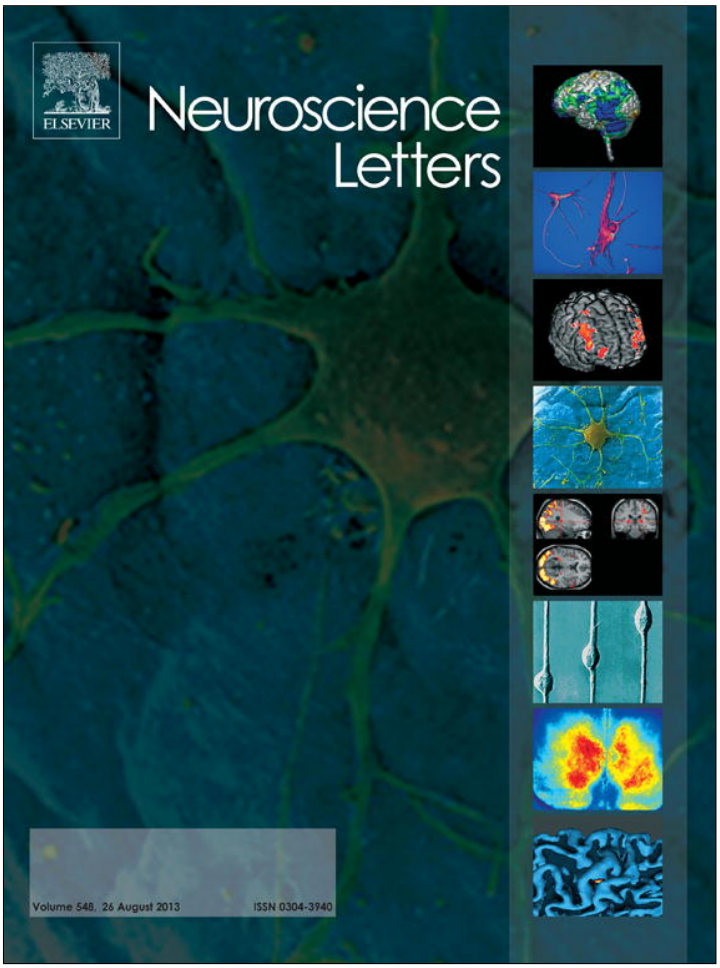

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Cocaine addiction related reproducible brain regions of abnormal default-mode network functional connectivity: A group ICA study with different model orders

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HIGHLIGHTS

- We explored cocaine addiction related DMN functional connectivity using group ICA.
- The reproducible abnormal regions were revealed by different model order settings.
- The hippocampus was found to be a reproducible abnormal brain region.

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ABSTRACT

Model order selection in group independent component analysis (ICA) has a significant effect on the obtained components. This study investigated the reproducible brain regions of abnormal default-mode network (DMN) functional connectivity related with cocaine addiction through different model order settings in group ICA. Resting-state fMRI data from 24 cocaine addicts and 24 healthy controls were temporally concatenated and processed by group ICA using model orders of 10, 20, 30, 40, and 50, respectively. For each model order, the group ICA approach was repeated 100 times using the ICASSO toolbox and after clustering the obtained components, centrotype-based anterior and posterior DMN components were selected for further analysis. Individual DMN components were obtained through back-reconstruction and converted to *z*-score maps. A whole brain mixed effects factorial ANOVA was performed to explore the differences in resting-state DMN functional connectivity between cocaine addicts and healthy controls. The hippocampus, which showed decreased functional connectivity in cocaine addicts for all the tested model orders, might be considered as a reproducible abnormal region in DMN associated with cocaine addiction. This finding suggests that using group ICA to examine the functional connectivity of the hippocampus in the resting-state DMN may provide an additional insight potentially relevant for cocaine-related diagnoses and treatments.

1. Introduction

In drug addiction studies, resting-state fMRI experiment, in which participants are scanned without performing any tasks, has been widely adopted to explore abnormal brain mechanisms [9,13,19,21,24]. Resting-state functional connectivity, defined as the temporal correlation of blood-oxygenation-level-dependent (BOLD) signals in different regions of the "resting" brain, is a kind of measurement of the brain's functional organization [10].

The default-mode network (DMN) [11], including a set of brain regions that exhibits increased activity during the resting-state, is an acknowledged large-scale brain network in functional connectivity analyses. It is associated with memory, attention and decision-making [3,7]. Since the brain circuits of memory and self-monitoring are believed to be impaired in drug addicts, the DMN has attracted specific attention in drug addiction studies [9,18,21].

The DMN can be identified using a blind source separation algorithm called independent component analysis (ICA) [4]. A more commonly adopted ICA approach is the group ICA method, which is used for making group inferences from fMRI data of multiple subjects [5,8]. Theoretically, the number of calculated independent components, which is called model order, can be freely selected in ICA. However, researchers have found that model order selection in group ICA has a significant effect on the characteristics of the obtained components in functional connectivity analyses [1]. Lower model orders provide a general picture of large-scale brain networks, whereas detecting more specific and detailed components requires higher model orders (60–80), but over-high model orders (>100) show a decrease in ICA reproducibility.

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Up to now, there is still a lack of studies that investigate the cocaine (or the other drugs) addiction related abnormal brain regions in the resting-state DMN using the group ICA method with different model order settings. We hypothesized that for cocaine addicts, some brain regions would show the same abnormal functional connectivity responses with no regard to different model order settings in group ICA. Finding these regions may provide a more precise knowledge of the cocaine-related brain damage. This study therefore aims to identify such reproducible abnormal brain regions in the resting-state DMN.

2. Materials and methods

Twenty-nine right-handed cocaine addicts (CA, meeting the DSM-IV criteria for cocaine dependence within the past twelve months but currently abstaining for more than two weeks) and twenty-four right-handed healthy controls (HC) were recruited and scanned at New York University (NYU) using a Siemens Allegra 3T scanner. For each participant, at least one six-minute resting-state scan (multi-slice echo planar imaging (EPI), TR = 2000 ms, TE = 15 ms, flip angle = 90°, 180 volumes, 33 slices, voxel size = $3 \times 3 \times 4\,mm^3$) and a T_1-weighted anatomical image (MPRAGE, TR = 2530 ms, TE = 3.25 ms, TI = 1100 ms, flip angle = 7°, 128 slices, voxel size = $1 \times 1.3 \times 1.3\,mm^3$) were acquired. For most participants, a second resting-state session was also acquired. All CA and 11 HC were scanned with eyes open. The remaining 13 HC were scanned with eyes open in one session and eyes closed in the other session. The raw dataset was shared for our secondary analysis under the approval of Institutional Review Boards of Korea University and NYU School of Medicine. Full details of the sample characteristics and data collection are in [16].

The raw EPI data were preprocessed using SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm). The first five volumes were discarded to eliminate non-equilibrium effects of magnetization. Slice timing differences were corrected for each volume. Functional volumes were realigned to the first volume for head motion correction. A mean image created from the realigned volumes was coregistered with the subject's individual T_1-weighted anatomical image. The functional data were then normalized into standard MNI space with $3 \times 3 \times 3\,mm^3$ voxels and smoothed with an isotropic Gaussian kernel (full width at half-maximum (FWHM) = 8 mm). Considering the possible impacts of head motion and scanning condition on resting-state functional connectivity measures [20,23], we selected one session data of 24 CA and 24 HC in this study to satisfy two requirements: (1) subjects in the selected sessions were scanned with eyes open; and (2) there are no significant group differences in the head motion testing. The two groups were also matched on age, sex, race and education. Demographic details of the selected subjects are contained in Supplements (Table S1).

The selected preprocessed data were analyzed using the group ICA method [8] with the aid of the GIFT toolbox (http://icatb.sourceforge.net). Individual data were temporally concatenated (data of CA followed by data of HC) and processed via a dimension reduction procedure through two stages of principal component analysis. The final dataset was then decomposed by ICA (Infomax algorithm [6]) with model orders of 10, 20, 30, 40, and 50, respectively. For each model order, the ICA approach was repeated 100 times with randomly initialized decomposition matrices and the same convergence threshold (1×10^{-7}) using ICASSO [14] in the GIFT toolbox. After clustering the obtained components according to their mutual similarities, centrotype-based estimates were considered as the stable independent components for the current model order. Among these, two main components of the DMN, that is, the anterior DMN (aDMN, containing the anterior cingulate cortex as well as the medial and superior frontal areas) and the posterior DMN (pDMN, containing the posterior cingulate cortex along with the precuneus and inferior parietal lobe) [22], were selected by spatial sorting using two predefined automated anatomical labeling (AAL) templates. The individual aDMN and pDMN components were obtained through a back reconstruction process and then converted to *z*-score maps. Finally, a whole-brain mixed effects factorial ANOVA including the between-subjects factor of group and the within-subjects factor of model order was performed to investigate the "group" and "model" main effects as well as the "group × model" interaction using the *F*-tests. It also facilitated the examination of the group differences within each model order using the *T*-tests.

3. Results

Fig. 1 exhibits the group-level resting-state aDMN and pDMN patterns, which were revealed using voxel-wise one-sample *t*-tests for the two groups according to different model orders (FWE $P < 0.05$). It shows that from model order 30, the pDMN remained similar, whereas the areas of significant activation in aDMN continued to decrease along with the increase of model orders, which may indicate that the pDMN is more robust than the aDMN [17].

The main effect of "group" was located in the left precentral gyrus, hippocampus and the left middle frontal gyrus (Fig. 2 and Table 1, FWE $P < 0.05$). Figures and tables revealing the main effect of "model", as well as the "group × model" interaction, are contained in Supplements. In order to identify the reproducible abnormal regions, we examined the differences between the two groups within each model order. Among the detected significant regions (see Table S4 in Supplements), the hippocampus, which showed decreased functional connectivity in cocaine addicts for all the tested model orders, appeared to be a reproducible abnormal region in DMN (Fig. 3 and Table 2, uncorrected $P < 0.005$). More specifically, the left hippocampus had the reduced connectivity in pDMN of the addicts for model orders 10, 40, and 50; and the right hippocampus in aDMN for model order 20 as well as in pDMN for model order 30, showed the decreased connectivity in addicts.

4. Discussion

This study investigated the discrepant regions in DMN functional connectivity between CA and HC using the group ICA method with different model order settings. The hippocampus, which showed decreased functional connectivity in cocaine addicts, was found to be a reproducible abnormal region in the resting-state DMN.

The model orders tested in our experiment were between 10 and 50, since the common model order settings in functional connectivity analyses of large-scale brain networks are within this range (e.g., [9,12,15,18]). In our experiment, from model order 60, the DMN was decomposed into more than two parts (i.e., aDMN and pDMN). The separated DMN parts were highly correlated across their time courses. Some recent studies utilize the cross-correlation among component time courses to assess how components in a high model order ICA might combine in a low model order ICA [2]. In addition, it is worth noting that other combinations of model order settings are also available. For example, we additionally tested the model order settings of 15, 25, 35, 45 and 55. The result was repeatable that the hippocampus was still revealed as a reproducible abnormal region with the reduced DMN functional connectivity in cocaine addicts.

It has been increasingly recognized that the hippocampus performs an important role in drug addiction. It was reported that the network-specific functional connectivity strength was reduced in cocaine addicts within a distinct system circuit between hippocampus and dorsal medial prefrontal cortex [13]. In our study, the

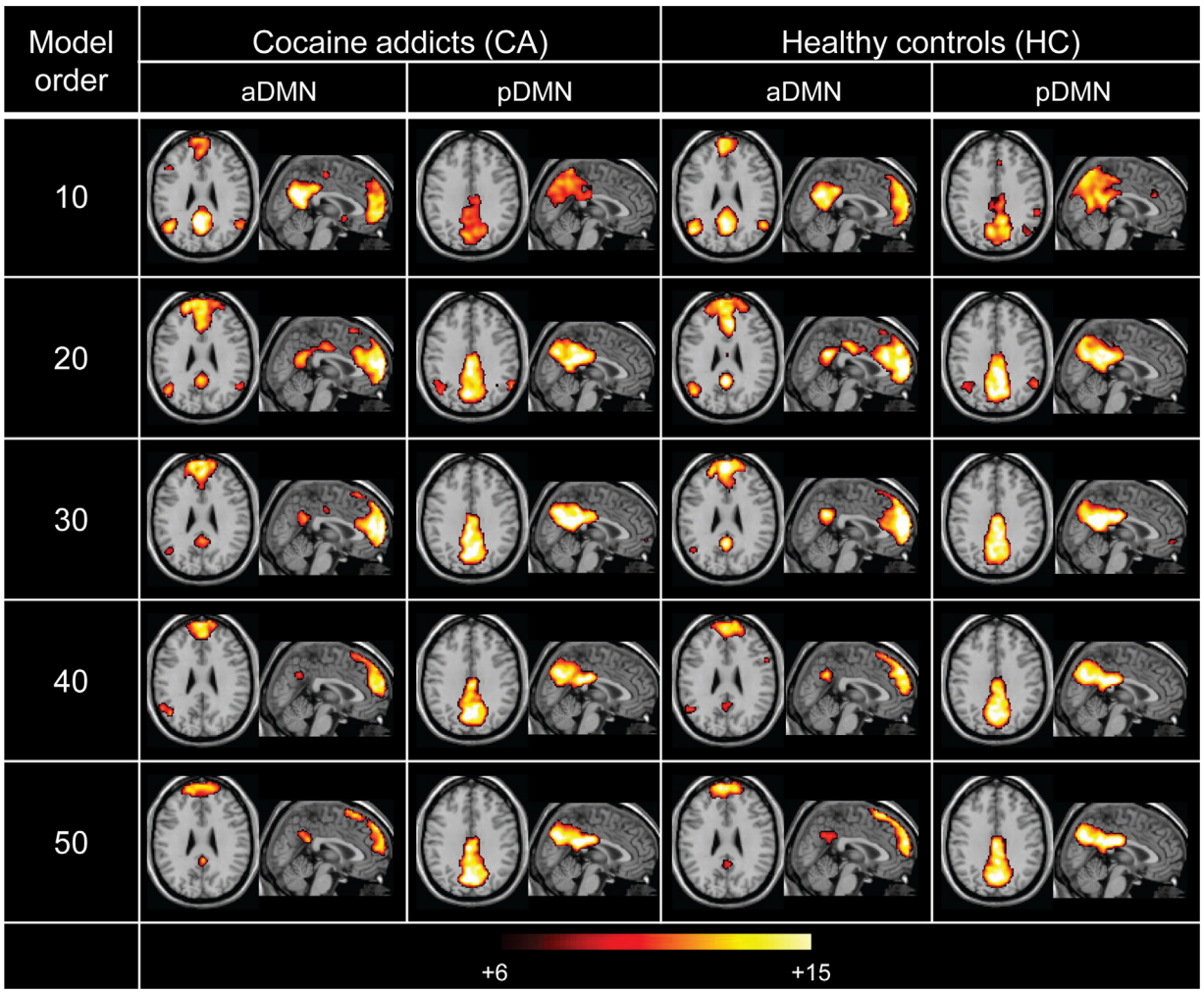

Fig. 1. The group-level aDMN and pDMN patterns corresponding to the tested model orders (FWE $P < 0.05$).

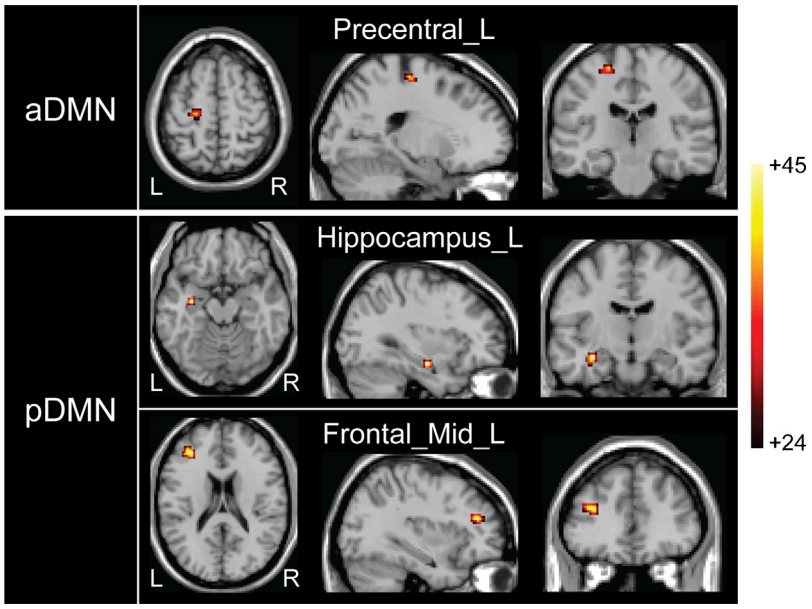

Fig. 2. The main effect of "group" was located in the left precentral gyrus, hippocampus and the left middle frontal gyrus (FWE $P < 0.05$).

Table 1
The main effect of "group" revealed using ANOVA (FWE $P < 0.05$).

	Anatomical location (AAL)	NmVx	MNI coordinate	Peak *F*-value
aDMN	Precentral_L	10	(−21, −22, 61)	35.59
pDMN	Hippocampus_L	10	(−33, −13, −17)	42.71
	Frontal_Mid_L	23	(−36, 38, 19)	42.69

The cluster information is described using the cluster size by the number of voxels, peak voxel's AAL location, MNI coordinate and its *F*-value.

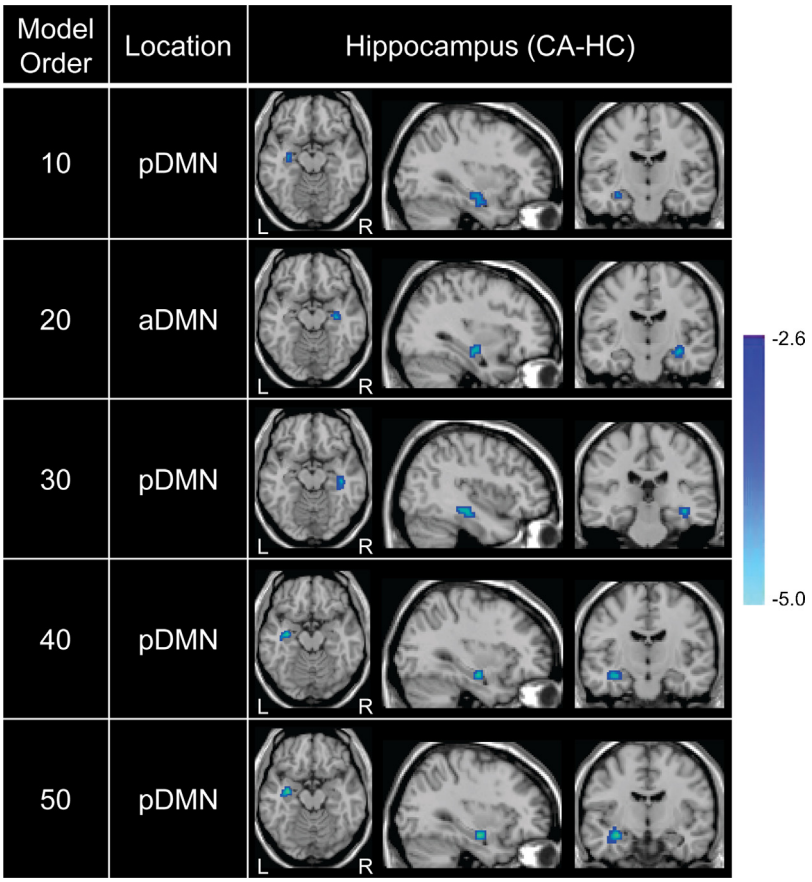

Fig. 3. Abnormal functional connectivity of the hippocampus corresponding to different model orders (uncorrected $P < 0.005$).

decreased resting-state functional connectivity in hippocampus implies the damage of salience identifying and memory processing in terms of cocaine addiction. In another study of heroin addiction [18], abnormal resting-state DMN was examined by means of applying ICA algorithm with a specific model order on each individual subject. Enhanced functional connectivity was discovered in hippocampus of heroin users. This discordant response in hippocampus may indicate that the neurobiological consequences of heroin addiction and cocaine addiction are different. Moreover, our results show a change in laterality of the hippocampus (i.e., the reduced hippocampal connectivity in cocaine addicts was left-lateralized for model orders 10, 40, and 50; yet it was right-lateralized for model orders 20 and 30), which may cause the statement of "reproducibility" to be questioned. However, since no study has pointed out that the left and right hippocampus perform different functions in terms of drug addiction, in this study we consider these two parts as a whole functional region rather than two anatomical parts, and thus draw the conclusion of the reproducibility of the abnormal hippocampus in cocaine addicts.

The results of the *T*-tests between CA and HC were inconsistent across analyses with different model orders. Referring to the result of the "model" effect (Table S2 and Fig. S1 in Supplements), some of the inconsistencies could be regarded as spurious group

Table 2
The hippocampus showed decreased functional connectivity in cocaine addicts for all the tested model orders (uncorrected $P < 0.005$).

Region	Model order	Location	NmVx	MNI coordinate	Peak *t* (CA-HC)
Hippocampus	10	pDMN	19	(−33, −16, −14)	−3.01
	20	aDMN	21	(33, −16, −14)	−3.70
	30	pDMN	27	(39, −25, −14)	−3.79
	40	pDMN	28	(−33, −13, −17)	−4.06
	50	pDMN	38	(−33, −10, −17)	−4.55

The hippocampus cluster information is described using the cluster size by the number of voxels, peak voxel's MNI coordinate and the peak *t*-value.

differences. However, it was reasonable to consider other inconsistencies as smaller effects of the group difference, which were only detectable with an optimal model order. Since this study aims to find the reproducible abnormality that could manifest across all analyses, the issue of making an appropriate standard to judge these inconsistencies would be remained for our future study.

Smoking may have a potential influence on the measured resting-state functional connectivity [9,21]. As the smoking status of some participants was not clear, it was hard to decide if the CA and HC groups were matched on smoking status. This might be a potential limitation of the present study.

5. Conclusion

In this study, we investigated cocaine addiction related abnormal brain regions of the resting-state DMN functional connectivity using the group ICA method with different model orders. We found that the hippocampus might be a reproducible abnormal region which showed decreased functional connectivity in cocaine addicts for all the tested model orders. It suggests that using group ICA to examine the functional connectivity of the hippocampus in the resting-state DMN may provide an additional insight potentially relevant for cocaine-related diagnoses and treatments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.05.029.

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