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Signal Valence in the Nucleus Accumbens to Pain Onset and Offset

Lino Becerra^a and David Borsook^{a,b}

^a P.A.I.N. Group, Brain Imaging Center, McLean Hospital, 115 Mill Street, Belmont MA

^b Athinoula Martinos Center for Biomedical Engineering, Massachusetts General Hospital, Harvard Medical School

Abstract

Pain and relief are at opposite ends of the reward-aversion continuum. Studying them provides an opportunity to evaluate dynamic changes in brain activity in reward-aversion pathways as measured by functional magnetic resonance imaging (fMRI). Of particular interest is the Nucleus Accumbens (NAc), a brain substrate known to be involved in reward-aversion processing, whose activation valence has been observed to be opposite in response to reward or aversive stimuli. Here we have used pain onset (aversive) and pain offset (rewarding) involving a prolonged stimulus applied to the dorsum of the hand in 10 male subjects over 120 seconds to study the NAc fMRI response. The results show a negative signal change with pain onset and a positive signal change with pain offset in the NAc contralateral to the stimulus. The study supports the idea that the NAc fMRI signal may provide a useful marker for the effects of pain and analgesia in healthy volunteers.

Keywords

fMRI; Nucleus Accumbens; Pain; Analgesia; Reward; Aversion

Introduction

The nucleus accumbens (NAc) is considered to be a ventral extension of the striatum. It is less well demarcated in humans than in rodents or primates; the structure is considered to be involved with the integration information related to cognitive, sensory, and emotional processing. The NAc receives excitatory input from limbic regions (prefrontal cortex, hippocampus, amygdala, midline intralaminar nuclei) and has efferent projections to a number of regions including the ventral pallidum and brainstem, including the midbrain. Some specificity of afferent and efferent connectivity as it pertains to the shell and core of the NAc has been described in rats (Groenewegen, et al. 1999) and non-human primates (Meredith, et al. 1996), suggesting that the accumbens contains neural systems (ensembles) with different inputs and outputs and thus, different functions.

Corresponding Author: Lino Becerra PhD, P.A.I.N. Group, Brain Imaging Center, McLean Hospital, 115 Mill Street, Belmont MA, Tel: 617 855 31 95, lbecerra@mclean.harvard.edu.

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Electrophysiological, pharmacological, lesion and imaging studies point to the NAc as one CNS site that may mediate functions involved in both reward and aversion ((Berridge and Robinson 2003) and Table 1). Pain and analgesia offer unique opportunities to understand reward and aversion circuitry in humans based on a large clinical background and the use of non-invasive methods such as functional magnetic resonance imaging (fMRI) to define neural circuits in these processes in acute and chronic pain. Recently we reported that aversion induced in human subjects by a noxious painful stimulus activates regions including the nucleus accumbens, a region classically associated with reward (Aharon, et al. 2006, Becerra, et al. 2001). The fMRI Blood Oxygenated Level Dependent (BOLD) activation to the aversive stimulus was negative and opposite to that observed for low dose morphine producing a euphoric affect (Becerra, et al. 2006). The data taken together with other studies suggests that the nucleus accumbens may provide a useful signal for aversive (painful) and rewarding (analgesic) effects (see Discussion). Here we explore this notion further by evaluating the BOLD signal change in the accumbens during pain onset and pain offset to the same stimulus. Our hypothesis is that the signal valence should be opposite in the two conditions (i.e., pain and pain relief).

Methods

Subjects

Ten healthy male subjects (27 ± 4.7 , mean $\pm$ sd) were recruited to the study. The study was approved by the IRB at MGH for experimentation on human subjects, and which also complied with the Helsinki Declaration on pain experimentation in humans.

Thermal stimulation

A Peltier thermode system (Becerra, et al. 2001) was used to deliver one stimulus to the back of the left hand within the scanner. A painful hot (46°C) stimulus was continuously administered for 120 seconds; ramp rate $4^{\circ}/\text{sec}$; baseline temperature = 35°C (Fig. 1). Subjects rated their pain on a visual analogue scale (0 : no pain to 10 : maximum pain) at the end of the functional scan.

Imaging

Scanning was performed in a 1.5 T scanner (GE Medical systems, Milwaukee, WI, USA). A conventional 3D sagittal T1-weighted, SPGR sequence was acquired (60 slices 2.8 mm thick, 1.2 mm resolution in-plane) 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 echoplanar sequence was acquired for preliminary analysis of statistical maps. For the functional studies, an asymmetric spin echo echoplanar sequence was used ($\text{TR}/\text{TE} = 2.5\text{s}/70\text{ ms}$) on the 20 prescribed slices, 100 images per slice were acquired for each functional scan.

Data Analysis

fMRI data was processed using fsl 3.0 (fmrib, Oxford). Functional data had the skull removed, motion-corrected and spatially-smoothed with a Gaussian kernel of 5 mm using fsl standard tools (fsl, <http://www.fmrib.ox.ac.uk/fsl/>). Statistical analysis was carried out using a generalized linear model approach. The model was deduced from a previous work (Becerra, et al. 2001) in which a 25 second heat stimulus was analyzed with two responses delayed 13 seconds from each other. The 120 s stimulus of this report was modeled by extending the number of waves until the whole stimulus duration was covered (8 waves). An additional wave was added right after the stimulus ended to detect any changes following the termination of the stimulus (see Figure 1A). Statistical maps for each subject were co-registered with the

standard brain atlas (MNI 152 brain atlas, available through fsl). Group results were calculated using a mixed-effects approach (fsl). To determine activation in general, an F-test was carried out with all the waves. Significant activations were determined using a cluster approach with a cluster probability of 0.05 and individual voxel threshold of $p < 0.01$ ($z = 2.3$) (fsl feat tool). For the NAc, and based on previous results (Becerra, et al. 2001), we inspected activation in the NAc to the second wave ("late phase" in previous results). The cluster of activation to the second wave was used to extract amplitude of activation for all the other waves in the model for each subject and averaged across subjects.

Results

The average pain rated on a visual analogue scale was 7.4 ± 1.3 (mean $\pm$ SD), subjects described the stimulus as painful but tolerable.

Inspection of activation in the NAc to the second wave depicted significant negative activation in the contralateral side (see Figure 1, Lower Panel). As determined by the amplitude of each wave, activation in the NAc progressively tended to return to baseline after the onset of the heat stimulus. Co-localized with the activation on the onset of the heat stimulus, there was a positive response to the last (relief/pain offset) wave.

In addition, results from the F-test depicted activation in response to heat in a series of brain substrates known to be involved in pain processing: cortical activation was detected in frontal areas, anterior cingulate gyrus, insula, primary and secondary somatosensory cortex, subcortical activation was found in the thalamus, caudate and putamen as well as the cerebellum.

Discussion

Here we report on the activation in the NAc across the duration of a painful heat stimulus. Note that the BOLD signal decreases in the NAc at the onset of the stimulus and increases at the offset of the stimulus. Subjects were told that during the scan a painful stimulus 2-minutes long would be applied to the dorsum of their left hand. They did know that the onset would be painful and that with offset there would be less or decreased pain. Thus expectancy was clearly an issue for both onset and offset, perhaps increasing the pain response but probably not affecting the offset response. Previous work with healthy subjects have reported that expectation of pain and actual encoding of noxious stimuli have overlapping representations (Koyama, et al. 2005). Although expectation is typically measured preceding stimulus application, preparatory processes triggered by the threat of impending pain may alter subsequent nociceptive or other processing (Buchel, et al. 2002, Carlsson, et al. 2000, Helmchen, et al. 2006). In our experiments, we cannot dissociate the activation due to expected pain from actual pain encoding in the NAc. Termination of pain can be rewarding (Seymour, et al. 2005) and functional neuroimaging studies have determined the ability of the NAc to encode salience and valence (Cooper and Knudson, 2007 17904386).

An increase in the BOLD signal to rewarding stimuli has been observed across a number of studies (see Table 1). The mechanism of increased BOLD has been reviewed in a number of reports (Arthurs and Boniface 2002, Attwell and Iadecola 2002). Excitation within neural systems in the NAc may produce activation by excitatory systems (e.g., kainate (Crowder and Weiner 2002) or glutamate (Manzoni, et al. 1997). In addition, dopamine is considered to play a significant role in NAc activation (Salamone, et al. 2005, You, et al. 2001). Dopamine release in the NAc is thought to increase BOLD in the NAc via postsynaptic D1 receptors (Knutson and Gibbs 2007). However, this may be oversimplified, since different dopaminergic pathways

to the core and shell are known to exist and may drive differences in response to specific physiological or pharmacological stimuli (see (Ikemoto 2007) for review).

A decrease in BOLD signal has been considered to be a result of reduction in neural activity (Shmuel, et al. 2006, Shmuel, et al. 2002). Inhibition may take place as a result of the release of inhibitory neurotransmitters such as gabaergic and/or glycine within interneurons in the NAC (Taverna, et al. 2004) or as a result of afferent inputs that modulate NAc neural activity (Powell and Leman 1976). In the latter, it has been inferred that regulation occurs via the inhibition of excitatory inputs into the midbrain dopaminergic systems in a model of sciatic nerve stimulation (Kelland, et al. 1993).

Conclusion

In this study of healthy subjects undergoing a phasic painful stimulus, the NAc is observed to be dynamic in its response (positive and negative activation) and seems to be correlated with reward and aversion perceptions, respectively. Although the NAc is only one component of reward systems, it seems to play a pivotal role in hedonic state and motivated behavior by evaluating stimulus valence.

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Figure 1. Prolonged Heat Stimulus: Activation profile in the NAc

Top Panel – Multiwave model of response to a prolonged heat stimulus. A series of 9 waves (HR) was used to analyze the BOLD response to a prolonged heat stimulus (blue shaded area). An extra wave was added after the stimulus finished in order to capture any “relief” response. The blue background represents the time that the heat stimulus (46°C) was presented.

Middle Panel –Amplitude and direction of response in the NAC with a multiwave model. The amplitude of each wave in the NAC is displayed against wave number. The first and last (relief) waves show significant positive response in the NAC. Waves 2–8 (the “late” response) show negative signal change in the NAC. Shaded area = noxious stimulus.

Lower Panel - The figure shows statistical maps of activation within the NAc following the onset (initial pain) of a noxious painful stimulus (46°C) and after the pain has stopped (pain relief). Note that aversive stimulus produces a decrease in signal (blue) change while the rewarding stimulus produces an increase (red) in signal within the change structure. Data are averaged for 10 subjects ($p < 0.001$, t-test).

Table 1
Examples of fMRI Signal Change in the Human NAc in response to Reward and Aversion

Function	Response	Reference
<u>Pain</u>		
Experimental Pain	Decreased	(Becerra, et al. 2001) (Aharon, et al. 2006)
<u>Drugs</u>		
Morphine	Increased	(Becerra, et al. 2006)
Nicotine (smoking)	Increased	(David, et al. 2005)
<u>Sexual Arousal</u>		
Orgasm in Women	Increased	(Komisaruk and Whipple 2005)
<u>Humor</u>		
	Increased	(Mobbs, et al. 2003)
<u>Beautiful Faces</u>		
Pictures	Increased	(Aharon, et al. 2001)
<u>Money</u>		
Monetary Reward	Increased	(Breiter, et al. 2001)
<u>Social Emotions</u>		
Picture Stimuli	Increased	(Britton, et al. 2006)