Wavelet analysis of the small-world human brain functional network in adolescents prenatally exposed to cocaine

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INTRODUCTION

Children and adolescents prenatally exposed to cocaine and other psychoactive drugs are at high risk not only for attention/arousal dysregulation and possible inefficiencies in some cognitive functions, but also for problems such as antisocial behavior, substance abuse, and emotional disorders [1]. The exposure effect on specific cognitive abilities and default mode activity has been studied. Because functional brain networks detected in resting-state fMRI have a small-world architecture that reflects a robust functional organization of the brain, here we examined whether this functional organization is disrupted in prenatal cocaine exposure (PCE) by employing a wavelet analysis method.

METHODS

Resting-state scans (15 PCE subjects, 13 healthy controls) were performed using a T_2^*-weighted EPI sequence on a Siemens 3T MRI scanner with the following parameters: 210 volumes, matrix = 64×64, 20 axial slices without gap, thickness = 4 mm, TR/TE = 2000 ms/30 ms, flip angle =90^o, FOV = 192×192 mm^2. Corresponding high resolution (256 × 256) 3D T_1-weighted anatomical images were also collected from each subject. The task-free data were preprocessed using SPM8 software: realigned to the first acquired image; corrected for slice timing, normalized to the MNI template, and smoothed using a 5 mm (FWHM) kernel. In the next step, we applied a wavelet correlation approach to the fMRI time-series to assess functional brain connections during resting state. For each subject, the preprocessed datasets were parcellated into 90 regions (45 for each cerebral hemisphere) using anatomical template defined by Tzourio-Mazoyer [2]. A maximum overlap discrete wavelet transform (MODWT) [3] was applied to generate cross-correlation matrices between all these segmented regions and separated the signal into four different frequency bands: (1) 0.23–0.45 Hz, (2) 0.11–0.23 Hz, (3) 0.06–0.11 Hz (4) 0.03–0.06 Hz. The frequency interval (3) and (4) are known to correspond to typical default mode bands and constituted our main bands of interest. The other two bands are usually related to non-neuronal physiological oscillations like heart beat and respiration, and thus did not be investigated in our study. A network analysis was performed based on the thresholded correlation matrices to evaluate the characteristics of the network and in particular its similarity to a small-world network. In a small-world network model, each region is considered as a "node" and various measures can be computed for each node, such as its clustering coefficient (C), mean characteristic path length (L), and degree (k). To diagnose small-world properties, the mean path length (L_{net}) and clustering coefficient (C_{net}) of the thresholded network were compared with the same metrics estimated in random networks configured with the same number of nodes, mean degree K_{ran}, and degree distribution as the network of interest. Typically, in a small-world network, we expect the ratio $\gamma = C_{net}/C_{ran} > 1$ and the $\lambda = L_{net}/L_{ran} \sim 1$. A scalar summary of small-worldness is therefore the ratio $\sigma = \gamma/\lambda > 1$ [4].

Scale		Mean degree (k)	Clustering coefficient C_{net}/C_{ran} (γ)	Mean path length L_{net}/L_{ran} (λ)
3 (0.06-0.11 Hz)	Control	14.11	0.65/0.16	2.41/1.93
	PCE	6.38	0.49/0.07	3.26/2.61
4 (0.03-0.06Hz)	Control	7.44	0.57/0.09	2.89/2.44
	PCE	24.80	0.70/0.28	2.28/1.72

Table 1. Wavelet scale dependency of functional connectivity and small-world parameters for an entire human brain network

RESULTS

Table 1 shows the results of wavelet scale dependency of functional connectivity and small-world parameters for an entire human brain network. In the high frequency interval 0.06 to 0.11 Hz (Scale 3), functional brain networks in controls showed small-world organization of brain activity with a small-world scalar of σ = 3.25, characterized by a high clustering coefficient 0.65 and a low mean characteristic path length 2.41. In contrast, PCE subjects' small-world scalar is σ = 5.60 with a lower clustering coefficient 0.49 and a higher mean characteristic path length 3.26 compared with controls. However, contrary results were observed in the low frequency interval 0.03 to 0.06 Hz (Scale 4). The small-world scalar of PCE subjects (σ = 1.89) is much smaller than that of controls (σ = 5.35). The significant scalar difference between the two groups in both scale 3 and 4 means consisted of distorted small world properties in PCE subjects. In a small-world network, nodes with higher number of surviving connections after thresholding of the correlation matrices has the higher degree, and is considered as one of the hubs for that network. After the statistical analysis, some major hubs of network were distinguished and abnormal functional connectivity was found among several brain regions in the PCE subjects' network. Compared with controls' network, some major "hubs" of the network, for example, the supplementary motor area (ROIs 19 and 20) in the low frequency interval 0.03 to 0.06 Hz (scale 4) showed irregular strong connectivity for PCE subjects, whereas the middle temporal gyrus (ROIs 85 and 86) and precuneus (ROIs 67 and 68) in scale 3 became less dominant in the network. Details are shown in Table 2.

Area (scale)		Degree	Clustering coefficient	Characteristic path length
MTG (3)	Control	41	0.41	1.75
	PCE	8	0.39	2.54
PCUN (3)	Control	27	0.47	1.90
	PCE	18	0.27	2.26
SMA (4)	Control	-1	1.00	1.00
	PCE	46	0.72	1.72

Table 2. Comparison of small-world characterization of three major hubs of the network between PCE subjects and controls

DISCUSSION

In this study, we investigated whether global functional brain organization is disrupted in PCE subjects. Graph metrics–clustering coefficient and characteristic path length—were used to measure and characterize global functional organization in the brain. The results show that dysfunctional integrations occur in the brains of PCE individuals during the resting state. Differences between sub-bands were also observed in the small-world analysis. Our findings highlight the need to consider different frequency bands and demonstrate the usefulness of wavelets in functional connectivity analysis of resting state fMRI.

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