Time-related neural activity during cue-induced heroin craving: a preliminary study

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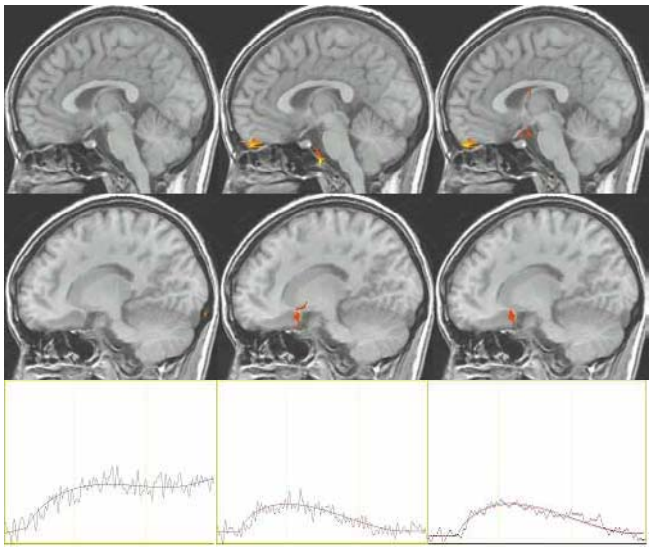
Introduction: Cue exposure has been repeatedly used to study craving (1-4). The neural circuits related to cue exposure and craving may be accessible with functional neuroimaging techniques. fMRI and PET can be used to identify specific brain regions that become active with presentation of drug-use cues. The functional connectivity of brain regions activated during opiate craving has been investigated by PET (4). Due to its high spatial and temporal resolution, fMRI can be used to explore more detailed information about craving. Here we did a preliminary study on the time relationship of the active brain regions during cue-induced heroin craving.

Methods: *Subjects:* Four right-handed male subjects with a history of heroin dependence were recruited from the drug treatment agency. The heroin subjects had about one month of heroin abstinence before the fMRI experiment. None of they had a history of abuse of other drugs or mental diseases. Age-matched healthy male volunteers were also recruited. *Protocol:* Upon arrival at the MRI scanner room, a consent form was obtained from each subject. Two video films were employed and each was consisted of three parts: 3-minute black screen, 4-minute movie (nature or heroin) and 5-minute black screen. The nature film was composed of some scenes in the field and park. The heroin film was composed of some scenes about a group of abusers taking heroin. The fMRI scans were conducted at a GE 1.5T Signa LX scanner with a birdcage RF head coil. Functional images were obtained by using single-shot EPI sequence (TE=30ms, TR=2000ms, Field of view=24×24cm, 64×64matrix, slice thickness=5mm, 25 sagittal slices). After the scan, subjects completed a form for their feelings about the movies. The heroin subjects expressed a desire of taking heroin while watching the heroin film. *Data analyses:* Data processing was conducted with AFNI version 2.56d. Motion correction was first applied to the functional data. All selected subjects for analysis had translational motion within 3mm of base value in any direction, rotation of less than 3^o from base position, and correctable by volume registration. Then spatial filter was applied. The last 10 minutes of each functional scan run were used for analysis. The first two minutes were excluded since we thought the stable state of the subjects could be reached after this time and it was better to use the third minute as the baseline. The beta distribution was chosen for non-linear regression. The onset time of the beta model was constrained to occur after the first 30s and other parameters were loosely constrained to obtain a best fitting. The time series data was filtered to exclude frequencies above 0.1Hz for a better fitting (3). The activity of each voxel was expressed by the percentage of the area under the curve relative to the baseline area. The time for the maximum absolute value of the signal for each voxel was also calculated for the study of the time relationship. The activity map and the t-max map were transformed to Talairach space. Two-sample t test was used for comparison between heroin and healthy subjects watching the heroin film. Paired t test was used for comparison between the heroin subjects watching the heroin and the nature film. A cluster with each voxel threshold at $P<0.05$ was used for the results, minimum cluster size=100 μL.

Results: Fig. 1 showed the result of the heroin subjects watching the heroin movie compared to the healthy subjects. Combined with the results obtained by comparing the heroin subjects watching the heroin and nature films, the neural activity related to craving appeared time-dependent after the movie onset. Table 1 showed brain regions most significantly activated during different time from the same result. The regions in the limbic system such as nucleus accumbens, thalamus, and parahippocampal gyrus were most significantly activated after 1.5 minutes after the onset of the heroin movie. There was also significant activity in Brodmann area 11 during this time. The anterior nucleus and lentiform nucleus had strongest activity during 2.5-4 minutes while the parahippocampal gyrus and the medial frontal gyrus had the strongest activity during 3-4.5 minutes, which indicated a time relationship between these areas.



2-3.5 minutes 2.5-4 minutes 3-4.5minutes

Fig. 1. Two rows of brain images represent the two-sample t test result. The active areas are brain regions related to craving and have most significant activity during three different time in two different sagittal positions (left 2mm and right 13mm). Third row represents the voxel time courses chosen from three different regions: right middle temporal gyrus, left rectal gyrus and left superior frontal gyrus of one heroin subject. Red lines are beta models fitting to the data

Discussion: This preliminary study shows the possibility of studying the time relationship of the neural activity related to craving. This method can provide some more detailed information about the brain circuitry important in drug addiction.

Table 1. Major brain regions related to heroin craving during three different time courses by two-sample t test.

	Mean	Voxel #	SD	L. Rectal Gyrus	2.159	77	0.409
2-3.5 minutes				L. Superior Frontal Gyrus	1.250	186	0.101
R. Middle Temporal Gyrus	0.748	19	0.020	R. Middle Temporal Gyrus	0.607	35	0.022
2.5-4 minutes				3-4.5 minutes			
R. Parahippocampal Gyrus	0.494	19	0.020	R. Parahippocampal Gyrus	0.353	35	0.022
R. Nucleus Accumbens	0.177	23	0.068	R. Nucleus Accumbens	0.190	16	0.063
L. Medial Frontal Gyrus	0.435	36	0.017	L. Medial Frontal Gyrus	0.477	45	0.020
R. Anterior Nucleus	0.121	12	0.025	L. Rectal Gyrus	2.134	78	0.408
R. Lentiform Nucleus	0.162	88	0.038	L. Superior Frontal Gyrus	1.227	166	0.097

Mean represents the mean activity of this region. SD represents standard deviation, R: right hemisphere, L: left hemisphere.

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