The ventral striatum is implicated in the analgesic effect of mood changes

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C Villemure, AC Laferrière, MC Bushnell. The ventral striatum is implicated in the analgesic effect of mood changes. Pain Res Manage 2012;17(2):69-74.

BACKGROUND: The ventral striatum, particularly the nucleus accumbens, is commonly associated with the processing of reward and positive stimuli, positive affect as well as antinociceptive processes.
OBJECTIVES: The present study examined whether the ventral striatum is implicated in analgesia resulting from positive mood change induced by pleasant odours.
METHODS: Functional magnetic resonance imaging studies were conducted in healthy individuals receiving painful heat stimuli in the presence of pleasant or unpleasant odours, which were used to induce positive and negative mood states. Ventral striatum activity was examined in the two mood states.
RESULTS: For most subjects, pleasant odours improved mood and reduced pain unpleasantness perception relative to unpleasant odours. In the pleasant odour condition, the maximum activation of both the left and right ventral striatum was positively correlated with the amount of pain reduction. Furthermore, the left and right ventral striatum activations positively covaried with one another, and the right ventral striatum activation positively correlated with that in the periaqueductal grey matter. Both ventral striatum activations negatively covaried with the activation of the right mediodorsal thalamus, left dorsal anterior cingulate cortex, left medial prefrontal cortex and right ventrolateral prefrontal cortex.
CONCLUSIONS: Because both the mediodorsal thalamus and anterior cingulate are involved in pain affect perception, and activation within the prefrontal areas and periaqueductal grey matter were previously shown to correlate with mood-related pain modulation, it is concluded that the ventral striatum is likely implicated in the analgesic effect of positive mood changes induced by pleasant odours on pain unpleasantness.

Key Words: *Analgesia; Emotion; Functional MRI; Pain; Ventral striatum*

Le striatum ventral participe à l'effet analgésique des changements d'humeur

HISTORIQUE : Le striatum ventral, notamment le noyau accumbens, s'associe souvent au traitement des récompenses et des stimuli positifs, à l'affect positif et aux processus antinociceptifs.
OBJECTIFS : La présente étude a permis d'examiner si le striatum ventral participe à l'analgésie découlant d'un changement d'humeur positif induit par des odeurs agréables.
MÉTHODOLOGIE : Les chercheurs ont mené des études fonctionnelles d'imagerie par résonance magnétique auprès de personnes en santé recevant des stimuli de chaleur douloureux en présence d'odeurs agréables ou désagréables, utilisés pour induire des humeurs positives et négatives. Ils ont examiné l'activité du striatum ventral selon les deux types d'humeur.
RÉSULTATS : Pour la plupart des sujets, les odeurs agréables ont amélioré l'humeur et réduit la perception déplaisante de douleur relative aux odeurs désagréables. Devant des odeurs agréables, l'activation maximale des striatums ventraux gauche et droit était corrélée de manière positive à la quantité de réduction de la douleur. De plus, les activations des striatums ventraux gauche et droit étaient covariées l'un avec l'autre de manière positive, et l'activation du striatum ventral droit était corrélé de manière positive avec la matière grise péri-épendymaire du mésencéphale. Les activations des deux striatums ventraux étaient covariées négativement avec l'activation du noyau médiodorsal droit du thalamus, du cortex cingulair antérieur dorsal gauche, du cortex préfrontal médial gauche et du cortex préfrontal ventrolatéral droit.
CONCLUSIONS : Puisque tant le noyau médiodorsal du thalamus que le cortex cingulaire antérieur participent à la perception d'affect de la douleur et que l'activation des zones préfrontales et de la matière grise péri-épendymaire du mésencéphale a déjà démontré qu'elle était corrélée avec la modulation de douleur liée aux humeurs, on conclut que le striatum ventral participe probablement à l'effet analgésique des modifications positives de l'humeur induit par les odeurs agréables sur le caractère déplaisant de la douleur.

The basal ganglia are a network of subcortical nuclei that have long been known to exert a powerful influence on the motor system. Nevertheless, it is now recognized that the ventral portion of the basal ganglia has an important role in emotional regulation, and this region has connections with limbic structures such as the amygdala, hippocampus, midline thalamus and parts of the prefrontal cortex (1). The ventral (or limbic) striatum (VST) includes the nucleus accumbens (NAc), the ventral caudate and the ventral putamen (2). In contrast to the amygdala, in which activation tends to be related to negative emotions, there is evidence that VST activation is frequently biased toward positive experience (3). In particular, the NAc is commonly associated with processing of reward and positive stimuli (4-9). In humans, increased VST activation has been observed in response to rewarding stimuli and natural reinforcers including food rewards (10,11), pharmacological agents such as cocaine (12), intensely pleasurable music (13,14), financial rewards (15,16), positive words (7), parenting (8) and even humour (17). Furthermore, although the NAc does not respond directly to odorants, it was found to be involved in olfactory associative learning involving positive conditioning; direct contrast of positively and aversively conditioned stimuli (previously neutral visual stimuli paired with either pleasant or unpleasant odours) uncovered bilateral activation of the VST for the positively conditioned stimuli, but not the negatively conditioned stimuli (18). Finally, animal studies have shown that the NAc plays a role in nociceptive regulation, usually being antinociceptive, which can be considered as rewarding (19-23).

We previously showed that pleasant and unpleasant odours induced mood changes that modulated the affective evaluation of pain (pain unpleasantness ratings), but not the perceived intensity of the stimulus (pain intensity ratings) (24,25). The decrease in pain unpleasantness perception observed when pleasant odours were presented together with pain was associated with markedly decreased anterior cingulate cortex (ACC) and medial thalamus activation (25). Given the reported involvement of the VST in reward processes, pleasure, positive affect and antinociceptive phenomena, we postulate that modulation of pain caused by positive mood changes induced by pleasant odours could involve the VST.

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METHODS

Subjects

Other analyses of the same dataset were presented in a previously published article (25). Fourteen subjects (five males) between 18 and 28 years of age (mean 23 years) completed the study and were paid for their participation. The study was approved by the McGill University Institutional Review Board (Montreal, Quebec), and written informed consents were obtained. Potential subjects were excluded if they presented any of the following: significant claustrophobia or other magnetic resonance imaging (MRI)-related contraindications; bronchopulmonary or neurological problems; chronic pain; pregnancy or breastfeeding; current cold or allergy symptoms; smoking; allergy to perfume; current use of any analgesics; use of alcohol within 12 h of the experimental procedure; and failing to demonstrate attentional or emotional modulations in a screening session using our experimental task. Subjects were instructed not to wear scented products and were told that the purpose of the present study was to investigate how odours can change how subjects feel pain, as well as how pain can change what subjects feel about smells.

General experimental procedure

In a preliminary session, olfactory and thermal stimuli were chosen for each subject. The specific temperatures were determined individually to produce moderate pain in the absence of odours. The odorants were individually chosen to ensure highly pleasant and unpleasant valences. No neutral odour was included because most subjects perceive all odourants as either positive or negative (26). Subjects also practised the intensity discrimination task involving either the olfactory or thermal stimuli, to direct attention to the olfactory or thermal modality, while simultaneously manipulating odour hedonics. Subjects demonstrating either attentional or emotional modulation of pain perception in the discrimination task were scheduled for an MRI session on a separate day. During the MRI session, an anatomical scan was first acquired, followed by the functional runs (described below). A within-subject design was used in which each subject was exposed to all conditions.

Painful heat stimuli

A temperature that evoked moderate pain in the absence of the experimental odours was chosen for each subject by presenting two ascending series of discrete temperatures ranging from 36°C to 50°C to three areas of the inner left calf using a 9 cm^2 thermode (TSA II NeuroSensory Analyzer, Medoc Advanced Medical System, Israel). Each stimulus had a plateau of 3 s and a rise/fall time of 10°C/s from a 38°C baseline. A temperature was identified that the subject rated as approximately 5 on a 0 to 10 pain intensity scale. A second heat stimulus was identified that subjects could distinguish from the first with approximately 80% accuracy to be used in the discrimination task (described below). The temperature of this stimulus was always 1°C higher. This above-chance, but submaximal performance was chosen to maximize the attentional demand in the discrimination task. Subjects were never notified that only two painful temperatures would be used in the experimental tasks.

Odour stimuli

Subjects evaluated six odorants diluted to 0.1% to 5% volume to volume (v/v) in an appropriate inodorous solvent (distilled water or propylene glycol). Different types of odorants were presented including pyridine (Sigma-Aldrich, Canada), which has a smell reminiscent of rotten fish at the concentration used, and cosmetic-grade fragrance oils with food and floral scents, including china rain, creamsicle, lemon meringue, mint and violet (K & W Specialties, Canada). For the odour selection the diluted fragrances (10 mL) were presented in 60 mL amber bottles identified with numbers. The most preferred and disliked odours were chosen based on the subjects' pleasantness and unpleasantness ratings. During the discrimination task, 5 s odour pulses were delivered by a computer-controlled olfactometer (Knosys Olfactometers, USA). A transistor-transistor logic pulse generated by the thermode at the beginning of each heat pulse triggered the opening of the appropriate valve of the olfactometer, resulting in the synchronized presentation of the thermal and olfactory stimuli. An air flow of 0.4 L/min was used. The odourized air from each independent channel reached the subjects through 10 m long Teflon-lined tubing. A vacuum pump operated between presentations to prevent lingering odours. A Y-shape glass piece was secured with tape just below the subject's nostrils for bi-rhinal stimulation. A 10 cm × 21 cm Teflon sheet was loosely taped over the subject's nose and mouth and in-scanner ventilation was stopped to prevent odour dispersion. Subjects were instructed to close their mouth and to breathe normally through the nose. The concentrations used in the discrimination task were 0.1% and 1% v/v for pyridine, 0.5% and 5% v/v for mint and 0.3% and 3% v/v for the other odours. These intensity differences were previously found to lead to above-chance but submaximal performance in the odour discrimination task (24). None of the odours was judged to be pungent or irritating.

Intensity discrimination task

Painful heat and odours were presented simultaneously. In 50% of the trials, subjects attended to the heat stimuli and performed a heat-intensity discrimination task. The lower painful temperature was always used as the first stimulus of the pair, whereas the higher painful temperature appeared pseudorandomly as the second stimulus of the pair (50% probability). In the other trials, subjects attended to the odours and performed an odour-intensity discrimination task. The stronger concentration was always used as the second stimulus of the pair, whereas the weaker concentration appeared pseudorandomly in 50% of cases as the first stimulus of the pair. The hedonic quality of the odourant was also manipulated so that in one-half of the trials subjects were exposed to their preferred odour, while in the other one-half they were exposed to their unpleasant odour. All stimuli were presented in pairs with an interstimulus interval of 4 s. The subjects' task was to decide whether the second stimulus of the pair (either heat or odour depending on attention direction) was stronger or the same intensity as the first one. They used a nonverbal code (using their left hand) to give their answer and received nonverbal feedback (tapping on ankle) about their performance after each pair. This nonverbal communication was performed during time periods excluded from functional MRI (fMRI) analysis. Each trial included the discrimination of 12 pairs of stimuli, with each pair separated by 12 s, leading to a total time of approximately 5 min/trial. There was one trial per condition. This design resulted in four conditions recorded as four separate fMRI runs: (1) attention to the thermal stimuli while being exposed to the pleasant odour; (2) attention to the thermal stimuli while exposed to the unpleasant odour; (3) attention to the pleasant odour while exposed to heat pain; and (4) attention to the unpleasant odour while exposed to heat pain. The order of the conditions was counterbalanced across subjects.

Response measures

Immediately following each fMRI acquisition run, subjects provided verbal ratings of the intensity and hedonic quality (pleasantness/unpleasantness) of the odour and painful stimuli, as well as of their mood and anxiety/calmness using numerical rating scales. The anxiety/calmness scores were analyzed in another study (25). The odour intensity scale was anchored with 0 (no odour) and 10 (extremely intense). The pain intensity scale was anchored with 0 (no pain) and 10 (most intense pain tolerable). The pleasantness scale was anchored with 0 (neutral) and 10 (extremely pleasant). The unpleasantness scale was anchored with 0 (neutral) and 10 (extremely unpleasant). The good and bad mood scales were anchored with 0 (neutral) and 10 (extremely good or bad). The calmness and anxiety scales were anchored with 0 (neutral) and 10 (extremely calm or anxious).

MRI

A 1.5 Tesla MRI scanner (Siemens AG, Germany) with a standard head coil was used. Anatomical scans were collected using a high-resolution

T1-weighted anatomical protocol (repetition time 22 ms; echo time 9.2 ms; flip angle 30°; field of view 256 mm^2; voxel size 1 mm × 1 mm × 1 mm). Functional scans were collected using a blood oxygenation level-dependent (BOLD) protocol with a T2* weighted gradient echoplanar imaging sequence (repetition time 4 s; echo time 50 ms; flip angle 90°; field of view 256 mm^2; matrix 64×64, voxel size 4 mm × 4 mm × 4 mm). The scanning planes were oriented parallel to the line between the anterior and posterior commissures. Thirty-six axial slices were acquired covering the brain from the top of the cortex to the base of the cerebellum.

Functional data were first corrected for motion and spatially smoothed with a 6 mm full-width half-maximum Gaussian kernel. The first three volumes were excluded to ensure steady-state magnetization. Both the anatomical and functional volumes were resampled into standard stereotaxic space based on the Montreal Neurological Institute (MNI) 305 template (27). Therefore, all activations are reported using MNI coordinates. Functional images were processed, and effect size maps and t statistic maps representing changes in BOLD contrast were generated with fMRISTAT-MULTISTAT (software developed at the MNI, Montreal, Canada [available at www.math.mcgill.ca/keith/BICstat]). Temporal drift was removed by adding polynomial covariates in the frame times, up to degree 3, to the design matrix.

Pain-related activation associated with the odour conditions

For each subject, the study contrasted the response to the painful temperature with the response to the baseline (nonpainful) temperature (see Villemure and Bushnell [25] for details). Both of our previous studies examined the effects of attending to and performing detection tasks related to the pain or odour stimuli (24,25). Direction of attention did not affect mood ratings – that is, mood changes were the same regardless of whether subjects attended to the odours. Because there was no interaction between attentional direction and mood ratings, in the current analysis, the data were collapsed across attention conditions and only evaluated the effects of smelling a pleasant or unpleasant odour were evaluated.

VST mask

Using the technique of Mawlawi et al (2), masks were drawn delineating the VST bilaterally on the anatomical scan of each subject. Landmarks were used to determine the VST to reproduce equivalent masks on all subjects' brains (Figure 1). Point A was determined by locating the most superior and lateral portion of the internal capsule and bringing down an imaginary vertical line to the outer edge of the putamen. Point B was the centre portion of the anterior commissure transaxial plane overlying the striatum. Finally, point C was established by extending the line between point A and B to the internal edge of the caudate. The lower boundary of the ventral striatum was visually determined by following the inner border of white matter (2). The VST mask was sampled from y=6 to y=16. These masks were applied to the individual BOLD signal effect size maps generated by FMRISTAT/MULTISTAT and the maximum effect size (ie, peak value) was extracted within the VST mask of each subject in the pleasant and unpleasant odour conditions. These values provided an index of activation of the VST for each subject in each condition and were used in the correlation analysis and as regressors in the co-variation analysis described below.

Correlation analysis

Correlations between the VST maximum effect size extracted in both odour conditions and the amount of analgesia (pain unpleasantness score in the pleasant odour condition subtracted from the pain unpleasantness score in the unpleasant odour condition) were performed using Statistica 7.1 (StatSoft, Inc, USA). A criterion of $P<0.05$ was adopted.

Covariation analysis

Covariation analysis was used to test whether the VST activation (maximal effect size) covaried with the magnitude of activation of regions previously identified as pain processing areas in the absence of odours (medial thalamus [mdTH], primary and secondary somatosensory cortices [S1 and S2], insula and dorsal anterior cingulate cortex) as well as areas possibly involved in the modulation of pain perception by mood (ventrolateral prefrontal cortex [VLPFC] and periaqueductal grey matter [PAG]) (25). The observation of a negative covariation between the activation of VST in the pleasant odour condition (if not seen in the unpleasant odour condition) and the activation of pain processing areas would suggest a role for VST in mood-related analgesia induced by pleasant odours, although no causal relationship can be identified with this method. The maximal effect sizes were extracted from the right and left VST masks in both the pleasant and unpleasant odour conditions and these values were used as regressors (weighting factors) in a new model to estimate covariation. The threshold t values were determined in the following manner. All t-statistic images were thresholded (P=0.05) using a Bonferroni correction based on the number of voxels in the search region or the random field theory, whichever gave the minimum threshold (28,29). The volume of the whole-brain grey matter was estimated to be 1,200,000 mm^3 yielding a t threshold of 4.8 for global searches. The present study had a priori hypotheses for the mdTH, S1, S2, insula and ACC, VST, PAG and VLPFC. For the VST the t threshold was calculated using the average VST volume of all subjects (1359 mm^3, t threshold = 2.9). For the PAG and VLPFC, the same volume estimated in Villemure and Bushnell (25) was used to calculate the peak t thresholds (PAG: 385 mm^3, t threshold = 2.4; inferior frontal cortex including the VLPFC: 9000 mm^3, t threshold = 3.5). For the mdTH, S1, S2, insula and ACC, the present study used volumes of 1000 mm^3 drawn following the anatomy of each area and centred on the y coordinates of the peak activations found in the average t statistical map representing pain areas in a condition where pain was presented without odours in the previous report (25). The 1000 mm^3 volume resulted in a threshold of 2.8.

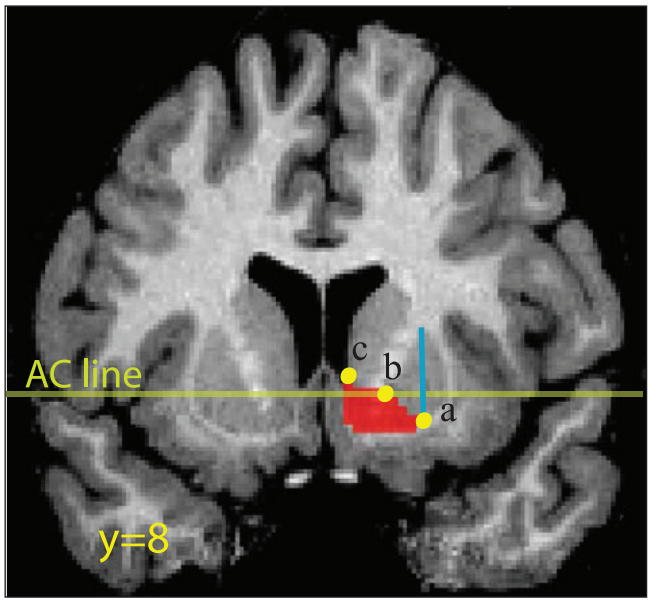

Figure 1) *Mask delineating the ventral striatum (VST). Masks were drawn delineating the VST bilaterally on the anatomical scan of each subject following the method described in Mawlawi et al (2). Landmarks were used to determine the VST to reproduce equivalent masks on all subjects' brains. Point 'a' was determined by locating the most superior and lateral portion of the internal capsule and bringing down an imaginary vertical line to the outer edge of the putamen. Point 'b' was the centre portion of the anterior commissure (AC) transaxial plane overlying the striatum. Point 'c' was established by extending the line between points 'a' and 'b' to the internal edge of the caudate. The lower boundary of the ventral striatum was visually determined by following the inner border of white matter*

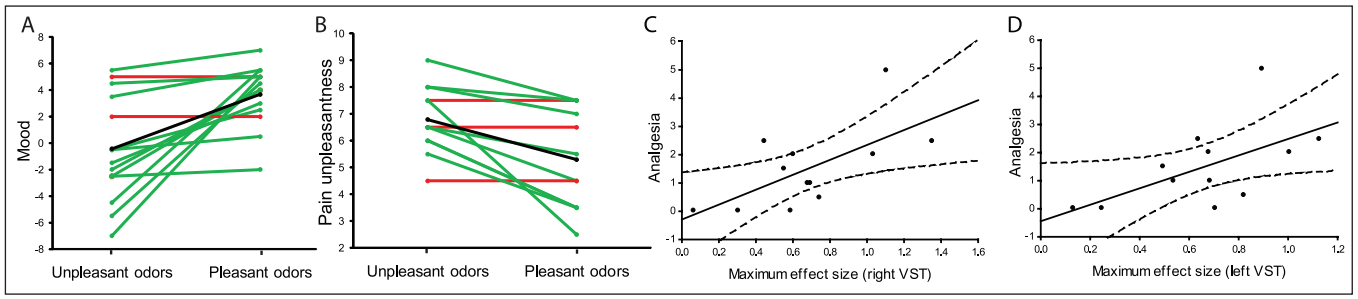

Figure 2) A *Odour-related mood modulation in the 14 subjects. Pleasant odours improved mood in all but two subjects. Green lines represent subjects who demonstrated mood improvement when smelling pleasant odours. Red lines represent subjects showing the same mood when smelling pleasant and unpleasant odours (excluded from further analyses). The average mood change of the group is represented by the black line. Please note that for illustration purposes bad mood ratings were attributed a negative number.* **B** *Analgesia in the 12 subjects showing odour-related mood change. Nine reported less pain unpleasantness when smelling pleasant odours (green lines) and three showed no analgesia (red lines). The average pain unpleasantness change is represented by the black line.* **C** *Correlation between the amount of analgesia and the maximum effect size in the right ventral striatum (VST) when subjects smelled pleasant odours. Analgesia was calculated by subtracting the pain unpleasantness score in the pleasant odour condition from the pain unpleasantness score in the unpleasant odour condition. Increasing activation in the right VST correlated with increasing analgesia.* **D** *Correlation between the amount of analgesia and the maximum effect size within the left VST when subjects smelled pleasant odours. Increasing activation in the left VST correlated with increasing analgesia*

Therefore, for any peak in the mdTH, S1, S2, insula and ACC to be considered significant, the t value had to be ≥2.8 and fall within these restricted 1000 mm^3 volumes.

RESULTS

Psychophysical results

The authors previously reported that, on average, mood was significantly better when pain was experienced while smelling the pleasant odours than when smelling the unpleasant odours, and that the resultant change in mood predicted ratings of pain unpleasantness (25). This effect of odour valence on mood was observed in 12 of the 14 subjects (Figure 2A). Because the present study's aim was to examine the involvement of the VST in the modulation of pain caused by mood changes induced by odorants, the two subjects whose mood was not modulated by odours were removed from further analyses. However, subjects were included whether or not their pain perception was modulated. All 12 subjects chose pyridine as the unpleasant odour. The majority of subjects chose nonfood related odours as their preferred odours (six chose violet, two chose china rain, two chose mint, one chose lemon meringue and one chose creamsicle). It was previously reported that, on average, mood changes induced by odour valence significantly influenced pain unpleasantness but not pain intensity ratings (25). Of the 12 subjects who showed mood modulation caused by odours, nine demonstrated an analgesic effect of the pleasant odour (giving lower pain unpleasantness ratings in the pleasant odour condition), and three showed no analgesia (giving equal pain unpleasantness scores in the pleasant and unpleasant condition) (Figure 2B). This lack of analgesia did not seem to be related to the type of odour chosen because these three subjects chose different odours (violet, lemon meringue and mint). A more comprehensive description of the psychophysical results can be found in the previous paper (25).

fMRI results

Correlation between analgesia and VST activation: There was a significant correlation between the maximum effect size found within both VST masks and the amount of analgesia induced by the pleasant odour (right VST: R2=0.42, P<0.05; left VST: R2=0.34, P<0.05) (Figures 2C and 2D). The subjects showing the highest VST effect size while breathing the pleasant odour demonstrated the highest level of analgesia. No such correlations were found in the unpleasant odour condition (right VST: R2=0.08, P>0.3; left VST: R2=0.14; P>0.2).

Covariation analyses: In the pleasant odour condition, only the medial prefrontal cortex (MPFC [Brodmann area (BA) 10]) activation significantly covaried (negatively) with both the right and left VST activations at the global search level (Figure 3B, Table 1). Significant covariations were found for several a priori hypothesized regions. Activation within the left VST and PAG positively covaried with maximum effect size in the right VST when subjects were exposed to their chosen pleasant odour (Figure 3A, Table 1). Similarly, activation within the right VST positively covaried with maximum effect size in the left VST in the pleasant odour condition (Figure 3A, Table 1). However, the covariation of the left VST and the PAG did not reach statistical significance. Activation within the mdTH, dorsal ACC and VLPFC negatively covaried with both the right and left VST activations when subjects were exposed to the pleasant odours (Figure 3B, Table 1). In addition, in the pleasant odour condition, S2 negatively covaried with the right VST but not the left. Inversely, the insular cortex (IC) covaried with the left VST but not the right. None of these brain regions covaried with the right or left VST maximum activation when the subjects smelled the unpleasant odours (Table 1).

DISCUSSION

In the majority of subjects, pleasant odours improved mood and decreased pain unpleasantness perception relative to painful stimuli experienced with unpleasant odours. We found that for the subjects whose mood was improved by pleasant odours, the magnitude of VST activation while smelling the pleasant odours positively correlated with the amount of analgesia. This correlation with VST activation was not observed when subjects smelled the unpleasant odours, suggesting that the effects of unpleasant odours were not mediated by the VST. Furthermore, activation within the mdTH and dorsal ACC, which are part of the ascending medial pain pathway known to be implicated in pain unpleasantness perception (30), negatively covaried with VST activation when subjects smelled the pleasant odours. We also found similar, less robust VST covariations in other pain-related cortical regions, including S2 and IC. None of those covariations were seen when subjects smelled the unpleasant odours. Positive VST covariations were observed between activations in the left and right VST and between the right VST and the PAG, suggesting the possibility that these regions function consonantly in their analgesic involvement in this context.

These findings suggest that the pleasant odours may have led to an increase in VST activation that, in turn, decreased the activation in structures of the ascending pain pathway involved in pain unpleasantness processing, leading to a decreased perception of pain unpleasantness. Exactly how this is achieved is unknown and cannot be completely elucidated from the present results. However, our data show that, aside form increased VST activation, analgesia following mood modulation by pleasant odours appears to involve a decrease in left MPFC (BA 10) and right VLPFC (BA 47) activations and a possible increase in PAG activation. The sequence of events leading to

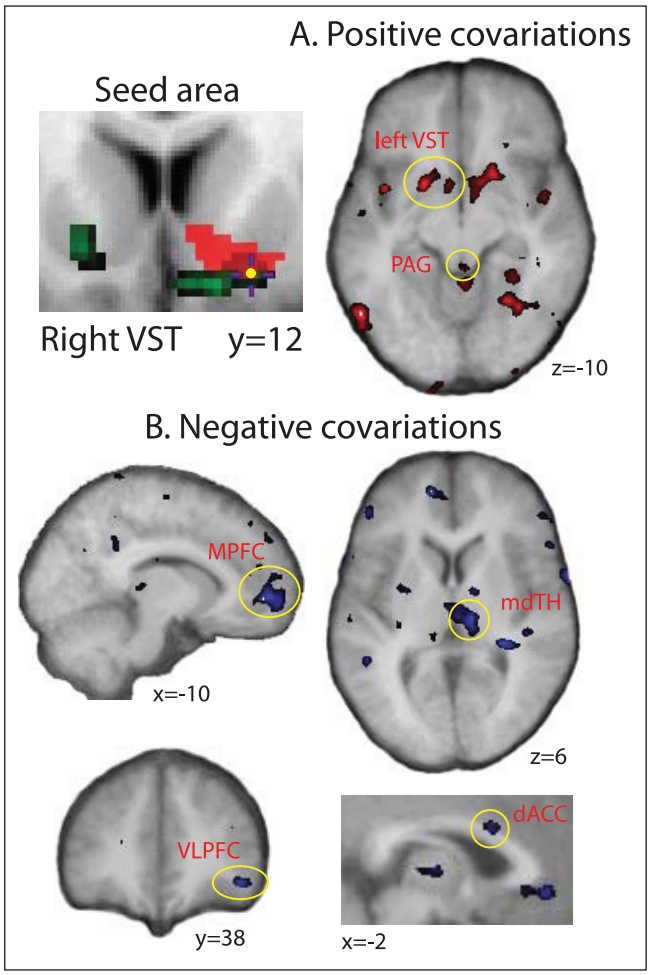

Figure 3) *Brain areas that covaried with the maximum effect size of the right ventral striatum (VST) in the pleasant odour condition. The seed area (yellow dot) refers to the location of the maximal effect size identified in the covariation analysis in the right VST. Similar covariations were found when the maximal effect size was extracted from the left VST and are not depicted here.* **A** *Positive covariations. Activation within the left VST and periaqueductal grey matter (PAG) positively covaried with the activation of the right VST.* **B** *Negative covariations. Activation within the mediodorsal thalamus (mdTH), dorsal anterior cingulate (dACC), medial prefrontal cortex (MPFC) and ventrolateral prefrontal cortex (VLPFC) negatively covaried with the right VST*

TABLE 1
Covariation analysis results

Brain region		Positively covaries with maximum effect size			
		In right VST		In left VST	
(BA)	Condition	x, y, z	t	x, y, z	t
Right VST	Pleasant odour			18, 12, –10	**3.3**
	Unpleasant odour				0.1
	Pleasant odour			6, 6, –6	**3.3**
	Unpleasant odour				0.6
	Pleasant odour			18, 18, –12	**3.0**
	Unpleasant odour				–0.6
Left VST	Pleasant odour	–20, 8, –8	**3.6**		
	Unpleasant odour		0.1		
	Pleasant odour	–18, 10, –6	**3.4**		
	Unpleasant odour		0.1		
	Pleasant odour	–6, 8, –10	2.8		
	Unpleasant odour		0.2		
PAG	Pleasant odour	2, –40, –10	**2.4**	2, –40, –10	2.2
	Unpleasant odour		0.5		–0.2
Brain region		**Negatively covaries with maximum effect size**			
		In right VST		**In left VST**	
(BA)	**Condition**	**x, y, z**	**t**	**x, y, z**	**t**
MPFC (BA 10)	Pleasant odour	–10, 50, –2	**–4.9**	–10, 50, –2	**–4.9**
	Unpleasant odour		–2.2		–2.2
VLPFC (BA 47)	Pleasant odour	46, 38, –10	**–4.6**	46, 38, –10	**–4.7**
	Unpleasant odour		1.3		0.5
mdTH	Pleasant odour	12, –20, 6	**–3.3**	12, –20, 6	**–3.2**
	Unpleasant odour		1.4		1.1
ACC (BA 24)	Pleasant odour	–2, 10, 24	**–3.1**	–2, 10, 24	**–2.9**
	Unpleasant odour		–0.7		0
S2	Pleasant odour	–46, –24, 24	**–3.0**	–46, –24, 24	–2.7
	Unpleasant odour		–0.4		–0.2
S1	Pleasant odour	10, –42, 70	–2.4	10, –42, 70	–2.2
	Unpleasant odour		–2.0		–1.6
IC	Pleasant odour	–38, –8, –2	–2.8	–38, –8, –2	**–3.2**
	Unpleasant odour		1.4		1.2

Significant t values for global searches are in bold and underlined. Significant t values for a priori hypothesized areas are in bold. ACC Anterior cingulate cortex; BA Brodmann area; IC Insular cortex; mdTH Mediodorsal thalamus; MPFC Medial prefrontal cortex; PAG Periaqueductal grey matter; S1 Primary somatosensory cortex; S2 Secondary somatosensory cortex; VLPFC ventrolateral prefrontal cortex; VST ventral striatum; x, y, z refer to the Montreal Neurological Institute (MNI) coordinates.

this analgesia is impossible to ascertain with the method used in the present study.

Activation of the MPFC was previously linked to pain-related anxiety during pain processing in healthy volunteers (31) and was found to be implicated in the emotional augmentation of clinical pain (32). The decreased activation of this region when VST activation is increased in the pleasant odour condition is particularly interesting because we found that, on average, subjects were significantly less anxious when they smelled the pleasant odours (25). We previously implicated the right VLPFC in the emotional modulation of pain (25). We found that the right VLPFC was significantly activated when subjects' mood and pain unpleasantness were worsened by the presence of unpleasant odours, but not when subjects' mood and pain unpleasantness were improved by pleasant odours. This was similar to the findings of Farrell et al (33) who found VLPFC activation when two negative events (pain and thirst) were experienced simultaneously but not separately. This is consistent with the fact that the VLPFC is usually associated with negative emotions (34). Because VST activation was found to covary negatively with the VLPFC, it is possible that the decrease in VLPFC seen when pain is experienced with pleasant odours is somehow linked to the activation of the VST. It is interesting to note that two of the neural structures implicated here (VST and VLPFC) are the same as those implicated in successful positive cognitive reappraisal of negative emotional stimuli such as aversive images (3). Cognitive reappraisal refers to the process of regulating emotional responses by changing the cognitive representation of events (35). In the case of negative events, positive reappraisal ultimately leads to a reduction of the negative emotional experience (3). Distraction has also been implicated in cognitive emotional regulation; however, consistent with our findings that distraction has only a minor effect on pain unpleasantness (24,25), reappraisal leads to greater decreases in negative affect than does distraction (36). Thus, it is possible that the reduced pain unpleasantness caused by mood changes due to the presence of pleasant odours taps into the same system that underlies positive cognitive reappraisal – in other words, it is possible that noncognitively driven and cognitively driven emotional changes exploit the same neural substrates.

There is accumulating evidence that part of the VST (the NAc) is an important neural substrate of opioid-mediated and nonopioid-mediated pain modulation (21). Presently, not much is known about the natural conditions under which antinociception involving the NAc might occur (19). One such condition involves pain-induced analgesia (20). However, given the role of VST in reward and positive affect, it seemed justified to hypothesize that such mechanisms would also be involved in mood-related pain modulations. Our results give support to this hypothesis.

CONCLUSION

We found that the VST is implicated in the analgesic effect of mood changes produced by pleasant odours relative to unpleasant odours: the more VST activation, the less activation within pain processing areas, the greater the analgesia. This form of analgesia also involved the medial and ventrolateral prefrontal cortices (BA 10 and BA47, respectively) and possibly the PAG.

ACKNOWLEDGEMENTS: The authors thank Nazma Mohammed for her skilled assistance at all stages of data acquisition, André Cormier, Nicole Fauteux and Louise Marcotte for expert MRI data acquisition and Mike Ferreira for his support with data analysis. They also thank Petra Schweinhardt for reviewing an earlier version of this manuscript.

FINANCIAL SUPPORT: NIH grant #1-ROI-NS44036-01

CONFLICTS OF INTEREST: None to declare.

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