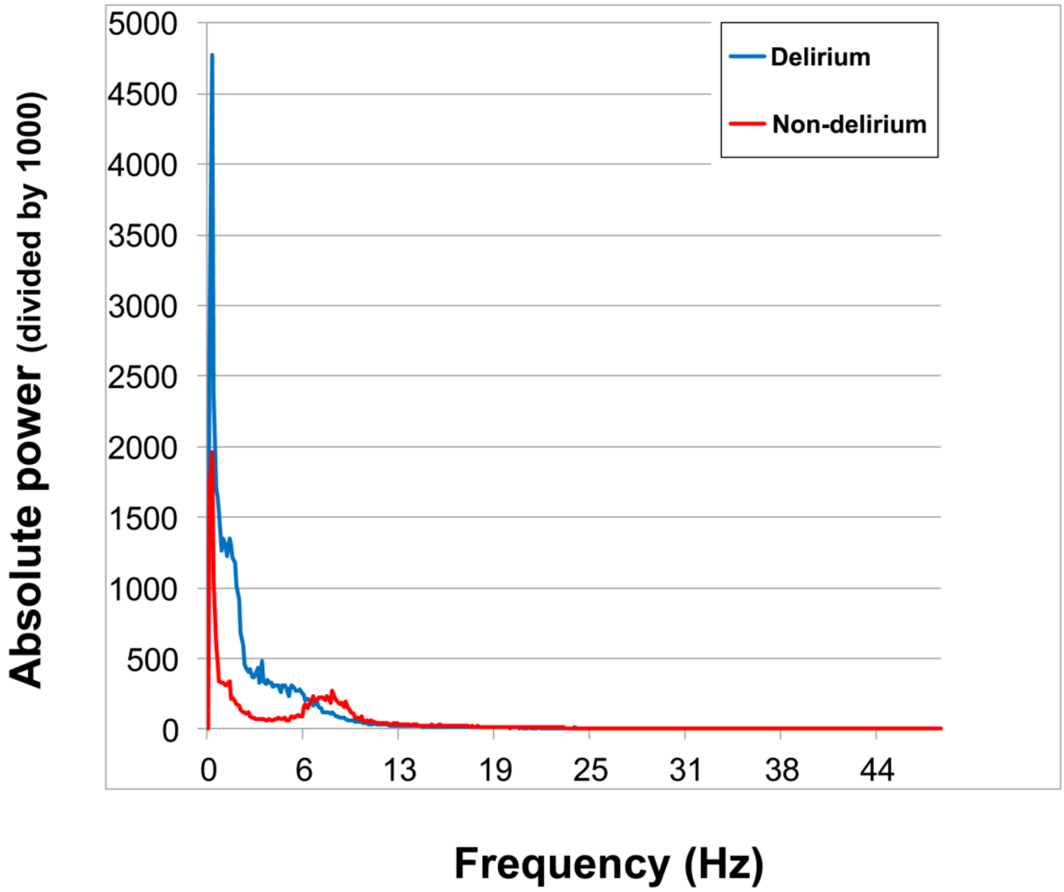

Figure 3: Average power spectrum for patients with delirium and without delirium.

References:

1. Watts DJ, Strogatz SH (1998): Collective dynamics of 'small-world' networks. *Nature*. 393:440-2.

2. Stam CJ, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, et al. (2009): Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. *Brain*. 132:213-24.