Network-based R-statistics software for longitudinal designs: application in a fMRI brain scan database

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Many biological systems can be modeled as a set of interacting elements, allowing its characterization from a systems perspective using network science. However, this implies a quadratic increases in the variables to take into account and traditional multiple comparison corrections tend to be conservative. To this regard, Zalesky et al. (2010) proposed Network-Based Statistics (NBS), an algorithm that identifies clusters of edges within the network, and tests their family-wise error (FWE) rate generating a null distribution of cluster maximum size via permutation. Nevertheless, NBS relies on the general linear hypothesis testing (GLHT) which limits its application to longitudinal samples, in particular, to unbalanced samples. To overcome this limitation, we developed a publicly available software (https://cran.r-project.org/package=NBR), NBR (Network-Based R-statistics), that performs mixed-effects models (LME) in the NBS framework, allowing the exploration of unbalanced longitudinal samples.

We used NBS and NBR softwares to test GLHT and LME in a publicly available SWU-SLIM database. The dataset includes 333 participants (145 males; 17-28 years old) with two (n=212) or three (n=121) sessions each. All sessions include a resting-state fMRI brain scan and psychometric data. State anxiety scores and brain connectivity network matrices were used. GLHT and LME tested the edgewise brain-behavior relationship for balanced (424 matrices) and unbalanced (787 matrices) samples, respectively. Significance was assessed based on permutation tests including 1000 permutations restricted to within-subject swapping.

The LME approach found a significant subnetwork of brain regions, which includes the cingulum, the frontal, parietal and occipital cortex, and the cerebellum (pFWE = 0.001), while GLHT found no significant results (pFWE = 0.355).

We showed that NBR overpowers GLHT-NBS when dealing with unbalanced longitudinal samples. This is relevant given that missing data is common in longitudinal studies, and balanced testing could dramatically undermine statistical power. Besides, we were able to show a brain network related to anxiety symptoms that vary over time, which would not be identified using standard methods. Considering the growth of longitudinal studies in biological sciences, we anticipate this method being potentially useful in the field.

This research was supported by CONACyT 619683/330142.

Keywords: network based statistics, linear mixed-effects, brain networks