Graph analysis of rs-fcMRI reveals modular changes associated with HIV and aging

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Target audience:

This abstract demonstrates applications of graph theory analysis techniques to resting-state functional MRI (rs-fcMRI) research and may be useful for investigators interested in characterizing the effects of aging or disease on brain function.

Purpose:

HIV infected (HIV+) individuals may experience age-related brain deficits earlier in life than uninfected (HIV-) individuals.[1] In this cross-sectional study, we applied graph-theory methods in the analysis of rs-fcMRI to understand the effects of HIV and aging.

Methods:

rs-fcMRI scans were collected in HIV+(N=46) and HIV- (N=59) participants on a 3T Siemens scanner. These groups were demographically similar with respect to age and education (p> 0.11), though there were more males in the HIV+ group (p<0.05). CD4+ white blood cell count was sampled in HIV+ individuals. rs-fcMRI time-series were sampled in 160 *a-priori* regions of interest (ROIs) for each subject. For each subject, a collection which contained graphs characterized by a range of edge counts was constructed by thresholding these 160 ROI cross-correlation matrices across a range of thresholds. Average degree (**k**) is a measure of graph size defined as [edge count/160 (# of ROIs)] (higher degree=more total graph connections). The clustering coefficient (**C**) (higher clustering= greater local connectedness), path length (**L**) (higher path length=lower global integration), and modularity (**Q**) (greater modularity= greater sub-network discreteness) were computed across a range of graph sizes for each subject. The effects of HIV, and the linear and quadratic effects of age on graph measures were assessed using an analysis of covariance (ANCOVA). We observed no interactions, so each of these factors was tested as an independent effect.

Results:

Higher **C**, lower **L**, and decreased **Q** were observed across a range of graph sizes for HIV+ (all p<.05) (Fig. 1). Only **Q** decreased independently with age and age^2 (all p<.05) (Fig.1b). **Q** in HIV+ individuals began to decline 10 years sooner than HIV- (Fig. 2a). Stronger immune system reactivity to HIV [computed as ([current CD4+]- [CD4+ nadir] was associated with lower **Q** (Fig 2b,p=0.04).

Discussion:

By investigating graph-structure measures, we present the first evidence that age-related rs-fcMRI changes may occur earlier in HIV+ individuals compared to healthy individuals. **L** and **C** were not been shown to change with respect to aging, suggesting that overall efficiency of information processing does not degrade with age, though a change in **Q** implies that this processing may be facilitated by an age-associated adaption in modular brain architecture.[2,3] We showed that **Q** decreases are possibly also explained by immune system reactivity. It may be that immune activation is an important underlying cause of brain deficits in HIV individuals and healthy aging.[4]

Conclusion:

Novel application of graph theoretical tools to resting-state functional connectivity reveals previously-unknown connections between the neuropathophysiology of HIV and aging.

References:

[1] J Neurovirol. 2012 Aug;18(4):291-302.

[2] PLoS Comput Biol. 2009 May;5(5):e1000381.

[3] Neuroimage. 2009 Feb 1;44(3):715-23.

[4] Aging Dis. 2012 Feb;3(1):16-33.

Fig. 1 rs-fcMRI graph measures as a function of graph size

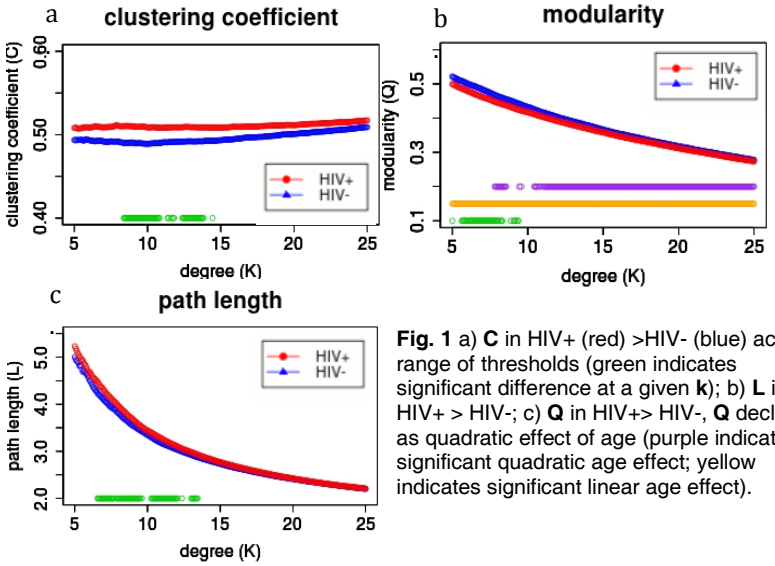

Fig. 1 a) **C** in HIV+ (red) >HIV- (blue) across range of thresholds (green indicates significant difference at a given **k**); b) **L** in HIV+ > HIV-; c) **Q** in HIV+> HIV-, **Q** declines as quadratic effect of age (purple indicates significant quadratic age effect; yellow indicates significant linear age effect).

Fig. 2 Graph measures correlate with age and immur immune system reactivity

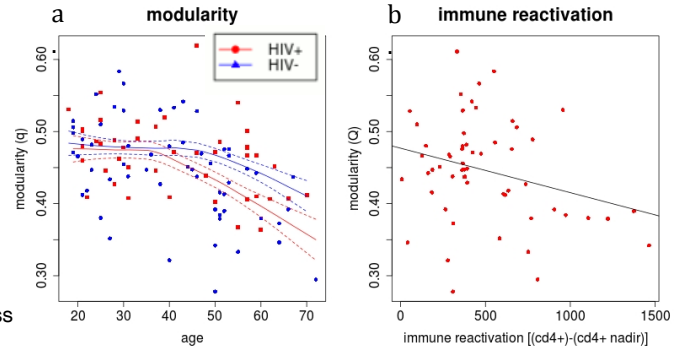

Fig. 2. a) for a representative graph size (**k**=7.8), modularity declines quadratically (p=10^5) with respect to age in HIV+(red) and HIV-(blue), but begins to do so at an earlier point in HIV+; b) for the same graph size, modularity declines inversely with strength of immune-system response (CD4+ - CD4 nadir) in HIV+. These effects hold across a range of thresholds.