Reliable modeling of resting-state emotional networks in major depressive disorder: Applicability of exploratory structural equation modeling to small sample sizes.

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Introduction: Structural equation modeling (SEM) is an increasingly popular technique for analyzing functional neuroimaging data. Unlike most connectivity analyses, SEM assesses the causal relationships among brain regions, thus allowing the testing of complex neuroanatomic hypotheses. Exploratory adaptations of SEM have been developed to describe neural interconnectivity independent of *a priori* models [1]. This work measures the reliability of exploratory SEM for modeling small sample sizes, a common limitation of functional MRI studies of clinical population. Specifically, we assessed the functional networks mediating emotion in healthy subjects and patients suffering from major depressive disorder.

Methods: Twenty-eight adults with no history of psychiatry or neurological disorder and five adults with major depressive disorder participated in accordance with Institutional Review Board policy. Participants underwent functional imaging in a 3T Siemens Trio scanner (Siemens AG). A z-SAGA pulse sequence [2] was used to acquire functional images of the temporal lobe (matrix=64x64, TR=2020ms, TE=30ms, FA=90°, 20 axial slices, FOV=220mm, slice thickness=4mm without gaps, voxel resolution 3.4 x 3.4 x 4 mm) while participants passively viewed a fixation point.

Data Processing: Functional preprocessing included slice timing correction, motion correction, linear drift removal, bandpass temporal filtering (0.008-0.08 Hz), and spatial smoothing. An SEM model of frontolimbic circuitry developed from PET neuroimaging data [3] served as the base model of emotional regulation. Mean BOLD timecourses were extracted for each of the model's 7 ROIs: 6mm radius spheres anatomically defined upon the MNI305 standardized brain. In-house Matlab programs (MathWorks, Natick, MA) employed LISREL (Scientific Software International) to iteratively test every possible subset of the base model. Models were excluded if PGFI<0.10 or if the 90% confidence interval of the least significant path included zero. Models were then ranked by Akaike Information criterion (AIC) and root-mean square error of approximation (RMSEA). Method reliability was assessed by splitting the sample into two halves and repeating this approach. A jackknife approach compared the best model against its rival models for every combination of the sample with removal of up to five subjects. Finally, exploratory SEM determined the optimal model for a sample of patients with depression.

Results and Discussion: The best model for all healthy participants shows a moderately negative (-0.18) influence of thalamus on anterior cingulate and reciprocal feedback loops between the anterior and subgenual cingulate and between the medial frontal and lateral prefrontal cortices. Ranking with Borda counts showed this model as superior to its rivals for removals of up to five subjects, thus suggesting resilience to outliers (Table 1). Repeating the exploratory approach produced comparable models for samples using one-half (Fig 1c, 1d) or one-fourth of the subjects (results not shown). Yet the depression sample yielded a starkly different model, with thalamus exerting a strongly negative (-0.96) influence on cingulate, less reciprocity for both cingulate and prefrontal regions, and an overwhelming interaction between anterior cingulate and medial prefrontal. These results demonstrate the feasibility of exploratory SEM for small sample sizes while denoting qualitative differences in emotion regulation for healthy controls subjects and patients with major depressive disorder.

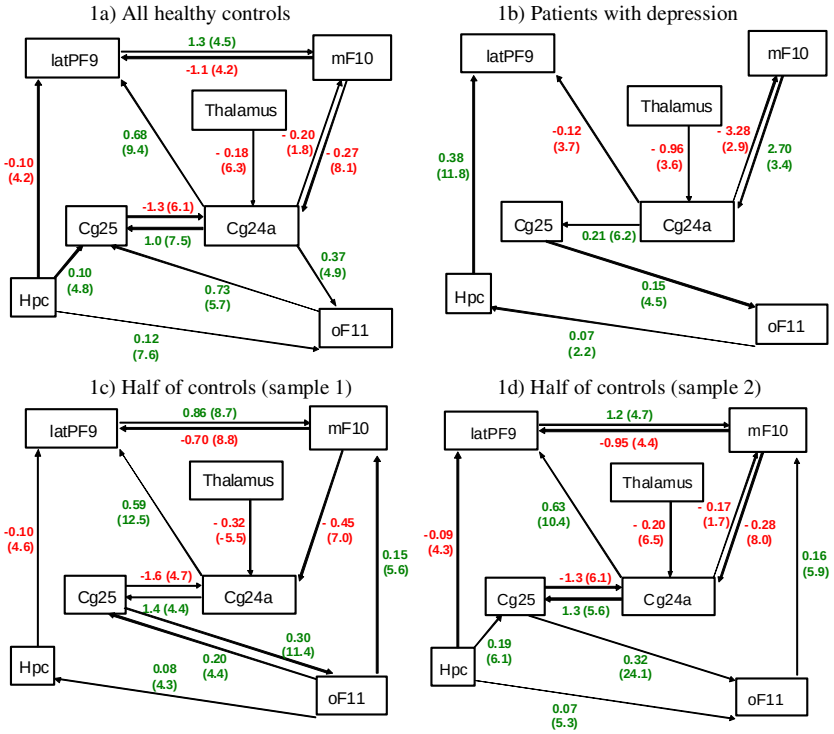

Figure 1: The best neuroanatomic models for emotional regulation as determined by exploratory SEM. 1a. 28 healthy subjects. 1b. 5 patients with major depressive disorder. 1c-d. the control group randomly split into two samples (n=14) each. Path loadings (green=positive, red=negative) are standardized with path significance (*t*-scores) in parentheses. Cg24a: mid-anterior cingulate; Cg25: subgenual cingulate; Hpc: hippocampus; latPF9: lateral prefrontal (BA9); mF10: medial prefrontal (BA10); oF11: orbitofrontal (BA11).

Subjects Removed	Number of Combinations	Mean Borda count by Model				
		A	B	C	D	E
1	28	4.61	3.00	3.82	2.39	1.18
2	378	4.12	3.26	3.65	2.47	1.51
3	3,276	3.91	3.47	3.45	2.51	1.66
4	20,475	3.96	3.64	3.20	2.50	1.71
5	98,280	4.02	3.75	3.05	2.48	1.69

Table 1. Mean Borda count by model. The five best models from the full sample were ranked (5=best, 1=worst) for every combination with removal of up to five subjects. Models were ranked by AIC and RMSEA. (Models were excluded if their PGFI<0.10 or if their least significant path's 95%confidence interval included 0.) Model rankings were averaged for all combinations with a given number of subjects removed. Model A was the best for all subjects (Figure 1a.)

References:
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