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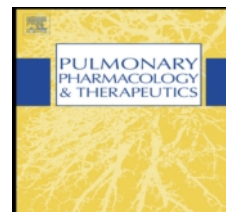
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Imaging the brain during sniffing: a pilot fMRI study

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Abstract

Whilst the act of sniffing can provide us with an indirect method to study the central mechanisms of respiratory control, functional neuroimaging now provides us with a tool to directly visualise the activity of the human brain during this voluntary action using functional magnetic resonance imaging (fMRI).

We performed fMRI during sniffing in 11 healthy volunteers where all subjects executed single, brisk sniffs of around 60% of their maximum sniff pressure at intervals of approximately every 20 s. Simultaneous nasal pressure and chest movements were also measured during the task and a statistical parametric map of activation correlating with the sniff manoeuvre was calculated.

A bilateral cortical and subcortical sensorimotor network was activated. The activations were localised within the primary sensorimotor cortex, lateral premotor cortex, supplementary motor area, anterior cingulate, insula, basal ganglia, thalami, mesencephalon, upper pons, cerebellar vermis, piriform cortex, entorhinal cortex and parahippocampal gyrus.

The activated brain areas identified, i.e. the cortical and subcortical respiratory network, are similar to those described in other neuroimaging studies of voluntary inspiration. Sniffing is a component of olfactory processing and activations of the olfaction-related cortical areas were also observed in our study.

The results of our study show that event-related fMRI can be successfully used to study sniffing. This provides a novel approach to our study of the central neural control of respiration.

Keywords: Functional neuroimaging; Functional magnetic resonance imaging; Neural control of respiration; Cortical motor system; Sniffing; Sniff nasal inspiratory pressure

1. Introduction

Neural control of respiration depends on a central drive to the respiratory muscles, which is modulated by both chemical and mechanical inputs. The central drive originates from neurones within the central nervous system, including the cortex, limbic system and brainstem. Voluntary control of respiration is mediated by corticospinal pathways descending from the motor cortex to the spinal cord. Automatic control originates in the pontomedullary respiratory oscillator from which a descending bulbospinal projection connects with the anterior horn cells in the cervical and thoracic spinal cord which innervate the respiratory muscles to cause rhythmic breathing [1]. A possible way to study the central mechanisms for the control of voluntary respiration is through different respiratory manoeuvres, e.g. sniffing and coughing. A sniff is a short, sharp voluntary or reflex inspiratory manoeuvre performed through one or both unoccluded nostrils. It involves contraction of the diaphragm and other inspiratory muscles [2] and it is an integral part of the olfactory processing [3]. It is also an useful voluntary test for evaluating the diaphragm strength in clinical setting [4].

Functional neuroimaging methods, especially functional magnetic resonance imaging (fMRI), can be used to explore networks of the human brain during the performance of different tasks. fMRI is a non-invasive technique with good spatial resolution (~ few millimetres) and temporal resolution (~ few seconds). Blood oxygenation level-dependent (BOLD) fMRI depends on the regional changes of blood oxygenation, i.e. the haemodynamic response, that follows the local neuronal activity in the brain with a lag of a few seconds [5,6].

The first functional neuroimaging study of voluntary breathing was published by Colebatch et al. [7]. Using positron emission tomography (PET), they found activations bilaterally in the primary motor cortex, in the right pre-motor cortex, in the supplementary motor area and in the cerebellum. fMRI was first used in human respiratory studies by Gozal et al. [8-10] studying a single slice of brain. Subsequent PET [11-13] and fMRI [14,15] studies confirmed the association between voluntary breathing and activation of primary motor cortex, lateral premotor cortex, supplementary motor area and cerebellum. They additionally described the activation of inferolateral sensorimotor cortex, prefrontal cortex and basal ganglia [14]. In an fMRI study by McKay et al. [15] activation of the superior dorsal medulla was reported, suggesting an additional role of brainstem centres in the control of voluntary breathing. fMRI was also recently used to study two voluntary respiratory manoeuvres, namely coughing and sniffing [16]. Both were associated with the activation of a cortical sensorimotor network

similar to that activated in voluntary respiration, and specifically there was activation of the pontomesencephalic region in coughing, and the hippocampus and piriform cortex in sniffing.

Our aim was to test whether it is feasible to use a voluntary sniffing task to explore the brain control of voluntary respiration using event-related fMRI. We hypothesised that sniffing is associated with activation of a network of cortical and subcortical brain regions similar to those activated in other voluntary respiratory manoeuvres.

2. Materials and methods

2.1. Patients

Eleven right-handed healthy volunteers (mean age 34 years, range 26-53, 8 males and 3 females) with no history of neurological or respiratory dysfunction were studied. All participants gave their written informed consent prior to their inclusion in the study. The study was approved by the Local Research Ethics Committee.

2.2. Respiratory Function Measures

Before scanning, the following respiratory tests were performed in all subjects: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), maximal expiratory pressure at the mouth (MEP), maximal inspiratory pressure at the mouth (MIP) and maximal sniff nasal inspiratory pressure (SNIP). Tests were performed according to the European Respiratory Society guidelines [2]. FVC and FEV1 were measured using the Micro Spirometer (Micro Medical Limited, Rochester, UK). MEP, MIP and SNIP were measured using the Micro RPM (Micro Medical Limited, Rochester, UK).

2.3. Functional Imaging

2.3.1 Task

The visual cue to perform a brisk sniff was presented using a laptop and back-projected on a semi-transparent screen located at the subject's feet. The stimuli were generated using the LabVIEW software (National Instruments, Austin, TX, USA). Subject performance during scanning was measured using a custom-built pressure transducer device which was located in

the MRI control room and connected to the subject using long plastic tubes (Festo Limited, UK). A plastic nasal plug (Micro Medical Limited, Rochester, UK) was connected to the device. Chest movements were measured using pneumatic bellows connected to the device. Before the functional image acquisition, the instrument was calibrated and the maximum sniff pressure was determined. The tasks were designed in a jittered event-related manner where a visual cue (red dot becoming green) prompted the subject to perform a single brisk sniff of around 60% of their maximum sniff pressure. The subjects were trained, both outside and inside the scanner, to achieve 60% of the maximum before the scanning commenced using a visual pressure feedback until satisfactory performance of task was achieved. The cue appeared pseudo-randomly every 19.5 to 21.5 seconds. Total task duration was 11 min 3 s.

2.3.2 Image acquisition

Imaging was performed on a 3 Tesla GE Excite II MR scanner (General Electric Medical Systems, Waukesha, MI, USA) with a GE quadrature head coil. Prior to the functional scans, high-resolution T1-weighted anatomical images were obtained. Functional images were acquired using a standard T2*-weighted EPI sequence (repetition time 3000 ms, echo time 20 ms, 43 transverse slices with in-plane resolution 3.75×3.75 mm, thickness 3 mm and interslice gap 0.3 mm). The slices were parallel to the line connecting anterior and posterior commissures. 221 whole-brain functional images were acquired for each subject.

2.3.3 Image analysis

The entire image analysis including slice-timing correction, realignment, normalization, smoothing and statistical analysis was performed using Statistical Parametrical Mapping (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK). The image time series was corrected for differences in the timing of the acquisition of different slices within the whole volume. The data series was then realigned to the first image to correct for head movement between scans. The realigned images were spatially normalized to the stereotactic MNI space and resliced to 2 mm isotropic voxels. Data were subsequently smoothed with an isotropic Gaussian kernel of 8 mm at full-width-half-maximum.

Following image pre-processing, a general linear model-based statistical analysis of the functional images was performed [17]. Data were analyzed by modelling the sniffs as events convolved with the haemodynamic response functions. Sniff onset times, together with their temporal and dispersion derivatives, were included as regressors. Also, movement parameters

were included in the model to account for residual head movements not cancelled during spatial realignment. After estimation of all model parameters, subject-specific activations during sniffing were assessed by applying appropriate linear contrasts to the parameter estimates, resulting in individual contrast maps for each subject. These canonical contrast maps were then taken to a second level, random effects analysis. One-sample t tests were used to explore the group-specific activations. A cluster threshold of $P < 0.05$ (corrected for multiple comparisons) was used.

3. Results

3.1. Functional measures

The subjects respiratory functional measures were well within the normal range [18,19] with the exception of SNIP in subject 3 and subject 8 (Table 1).

[Insert Table 1]

3.2. Functional imaging

A bilateral cortical and subcortical sensorimotor network was activated (measured as an increase in BOLD signal) during the sniffing task (Fig. 1, Table 2). The largest cluster with distinct local maxima consisted of bilateral activations within insula, basal ganglia, thalami, mesencephalon, upper pons and cerebellar vermis, as well as in bilateral piriform cortex, entorhinal cortex and parahippocampal gyrus. Additional separate activation clusters were located bilaterally in the primary sensorimotor cortex, lateral premotor cortex, supplementary motor area, anterior cingulate, left superior temporal gyrus and right cerebellar hemisphere. The activation of the cortical and subcortical areas was predominantly bilaterally symmetrical.

[Insert Figure 1]

[Insert Table 2]

4. Discussion

4.1. *The cortical and subcortical respiratory network*

The results of our pilot study show that sniffing is associated with the activation of a widespread network of cortical and subcortical areas. The cortical respiratory network consists of parts of the cortical sensorimotor system that controls voluntary movements: the primary sensorimotor cortex, lateral premotor cortex, supplementary motor area and cingulate motor area [20]. Similar activations were found in a recent fMRI study exploring sniffing and coughing [16] and also in a number of neuroimaging studies of voluntary breathing [7,11,12,14,15]. Activation of these cortical and subcortical regions was also described in an fMRI study exploring the urge-to-cough using capsaicin inhalation [21]. It is therefore possible that besides mediating the motor aspect, this network also has a role in the perception and modulation of the respiratory manoeuvres.

Sniffing involves an orchestrated recruitment of various respiratory muscles [22,23]. We found two distinct activation clusters within the primary sensorimotor cortex: a ventral area that probably represents the oral, facial and pharyngeal muscles and a dorsal area representing the cervical and thoracic respiratory muscles including the diaphragm. The activation of the dorsal cluster was also reported by McKay et al. [15]. They described two distinct peaks within this area and hypothesised that one belongs to the diaphragm and the other to the thoracic respiratory muscles. Cortical representation of the diaphragm within the primary motor cortex was first detected using cortical electrical stimulation by Foerster in 1936 [24]. It was also localised using transcranial electrical and magnetic stimulation [25,26]. It is situated within the primary motor cortex between the arm and leg representations. A second direct pathway to the diaphragm, probably originating in the supplementary motor area, was described recently [27]. The activation of the supplementary motor area found in our study could therefore represent execution of the sniff manoeuvre mediated by this pathway but also the planning and preparation of movement [28].

The activations within the cortical sensorimotor system probably also represent sensory input from the upper and lower airways, chest wall, lungs and proprioceptive feedback from the respiratory muscles. We would expect that the activations related to sensory input occur later than motor-related activity. The temporal resolution of fMRI does not allow us to distinguish

between the two, especially with block designs that have been used in previous neuroimaging studies of voluntary respiration. Our event-related fMRI design offers a possibility of detecting latency differences between different activations and therefore we may be able to make indirect inference about this [29]. Due to a better temporal resolution, electroencephalography is probably a more suitable method to distinguish between the sensory and the motor components of the sniffing-related cortical activation [30].

It is still not known to what extent the brainstem respiratory centres are involved in voluntary respiration [31]. We found activation within the upper pons and mesencephalon but not within the medulla. Simonyan et al. [16] described the activation of this region during coughing, but not during sniffing or breathing. Activation within the upper medulla was found in a study of voluntary breathing [15], but only by using a region-of-interest approach. The pons is also active during breath-holding [32], which may represent an inhibiting influence on medullary respiratory centres. It is not possible to conclude based on functional neuroimaging studies alone whether these brainstem activations are causally related to voluntary respiration or whether they just represent a concomitant activation. The brainstem is also, due to its size and location, very susceptible to imaging artefacts so interpretation of activations within this region or lack thereof merits caution.

The perception of smell is dependent on sniffing [3]. Functional neuroimaging studies of the olfactory system have shown activation of the olfaction-related cortical areas, such as piriform, entorhinal and parahippocampal cortex, even without the presence of any odour [3,16,33,34]. This was confirmed in our study as well. Sniffing probably facilitates the higher-order olfactory processing.

4.2. Methodological issues

Studying respiratory manoeuvres using fMRI involves a number of technical and methodological problems. fMRI is very sensitive to head motion which can produce false positive activations if the head movements are correlated with the task [35]. This is certainly the case when performing different respiratory manoeuvres. Movements within the oral cavity and pharynx that occur during swallowing and speaking, and presumably also during sniffing, can produce susceptibility-induced image distortions and compromise the fMRI analysis [36]. We tried to resolve these issues by using an event-related design. This enabled us to

temporally dissociate the movement- and susceptibility-related activations from the “true” activations related to the neuronal activity and thus measured by the increase in BOLD signal. Due to the haemodynamic response function this increase lags behind neuronal events, and therefore also behind the movements caused by the sniffing manoeuvre, by about 5-6 s [37]. The effect of head motion can then be to a certain extent regressed out by including the motion parameters as covariates in the statistical model. A different approach to this issue is to use sparse scanning [16] where functional images are acquired only during periods with no head movements.

Change of breathing rate or depth can cause significant fMRI signal changes, possibly due to the influence of chest movements on the magnetic field and due to the variations in the blood CO₂ level [38]. CO₂ is a potent cerebral vasodilator and any blood CO₂ level changes can cause a widespread increase of the BOLD signal within the brain [39]. Most of the previous fMRI studies used a block design where periods with respiratory manoeuvres were long enough to possibly cause significant blood CO₂ level changes and produce false positive fMRI activations. The authors therefore used a sophisticated design to maintain a constant end-tidal P_{CO2} [15] or employed mechanical ventilation in the control task [7]. In our event-related design brief sniffing manoeuvres occurred once approximately every 20 seconds and therefore did not cause any significant end-tidal P_{CO2} changes. Therefore no significant influence of CO₂ caused cerebral vasodilatation on BOLD signal could be expected in our study.

4.3. Conclusion

The results of our pilot study show that event-related design can be successfully used to study neural control of sniffing using fMRI. This methodological approach can also possibly be used for other respiratory manoeuvres like coughing. It provides a tool to study the central neural control of respiration both in healthy subjects and in patients with neurological or respiratory diseases.

5. Acknowledgements

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6. References

- [1] Guz A. Brain, breathing and breathlessness. *Respir Physiol* 1997;109:197-204.
- [2] American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166:518-624.
- [3] Mainland J, Sobel N. The sniff is part of the olfactory percept. *Chem Senses* 2006;31:181-196.
- [4] Miller JM, Moxham J, Green M. The maximal sniff in the assessment of diaphragm function in man. *Clin Sci* 1985;69:91-96.
- [5] Cohen MS, Bookheimer SY. Localization of brain function using magnetic resonance imaging. *Trends Neurosci* 1994;17:268-277.
- [6] Matthews PM, Jezzard P. Functional magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 2004;75:6-12.
- [7] Colebatch JG, Adams L, Murphy K, Martin AJ, Lammertsma AA, Tochon-Danguy HJ, Clark JC, Friston KJ, Guz A. Regional cerebral blood flow during volitional breathing in man. *J Physiol* 1991;443:91-103.
- [8] Gozal D, Hathout GM, Kirlew KA, Tang H, Woo MS, Zhang J, Lufkin RB, Harper RM. Localization of putative neural respiratory regions in the human by functional magnetic resonance imaging. *J Appl Physiol* 1994;76:2076-2083.
- [9] Gozal D, Omidvar O, Kirlew KA, Hathout GM, Hamilton R, Lufkin RB, Harper RM. Identification of human brain regions underlying responses to resistive inspiratory loading with functional magnetic resonance imaging. *Proc Natl Acad Sci U S A* 1995;92:6607-6611.
- [10] Gozal D, Omidvar O, Kirlew KA, Hathout GM, Lufkin RB, Harper RM. Functional magnetic resonance imaging reveals brain regions mediating the response to resistive expiratory loads in humans. *J Clin Invest* 1996; 97:47-53.
- [11] Ramsay SC, Adams L, Murphy K, Corfield DR, Grootenok S, Bailey DL, Frackowiak RS, Guz A. Regional cerebral blood flow during volitional expiration in man: a comparison with volitional inspiration. *J Physiol* 1993;461:85-101.

- [12] Fink GR, Corfield DR, Murphy K, Kobayashi I, Dettmers C, Adams L, Frackowiak RS, Guz A. Human cerebral activity with increasing inspiratory force: a study using positron emission tomography. *J Appl Physiol* 1996;81:1295-1305.
- [13] Brannan S, Liotti M, Egan G, Shade R, Madden L, Robillard R, Abplanalp B, Stofer K, Denton D, Fox PT. Neuroimaging of cerebral activations and deactivations associated with hypercapnia and hunger for air. *Proc Natl Acad Sci U S A* 2001;98:2029-2034.
- [14] Evans KC, Shea SA, Saykin AJ. Functional MRI localisation of central nervous system regions associated with volitional inspiration in humans. *J Physiol* 1999;520:383-392.
- [15] McKay LC, Evans KC, Frackowiak RS, Corfield DR. Neural correlates of voluntary breathing in humans. *J Appl Physiol* 2003;95:1170-1178.
- [16] Simonyan K, Saad ZS, Loucks TM, Poletto CJ, Ludlow CL. Functional neuroanatomy of human voluntary cough and sniff production. *NeuroImage* 2007;37:401-409.
- [17] Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 1995;2:189-210.
- [18] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *European Respir J Supp* 1993;16:5-40.
- [19] Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. *Thorax* 1995;50:371-375.
- [20] Roland PE, Zilles K. Functions and structures of the motor cortices in humans. *Curr Opin Neurobiol* 1996;6:773-781.
- [21] Mazzone SB, McLennan L, McGovern AE, Egan GF, Farrell MJ. Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med* 2007;176:327-332.
- [22] Nava S, Ambrosino N, Crotti P, Fracchia C, Rampulla C. Recruitment of some respiratory muscles during three maximal inspiratory manoeuvres. *Thorax* 1993;48:702-707.
- [23] Katagiri M, Abe T, Yokoba M, Dobashi Y, Tomita T, Easton PA. Neck and abdominal muscle activity during a sniff. *Respir Med* 2003;97:1027-1035.
- [24] Foerster O. Motorische Felder und Bahen. In: Bumke O, Foerster O. (eds.). *Handbuch der Neurologie*. Berlin: Springer, 1936:50-51.
- [25] Gandevia SC, Rothwell JC. Activation of the human diaphragm from the motor cortex. *J Physiol* 1987;384:109-118.

- [26] Maskill D, Murphy K, Mier A, Owen M, Guz A. Motor cortical representation of the diaphragm in man. *J Physiol* 1991;443:105-121.
- [27] Sharshar T, Hopkinson NS, Jonville S, Prigent H, Carlier R, Dayer MJ, Swallow EB, Lofaso F, Moxham J, Polkey MI. Demonstration of a second rapidly conducting cortico-diaphragmatic pathway in humans. *J Physiol* 2004;560:897-908.
- [28] Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 1996;6:342-353.
- [29] Henson RN, Price CJ, Rugg MD, Turner R, Friston KJ. Detecting latency differences in event-related BOLD responses: application to words versus nonwords and initial versus repeated face presentations. *NeuroImage* 2002;15:83-97.
- [30] Macefield G, Gandevia SC. The cortical drive to human respiratory muscles in the awake state assessed by premotor cerebral potentials. *J Physiol* 1991;439:545-558.
- [31] Corfield DR, Murphy K, Guz A. Does the motor cortical control of the diaphragm 'bypass' the brain stem respiratory centres in man. *Respir Physiol* 1998;114:109-117.
- [32] McKay LC, Adams L, Frackowiak RS, Corfield DR. A bilateral cortico-bulbar network associated with breath holding in humans, determined by functional magnetic resonance imaging. *NeuroImage* 2008;40:1824-1832.
- [33] Sobel N, Prabhakaran V, Desmond JE, Glover GH, Goode RL, Sullivan EV, Gabrieli JD. Sniffing and smelling: separate subsystems in the human olfactory cortex. *Nature* 1998;392:282-286.
- [34] Kareken DA, Sabri M, Radnovich AJ, Claus E, Foresman B, Hector D, Hutchins GD. Olfactory system activation from sniffing: effects in piriform and orbitofrontal cortex. *NeuroImage* 2004;22:456-465.
- [35] Hajnal JV, Myers R, Oatridge A, Schwieso JE, Young IR, Bydder GM. Artifacts due to stimulus correlated motion in functional imaging of the brain. *Mag Reson Med* 1994;31:283-291.
- [36] Birn RM, Bandettini PA, Cox RW, Jesmanowicz A, Shaker R. Magnetic field changes in the human brain due to swallowing or speaking. *Mag Reson Med* 1998;40:55-60.
- [37] Birn RM, Bandettini PA, Cox RW, Shaker R. Event-related fMRI of tasks involving brief motion. *Hum Brain Mapp* 1999;7:106-114.
- [38] Birn RM, Smith MA, Jones TB, Bandettini PA. The respiration response function: The temporal dynamics of fMRI signal fluctuations related to changes in respiration. *NeuroImage* 2008;40:644-654.

[39] Corfield DR, Murphy K, Josephs O, Adams L, Turner R. Does hypercapnia-induced cerebral vasodilation modulate the hemodynamic response to neural activation. *Neuroimage* 2001;13:1207-1211.

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Tables

Table 1. Respiratory function test results (FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, SNIP = sniff nasal inspiratory pressure, MIP = maximal inspiratory pressure at the mouth, MEP = maximal expiratory pressure at the mouth).

Subject No.	Sex	Age	FEV1 (l)	FVC (l)	SNIP (cm H ₂ O)	MIP (cm H ₂ O)	MEP (cm H ₂ O)
1	M	33	4.04	4.81	-113	-132	203
2	M	32	4.86	5.61	-87	-82	118
3	M	47	3.60	4.24	-39	-94	104
4	M	26	4.84	6.20	-132	-133	130
5	F	33	3.11	3.52	-61	-118	119
6	F	28	3.08	3.53	-83	-101	102
7	M	53	3.77	4.83	-149	-150	148
8	F	34	2.92	4.07	-52	-83	120
9	M	27	4.80	6.10	-68	-97	117
10	M	33	4.10	5.55	-151	-156	181
11	M	29	5.10	5.70	-99	-166	145

Table 2. Group analysis demonstrating statistically significant clusters of activation (random effects analysis, cluster level $P < 0.05$ corrected).

Cluster volume [cm ³]	<i>P</i> (corrected)	Talairach coordinates of the maximum voxel [x y z]	<i>t</i> -value of the maximum voxel	Location
55.7	<0.001	-14 -4 -8	10.52	Bilateral insula, basal ganglia, thalamus, mesencephalon, upper pons, cerebellar vermis, piriform cortex, parahippocampal gyrus, left primary sensorimotor cortex (ventral), left lateral premotor cortex
27.1	<0.001	-8 -20 60	8.24	Bilateral supplementary motor area, anterior cingulate, right lateral premotor cortex
12.3	<0.001	36 -6 52	6.99	Right primary sensorimotor cortex (ventral)
7.7	<0.001	-22 -40 72	6.81	Left primary sensorimotor cortex (dorsal)
2.1	0.022	12 -46 56	5.93	Right primary sensorimotor cortex (dorsal)
1.9	0.041	-48 -38 30	5.67	Left superior temporal gyrus
1.8	0.045	36 -62 -18	5.14	Right cerebellar hemisphere

Figure captions

Fig. 1. Group activation map from 11 healthy subjects showing activated areas during sniffing (cluster level $P < 0.05$ corrected; transverse slices, L = left, R = right).

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