## REPRODUCIBILITY ASSESSMENT OF THE FIRST PRINCIPAL NETWORK CALCULATION: A TOOL FOR STUDYING ANATOMICAL BRAIN CONNECTIVITY

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Target audience: Scientists and physicians interested in methods to study brain connectivity through identification of relevant networks of cortico-

Introduction and purpose: Cortico-cortical connectivity refers to a pattern of structural, statistical or causal association between anatomically segregated areas of the grey matter (GM). At a macro-scale human brain is a "small-world network", so, neural connectivity is meaningfully characterised only in relevant subnetworks. The "Principal Networks" (PNs) analysis enables the calculation of highly-interconnected corticocortical patterns from measures of between-subject correlation of cortical thickness. In this work, 1) we evaluate the reproducibility of the main brain subnetwork, called "first PN"; 2) we assess the influence of individual subjects over the first PN calculation; 3) we evaluate the dependency of the outcome on the size of the data set.

| Lobe      | Cortical gyri included in the first PN        |
|-----------|---|
| Frontal   | Superior Frontal                              |
|           | Caudal/Rostral Middle Frontal                 |
|           | Pars Opercularis/Triangularis/Orbitalis**     |
|           | Medial/Lateral Orbitofrontal                  |
|           | Precentral                                    |
|           | Paracentral**                                 |
|           | Caudal*/ Rostral Anterior Cingulate           |
| Parietal  | Superior/Inferior Parietal                    |
|           | Supramarginal                                 |
|           | Postcentral                                   |
|           | Precuneus                                     |
|           | Posterior Cingulate                           |
| Temporal  | Superior/Middle/Inferior/Transverse* Temporal |
|           | Fusiform                                      |
|           | Parahippocampal**                             |
| Occipital | Lateral Occipital                             |
|           | Lingual                                       |
|           | Cuneus**                                      |

Table 1 Regions in the first PN. \*/\*\* detected only in the left/right hemisphere (LH/RH).

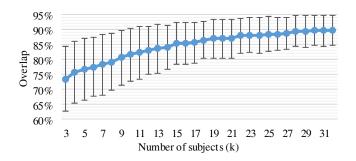


Figure 1 Proportion of vertices (mean and SD) common to the first PN calculated with the full data set and first PN recalculated 1000 times from random samples of k subjects (with replacement).

Methods: Subjects: 32 healthy controls (HC) (16F and 16M, mean age 39 ± 13 yrs); a previous study<sup>3</sup> implemented a scoring system and selected these subjects in which performance of FreeSurfer cortical reconstruction process was excellent. Image acquisition: Images were acquired on a 3T Philips Achieva MRI scanner. All subjects underwent a 3D sagittal T1-w FFE scan ( $1x1x1 \text{ mm}^3 \text{ voxel size}$ , TR/TE = 6.9/3.1 ms). Cortical thickness measurement: Each HC's cortical thickness was measured in 64 areas (FreeSurfer, Desikan-Killiany atlas). First PN calculation: The network was calculated<sup>2</sup> from the full cortical data set. Leave-one-out: The first PN was recalculated 32 times using a leave-one-out approach. To evaluate the influence of single subjects over the link between region i and j, two values were determined: 1) link frequency of appearance in the leave-one-out iterations; 2) difference between link weight determined from the full data set and mean link weight determined in the leave-one-out iterations. Dependency on the <u>number of subjects</u>: The first PN was recalculated from k HC randomly sampled from the original data set (with replacement), for each of 1000 replicates ( $1 \le n \le 1000$ ). The percentage of overlap between regions in the first PN (A) and regions in the network calculated from the resampled data set  $(\mathbf{A}_{k,n})$  was calculated as Overlap = dim(regions in **A**'s graph  $\cap$  regions in  $\mathbf{A}_{k,n}$ 's graph) \* 100 / dim(regions in **A**'s graph). Mean and standard deviation of the overlap were calculated for each k.

**Results:** Measured thickness values were within the physiological range (min:  $1.63 \pm 0.13$ 

mm, max:  $3.72 \pm 0.30$  mm). Table 1 shows the 48/64 cortical regions included in the first PN. This result overlapped by 73% with previously reported finding<sup>2</sup>. The overlap increased to 78% when only the highlyinterconnected regions of the network (weights  $\geq 0.5$ ) were considered. In the leave-one-out, interconnections detected from the full data set appeared with probability  $\geq 0.9$ . On the other hand, new interconnections were observed with probability < 0.2. Link weights determination in both the cases had variability  $\leq 0.05$ . The only exception was detected in a group of 4 cortical areas (precentral gyrus left and right, posterior cingulate gyrus right, postcentral gyrus left), which formed new interconnections with probability between 0.5 and 0.9, and had weights variable between 0.05 and 0.25. However, those areas had very low influence over the first PN calculated from the full data set. Finally, Figure 1 shows the mean overlap between the vertices in the first PN calculated from the full data set and the vertices in the first PN recalculated from a sample of size k of the original data set. The mean of the overlap monotonically increased with the number of subjects in the sample, whilst the standard deviation decreased.

Discussion and conclusion: We suggest the PNs technique to calculate the main influential subnetwork in the brain along with a leave-one-out approach to assess the influence of individual subjects over the final result. We underline that determination of the first PN is robust against the exclusion of a single subject, but dependent on the total number of subjects involved in the calculation. In fact, with reference to previously reported finding<sup>2</sup>, we showed that calculation of the first PN was reproducible using two different data sets, and that our outcome appeared to be stabilising considering 28 subjects (or more) out of 32. This fact, in particular, shows that it was meaningful to compare our first PN with the one previously published, for which 28 subjects were considered. Differences between our network and the reference may have been caused by different imaging protocols and MRI scanners or by FreeSurfer cortical reconstruction process itself, which has 0.5 mm accuracy, while thickness of the human cerebral cortex varies between 1 and 4.5 mm. However, good overlap of the networks obtained from two different data sets encourages future use and development of this technique.

References: 1) E. Bullmore et al. in Nat. Rev. Neurosci. 2012. 2) J. D. Clayden et al. in PLoS ONE 2013. 3) V. Lippolis et al. in Proc. Intl. Soc. Mag. Reson. Med. 2014.