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# Noxious heat induces fMRI activation in two anatomically distinct clusters within the nucleus accumbens

I. Aharon [a,1], L. Becerraa [c,1], C.F. Chabris [b], D. Borsooka [c,*]

[a] *Athinoula Martinos NMR Center for Medical Imaging, Massachusetts General Hospital, MA, USA*
[b] *Department of Psychology, Harvard University, Cambridge, MA 02138, USA*
[c] *P.A.I.N. Group, Brain Imaging Center, McLean Hospital, Belmont, MA 02478-9106, USA*

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**Abstract**

Using functional magnetic resonance imaging (fMRI) we found that a noxious thermal stimulus (46 °C) to the hand activates the nucleus accumbens (NAc) in humans, while a non-noxious warm stimulus (41 °C) does not. Following the noxious stimulus, two distinct foci of decreased activation were observed showing distinct time course profiles. One focus was anterior, superior, and lateral and the second that was more posterior, inferior, and medial. The anatomical segregation may correlate with the functional components of the NAc, i.e., shell and core. The results support heterogeneity of function within the NAc and have implications for the understanding the contribution of NAc function to processing of pain and analgesia.


*Keywords:* Nucleus accumbens; Pain; Aversion; fMRI

Electrophysiological, pharmacological and imaging studies point to the nucleus accumbens (NAc) as one CNS site that may mediate functions involved in both reward and aversion [5,15]. One hypothesis to explain how the NAc could serve this putative dual role is that neurons within the structure can be separated into distinct functional groups, each playing a different role in hedonic responses or motivated behavior [10]. Based upon histological characteristics in animals and humans, the NAc is divided into at least two major sub-territories, the core and the shell, distinguished by unique input–output patterns [14,18]. Differential function within each component of the NAc, while reported in animal studies [13,27] has not been reported in humans.

Functional activity in the human accumbens has been reported using imaging studies following rewarding [1,19] and aversive stimuli [5,11]. Differential function within each component of the NAc, while reported in animal studies [13,17,27] has not been reported in humans. Some animal work suggests that the overall function is that the shell is involved in motivational valence and motivational value in the core [3].

Here, we report in healthy human subjects, a noxious thermal stimulus (46 °C) that produces a decrease signal in the NAc could be separated into two clusters. Each cluster may represent functional components of the core and shell.

Six healthy volunteers (male, right-handed, 31.0 ± 3.7 mean ± S.E.M.) participated in the study, which was approved by the Massachusetts General Hospital committee for experimentation on human subjects. Prior to scanning, subjects were instructed on how to rate their pain intensity during the scan using a standard 11-point Likerts visual analogue scale (VAS), where one end represents no pain and the other represents maximal pain imaginable.

A Peltier thermode system [6] was used to deliver two (a non-painful warm (41 °C) stimulus and a painful hot (46 °C) stimulus) square-wave stimuli (stimulus duration = 29 s; interstimulus interval = 36 s; ramp rate 4°/s; baseline temperature = 35 °C, Fig. 1A) to the back of the left hand (using an elastic strap) within the magnet. The 41 °C stimulus was administered prior to the 46 °C stimulus ash shown in Fig. 1A. Each thermal stimulus was presented four times in the run.

Scanning was performed in a 1.5 T scanner (GE Medical systems, Milwaukee, WI, USA). For the anatomical scan, a conventional 3D sagittal T1-weighted, SPGR sequence was acquired (60 slices 2.8 mm thick, 1.2 mm resolution in-plane)

* Corresponding author: Tel.: +1 617 855 31 95; fax: +1 617 855 3772.
*E-mail address:* dborsook@mclean.harvard.edu (D. Borsooka).
[1] Both the authors contributed equally.

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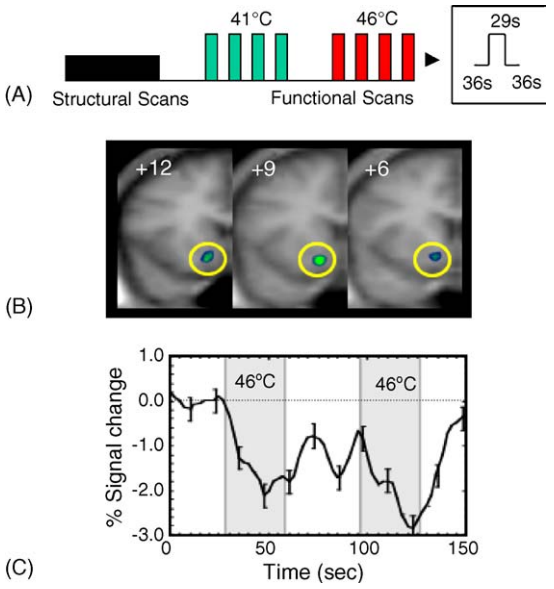


Fig. 1. Experimental paradigm and fMRI activation in the NAc following noxious heat: (A) the experimental paradigm indicating the four stimuli for 41 and 46 °C; (B) statistical maps of decrease activation from the 46 °C stimulus in three slices through the region of the brain containing the NAc; and (C) average decrease signal (±S.E.M.) change following 46 °C stimulus. A voxel-by-voxel analysis was done using a Bonferroni correction of $4 \times 10^{-4}$ for statistical significance. Prior to generating statistical maps data was motion-corrected and inspected for gross motion larger than 2 mm. Statistical maps were generated for each individual using a *t*-statistics. Individual probability maps were multiplied and the resulting map used for inspection of activated areas. Percent signal changes were calculated using the baseline time points as 100% reference. Each time course was time adjusted before averaging. The gray bars indicate the time when the thermal stimulus was applied.

for atlas registration and for prescription of functional scans. Twenty contiguous slices (7 mm thick) were prescribed perpendicular to the AC–PC line extending from the anterior frontal pole through the cerebellum. A high-resolution T1-weighted echo planar sequence was acquired for preliminary analysis of statistical maps. For the functional studies, an asymmetric spin echo echo planar sequence was used (TR/TE = 2.5 s/70 ms) on the 20 prescribed slices, 100 images per slice were acquired for each functional scan.

Two analyses were performed on the data: (a) a standard analysis and (b) a cluster analysis. The standard analysis was used to obtain statistical maps of activation and average time courses for activated structures. Given that registration to an atlas does not always accurately map brain structures, a cluster approach was applied to the original data.

Data was preprocessed as described previously [5,6]. Briefly, functional data was motion corrected, globally normalized, and transformed into Talairach space. Functional data was averaged in time across subjects. Averaged data was smoothed using a Gaussian filter with an isotropic kernel of 5 mm. Voxel-by-voxel statistical analysis (*t*-test) was performed.

To probe for possible heterogeneity of activation time courses within the NAc we used an exploratory procedure based on cluster analysis. First, we manually selected all of the voxels comprising the NAc in each hemisphere of each subject (i.e., 12 clusters for the six subjects), using a segmentation method that has previously been reported [7] for obtaining the time course of the blood oxygen level dependent (BOLD) signal from each of these voxels. The signal time-course from each voxel was normalized to begin at a value of 1000, and any linear trend was removed. We used the SYSTAT software package (SPSS, Richmond, CA) to conduct separate hierarchical cluster analyses of the Pearson correlation matrices for the left and right NAc voxel sets for each individual subject (using the complete linkage method). This was necessary because each subject's NAc morphology is different, thus there is no simple way to average their voxel sets, and there are too few voxels involved to make an anatomical warping procedure worthwhile.

VAS scores of pain intensity reported by subjects during the experiment averaged $3.1 \pm 1.1$ for the 41 °C stimuli and increased significantly to $8.2 \pm 1.6$ for the 46 °C stimuli ($p < 0.01$; *t*-test).

Using voxel-by-voxel statistical analysis (*t*-test), we observed deactivation or a decrease in signal ($2.1 \pm 0.7\%$) bilaterally in the NAc following noxious (46 °C; $p < 1.5 \times 10^{-7}$) but not non-noxious (41 °C; $p > 0.05$) thermal stimuli (Fig. 1 B). When the thermal stimulus is terminated the signal begins to increase towards baseline, decreasing again at the onset of the second stimulus in the train (Fig. 1C). We do not show time courses for the third and fourth epochs since we have previously reported (in a similar paradigm) that there is attenuation of the signal at these points following a 46 °C stimulus [6]. To confirm this with respect to the NAc data collected in this experiment we calculated the standard deviation of the average BOLD signal time course from each subject's left and right NAc separately for the first two noxious thermal epochs and the last two noxious thermal epochs. For both the left and right NAc, the S.D. was higher during the first two epochs than the last two epochs (9.99 versus 9.21, $t$ [5] = 2.12, $p = 0.044$, one-tailed). The remainder of the data presented here refers to the first two 46 °C stimuli. NAc activation has been previously detected in groups of six subjects using the same paradigm [6].

Using the method described above for cluster analysis, we analyzed data from 12 clusters (left and right from each subject). In 9 of 12 cases the algorithm produced two relatively large top-level clusters, which we used for further analysis (Fig. 2). In the remaining three cases, one very small and one very large top-level cluster were produced. In these cases, we discarded the very small cluster and used the two largest sub-clusters of the very large cluster for further analysis. Thus, in each case we were able to group all or nearly all of the voxels into two large clusters.

For each subject's left and right NAc, we computed the Pearson correlations between the time course of each voxel with the average time course of all the voxels in its cluster. Voxels that were "in between" the two clusters, defined as having correlations with the two cluster averages that differed by less than 0.10, were iteratively removed from the clusters by removing the voxel with the smallest difference at each iteration until all voxels in each cluster were at least 0.10 more correlated with their own cluster than with the other cluster. As a result, the correlation between the average time courses (across subjects) of