Rethinking correlation in the brain: a resting-state fMRI study on the progression of cognitive decline

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INTRODUCTION AND PURPOSE

Most resting-state functional connectivity studies are based on Pearson correlation coefficient (CC). Unfortunately, being a measure of covariance CC depends on the relative phase (i.e., delay) between two signals, and two identical oscillating signals can exhibit positive, negative or zero correlation if opportunely time-shifted. As such, the CC method may lead to false positive and/or false negative correlations. An interesting possibility could be calculating the "windowed" (i.e. instantaneous) CC, but even this approach fails when delays between putative responses are larger than window size. Here we computed the maximum positive and minimum negative values of the cross-correlation (XC) to obtain a delay-independent measure of the correlation between brain voxels and a seed region. We applied our analysis to resting-state fMRI data acquired on subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI) as well as normal control subjects (NCS).

METHODS

Subjects with AD (N=20), MCI (N=16) as well as NCS (N=16) participated in this study. Resting-state data were collected during a 7 min 20 sec scan in eye-closed condition (3 T Siemens Allegra; EPI sequence: TR/TE=2080/30 ms, resolution 3x3x2.5 mm^3). Functional images were analyzed (slice-timing, realign, normalization in MNI space and smoothing) using CONN toolbox. Before correlation analysis images were detrended, band-pass filtred (0.01-0.07 Hz) and corrected for physiological noise using CompCor [1]. To identify the default-mode network (DMN), we chose the posterior cingulate cortex (PCC) as the seed. Positive and negative cross-correlation (PosXC and NegXC, respectively) between the time-course of the seed (s) and that of each voxel (v) were determined by the following expressions:

$$PosXC = \left| \max \sum_k s(t_k) v(t_k + \tau) > 0 \right| \; ; \; NegXC = \left| \min \sum_k s(t_k) v(t_k + \tau) < 0 \right| .$$

RESULTS AND DISCUSSION

We first performed standard correlation analysis using CC for the three groups, which indicates that the progression of cognitive decline is accompanied by a decrease in spatial extension and amplitude of the DMN areas (Figures 1A and 2A), in agreement with previous work [2]. The figure also shows the results of our novel analysis based on XC. As long as PosXC is concerned (Figures 1B and 2B), we found a very high similarity between the DMN of NCS, MCI and AD groups ($p<0.001$; one-way ANOVA yields no significantly different voxels). This result indicates that the loss of correlation of the DMN is possibly the result of an increase in the delay of the propagation of oscillations (which CC cannot appreciate, but XC can) rather than a decrease in the strength of mutual responses. NegXC coexists in the PCC seed together with PosXC (Figure 2C), which implies that PCC is positively and negatively correlated with itself at the same time. Furthermore, NegXC seems to identify a network different from the DMN, including supramarginal gyrus, which belongs to the areas previously reported to be anticorrelated to the PCC [3]. Overall, these finding put forth the ambiguity in the interpretation of the sign of the CC as indicative of correlation/anticorrelation or simply variable delays.

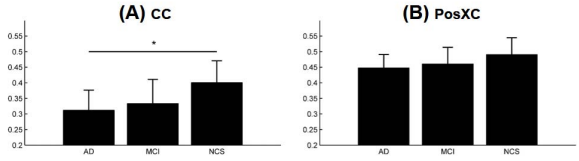

Figure 1. Mean CC and PosXC calculated for the AD, MCI and NCS groups in the DMN mask identified by correlation analysis. The decrease from NCS to AD is statistically significant for CC but not for PosXC (two-tailed t-test, $p<0.001$).

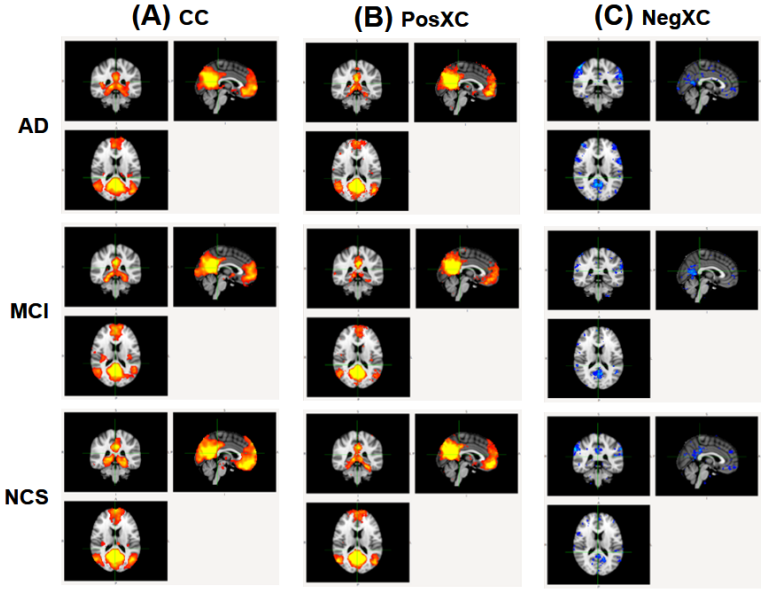

Figure 2. Resting-state correlation analysis for AD, MCI and NCS subjects. (A) Standard Pearson CC. (B) PosXC. (C) NegXC. Loss of correlation in the transition NCS>MCI>AD is not appreciated in the PosXC analysis. The NegXC analysis further shows that PCC exhibit both positive and negative correlation with itself.

CONCLUSION

We performed resting-state analysis by computing XC instead of CC, and further constraining XC for the "best" and "worst" correlation between two signals. Our results indicate that analysis of resting state fMRI data should be refined using methods similar to those presented in this work, which may help in interpreting how correlation should be linked to connectivity.

REFERENCES

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