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Brain activation and sexual arousal in healthy, heterosexual males

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Summary

Despite the brain's central role in sexual function, little is known about relationships between brain activation and sexual response. In this study, we employed functional MRI (fMRI) to examine relationships between brain activation and sexual arousal in a group of young, healthy, heterosexual males. Each subject was exposed to two sequences of video material consisting of explicitly erotic (E), relaxing (R) and sports (S) segments in an unpredictable order. Data on penile turgidity was collected using a custom-built pneumatic pressure cuff. Both traditional block analyses using contrasts between sexually arousing and non-arousing video clips and a regression using penile turgidity as the covariate of interest were performed. In both types of analyses, contrast images were computed for each subject and these images were subsequently used in a random effects analysis. Strong activations specifically associated with penile turgidity were observed in the right subinsular region including the claustrum, left caudate and putamen, right middle occipital/middle temporal gyri, bilateral cingulate gyrus and right sensorimotor and pre-motor regions. Smaller, but significant activation was observed in the right hypothalamus. Few significant activations were found in the block analyses. Implications of the findings are discussed. Our study demonstrates the feasibility of examining brain activation/sexual response relationships in an fMRI environment and reveals a number of brain structures whose activation is time-locked to sexual arousal.

Keywords: brain activation and sexual response; functional MRI; right insula/subinsular region; claustrum; striatum

Abbreviations: BA = Brodmann area; MNI = Montreal Neurological Institute; rCBF = regional cerebral blood flow; SPM99 = statistical parametric mapping (1999 software version)

Introduction

Recent research has substantially increased our knowledge of the physiology of peripheral sexual response, particularly in men. This has led to important advances in the treatment of erectile dysfunction (Lue, 2000). However, despite the brain's role as the 'master organ' governing sexual function (McKenna, 1999), little is known about relationships between brain activation and sexual response. While an extensive animal literature has provided data regarding these relationships, the extent to which such findings can be generalized to humans is unclear (McKenna, 1999). The advent of non-invasive methods of mapping brain activation now present the opportunity to significantly increase our understanding of relationships between brain activation and sexual arousal in humans.

Previous PET studies investigating male sexual response (Stoleru *et al*., 1999; Redoute *et al*., 2000) have reported frontal, temporal, cingulate and subcortical involvement. In the first (Stoleru *et al*., 1999), eight males age 21–25 years were exposed to three types of film clips (humorous, neutral and sexual) while undergoing PET and objective assessment of tumescence. Findings revealed that visual sexual stimulation was associated with increased regional cerebral blood flow (rCBF) in the inferior temporal cortex, the right insula and right inferior frontal cortex, and the left anterior cingulate cortex. Increased tumescence was associated with activation in the right inferior occipital gyrus. In a second study with nine males age 21–39 years and similar visual conditions (Redoute *et al*., 2000), the magnitude of tumescence was

associated with increased rCBF in a number of regions including the claustrum, anterior cingulate, putamen and caudate nucleus. Visual sexual stimuli were associated with increased rCBF in a number of areas including the left anterior cingulate gyrus, left midcingulate, right medial frontal gyrus and right orbitofrontal cortex, claustrum, caudate nucleus and putamen.

Functional fMRI, which has been used to characterize and map a variety of complex human functions such as vision (Belliveau *et al*., 1991; Engel *et al*., 1994) and motor skills (Kim *et al*., 1993; Jack *et al*., 1994), has a number of features suitable for examining relationships between brain activation and sexual arousal. Compared with PET, fMRI: (i) is noninvasive; (ii) has superior spatial resolution; (iii) permits focus on single subject findings where appropriate as opposed to reliance on pooled data; and most importantly (iv) has substantially higher signal-to-noise ratios enabling superior temporal correlation between brain activation and peripheral response (Moseley and Glover, 1995). While the PET studies cited above assessed tumescence, these studies are unable to gather data on direct temporal relationships between changes in regional brain activation and changes in sexual arousal.

Park and colleagues (Park *et al*., 2001) investigated relationships between brain activation and sexual response using fMRI. This study, which used a 1.5T scanner and blood oxygenation level-dependent (contrast) (BOLD) fMRI, involved 12 males with normal sexual function (mean age = 23 years) and two hypogonadal males. Erotic and non-erotic film clips were alternated. Findings included activation in seven of the 12 healthy subjects associated with erotic segments in the following areas: inferior frontal lobe, cingulate gyrus, insula, corpus callosum, thalamus, caudate nucleus, globus pallidus and inferior temporal lobe. Subjective sexual arousal as well as subjective perception of erection were assessed using 5-point scales ranging from 1 (no change) to 5 (maximal increase).

The present study involves use of a 3T fMRI scanner to investigate brain activation and sexual arousal in males. Our aims were:

(i) To develop an experimental paradigm for studying the relationship between sexual arousal and brain activation in males using fMRI technology, including both neutral and visually stimulating control segments and objective assessment of tumescence; and

(ii) To use the 3T scanner's superior temporal resolution to identify brain regions whose activity changes are directly related to physiological changes in sexual arousal in a sample of young, healthy, heterosexual men.

Based on the findings reported in the neuroimaging studies discussed above (Stoleru *et al*., 1999; Redoute *et al*., 2000; Park *et al*., 2001) we expected to find significant correlations between sexual arousal and activation in the following areas: (i) anterior cingulate; (ii) putamen; (iii) caudate nucleus; and (iv) insula/claustrum. In addition, given the extensive evidence in the animal literature documenting relationships between hypothalamic activity and sexual response (for example, Carmichael *et al*., 1994; Chen *et al*., 1997), we expected to see significant correlation between sexual response and activation in the hypothalamus.

Material and methods

Subjects

Between April and October 2000, 14 heterosexual, right-handed males, age 18–30 years, with normal sexual function were entered into the study. Participants were recruited via flyers posted on the Stanford University campus and advertisements in the campus newspaper and the local Palo Alto paper. All potential subjects were screened over the phone and, if they appeared eligible, underwent a 1-h interview with a clinical psychologist (L.L.B.) and filled out a number of questionnaires including the International Index of Erectile Function (IIEF) (Rosen *et al*., 1997), Sexual Behaviour Inventory (SBI) (Bentler, 1968), Sexual Arousal Inventory (SAI) (Hoon *et al*., 1976) and SCL-90-R (Derogatis, 1983). The study design was explained in detail and all subjects read and signed informed consent prior to being interviewed or filling out questionnaires. Subjects' consent was obtained according to the Helsinki Declaration. The study was approved by the Stanford University Medical School Institutional Review Board and the Magnetic Resonance Research Committee in Stanford's Radiology Department.

Exclusions were as follows: (i) history of erectile dysfunction as assessed by interview and the IIEF; (ii) lacking experience of sexual intercourse; (iii) not responding either 'usually,' 'almost always' or 'always' to the SAI query regarding frequency of arousal with sexually explicit video material; (iv) meeting DSM-IV criteria for claustrophobia or any other axis 1 mood, anxiety, substance use or psychotic disorder assessed with interviewer-administered SCID-I (First *et al*., 1996) screening questions; (v) score higher than one standard deviation above the mean for non-distressed individuals on the General Symptom Index of the SCL-90-R; (vi) use of any psychoactive medications, other prescription medication or over-the-counter medications that might affect sexual function; (vii) use of recreational drugs within the past 30 days; (viii) use of sildenafil or any other medication designed to enhance sexual performance; (ix) history of committing any sexual offences including harassment, rape and molestation; (x) vision not adequate to view video material under fMRI conditions; and (xi) wearing any external or internal device such as a cardiac pacemaker precluding fMRI procedures.

Once accepted into the study, subjects were scheduled for a subsequent visit for the fMRI scan.

Study design and stimuli

Two videos were presented to each subject, each lasting 15 min and 3 s. In the first video, subjects received alternating segments of relaxing scenes (R), sports highlights (S) or

sexually arousing (E) video in the following order: S, R, E, R, E, R, S, R, S, R and E. The respective times for these segments in seconds were: 129, 60, 120, 30, 120, 30, 120, 33, 123, 30 and 108. In the second scan, short video clips of relaxation scenes and sports videos occurred before and after a long presentation of sexually arousing video. The condition order for video 2 was: S, R, E, R and S, and the respective times in seconds for each condition were 123, 60, 543, 60 and 117. The longer erotic segment in video 2 was used because, at the outset of the study, we did not know to what extent arousal would develop in shorter blocks in the scanner environment. For both scans, subjects pressed one of three buttons using the first three fingers of the right hand to indicate sexual interest, onset of erection or loss of sexual interest.

A number of considerations informed the design and specific stimuli. Given data suggesting that subject disengagement from emotionally stimulating visual material under fMRI conditions takes approximately 15 s (Garrett and Maddock, 2001), the S and E segments were not contiguous and were separated by a minimum of 30 s of R. The content of the erotic segments involved four types of sexual activities: rear entry intercourse, intercourse with the female in the superior position, fellatio and sexual intercourse with the male in the superior position. Of eight different sexual activities depicted in film, these four activities were associated with the highest levels of penile tumescence in a sample of 36 males (Koukounas and Over, 1997). Finally, in order to control for possible anticipation effects, subjects were not informed about the ordering of segments.

The experiment was controlled by a Macintosh computer using PsyScope(1) to start the scanner and video-cassette recorder (VCR) and record subject responses from the button box. The VCR (Panasonic Pro AG-6300, Secaucus, NJ, USA) was cued to the start of the video sequence and placed in pause mode. The VCR then began with minimal delay (estimated at ~50 ms) when the transistor–transistor logic trigger was received. This precision in timing ensured ease in analysis and interpretation of the data. The subject viewed the videos on a back projection screen mounted on the head coil through a mirror.

Penile turgidity was monitored with a specially constructed magnetic resonance compatible device based on a newborn-sized blood pressure cuff (W. A. Baum Co., Copiague, NY, USA) placed on the penis using a condom. The inflation hose was extended and connected to a tee, with one arm of the tee connected to an arterial line blood pressure transducer (4285–05, Abbott Laboratories, Chicago, IL, USA) and the other connected through a valve to the inflation bulb. The cuff was inflated to 50 mm Hg with the subject supine on the table outside the magnet. The valve was then turned off and the inflation bulb disconnected and removed (as its pressure gauge contained magnetic parts). The transducer was connected to a standard bioinstrumentation amplifier (ETH-250, CB Sciences Inc, Dover NH, USA). The analogue signal was recorded by a data logger sampling at 40 Hz (MacLab, AD Instruments, Inc, Castle Hill, NSW, Australia). Respiration and cardiac rate were simultaneously recorded by the data logger using the scanner's bellows and pulse oximeter placed on the subject's abdomen and the middle finger of the left hand, respectively. The data logger was triggered by a pulse from the scanner to ensure synchronization between the physiological and fMRI data records.

Data acquisition

fMRI data were acquired on a 3 T GE Signa magnet using a T_2*-weighted gradient echo spiral pulse sequence (Glover and Lai, 1998) and using a custom-built quadrature 'dome' elliptical bird cage head coil. Head movement was minimized using a bite-bar that was formed with the subject's dental impression and further corrected (Friston *et al*., 1995*a*) using the statistical parametric mapping (1999 software version) (SPM99) software package (Wellcome Department of Cognitive Neurology, University College, London, UK). fMRI scans were obtained from 25 axial slices using parameters of TR (relaxation time) = 3000 ms, TE (echo time) = 30 ms, flip angle = 80°, single shot, inplane resolution = 3.75 mm, and thickness = 5 mm. A T_2-weighted fast spin-echo was acquired in the same plane as the functional scans with parameters of TR = 4000 ms, TE = 68 ms, echo train length = 12, and NEX (number of excitations) = 1. These structural data were co-registered with the mean post-motion-corrected fMRI volume and spatially normalized to the Montreal Neurological Institute (MNI) brain template ($2 \times 2 \times 2$ mm voxels) using a 9-parameter affine transformation in SPM99 (Friston *et al*., 1995*a*) and spatially smoothed using a Gaussian kernel with FWHM (full width at half maximum) = 5 mm.

Data analyses

Statistical analyses were performed using the general linear model approach available in SPM99 (Friston *et al*., 1995*b*). Two types of analyses were performed: (i) traditional block analyses (n = 14) using contrasts between the sexually arousing and non-arousing video clips; and (ii) a regression analysis using penile turgidity within the scanning session as the covariate of interest (n = 11; penile turgidity data was not obtained for three subjects, once due to malfunction and, in two cases, most likely due to misplacement of the device by the subject or slippage during the scan).

For the block analysis, the high pass filter cut-off period of SPM99 was set to default values for session 1 and session 2 protocols, which were 246 and 360 s, respectively, whereas for the penile regression analysis, the default cut-off period was 512 s. For both analyses, data from video 1 and video 2 were pooled, and low pass filtering of the time series was achieved by convolving with the built-in haemodynamic response function estimate of SPM99. For both types of analyses, contrast images were computed for each subject. These images were subsequently used in a random effects

analysis (Holmes and Friston, 1998), with the number of degrees of freedom (DF) equal to the number of subjects minus 1 (i.e. DF = 13 for block analysis and DF = 10 for turgidity regression analysis). Corrections for multiple voxel comparisons were performed using the cluster-size method of Friston *et al*. (1994). In order to control for multiple comparisons, but also consider activations in smaller regions of the brain, two statistical criteria were used in reporting activations. The first criterion, which was appropriate for identifying the largest activation clusters, used a whole-brain multiple comparison correction at $P < 0.05$. The second criterion, which was less stringent and used to identify structures with prior expectation of activation (including hypothalamus, anterior cingulate gyrus, putamen and insula/claustrum) used an uncorrected P value of 0.001 and small volume correction at $P < 0.05$. For these small volume corrections, boxes of the following dimensions (in mm) were used for calculating Z thresholds for a corrected P value of 0.05: (i) hypothalamus: $10 \times 12 \times 10$ (bilateral);, (ii) anterior cingulate gyrus: $17 \times 20 \times 20$ (bilateral); (iii) putamen: $15 \times 40 \times 20$ (each side); and (iv) insula/claustrum $15 \times 40 \times 20$ (each side). MNI coordinates were transformed into the coordinate system of the Talairach and Tournoux stereotaxic atlas (Talairach and Tournoux, 1988) using the following transformations (Matthew Brett, http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). For MNI coordinates superior to the anterior commissure–posterior commissure (AC–PC) line (i.e. z coordinate $\geqslant 0$):

$$x' = 0.9900x$$
$$y' = 0.9688y + 0.0460z$$
$$z' = -0.0485y + 0.9189z$$

where x, y, z refer to MNI coordinates and x', y', z' refer to Talairach coordinates. For MNI coordinates below the AC–PC line (i.e. $z < 0$), the transformations were:

$$x' = 0.9900x$$
$$y' = 0.9688y + 0.0420z$$
$$z' = -0.0485y + 0.8390z$$

Results

Behavioural data

Button presses and average penile turgidity measures for 11 subjects are illustrated in Fig. 1 for video 1 and Fig. 2 for video 2. It can be seen that button presses indicating subjective sexual arousal (Button A in the figures), as well as perceived erection responses (Button B), are closely coupled with the rising phase of the measured turgidity response, whereas the button presses indicating loss of erection (Button C) appear on the downward phase, or during the sports or relaxation video segments.

Heart rate, respiration and turgidity measures averaged over the subjects are illustrated in Fig. 3. Pearson product–moment correlations computed on the averaged waveforms for these three measures gave the following results for

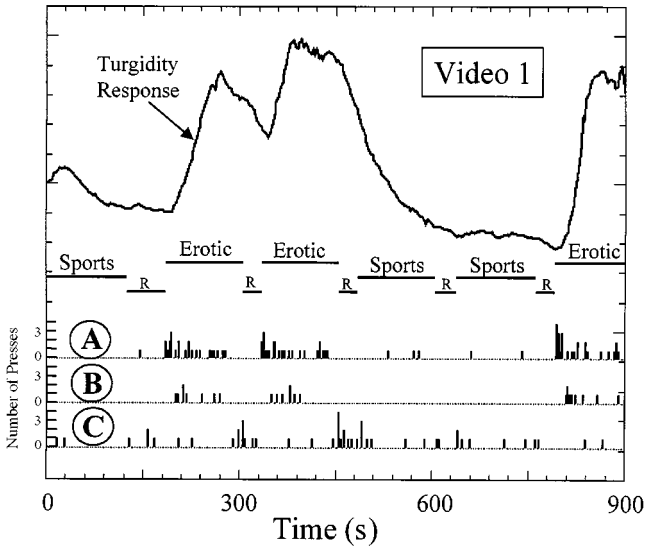

Fig. 1 Average penile turgidity and button presses for 11 subjects for video 1. Button A was pressed to indicate sexual interest, Button B was pressed to indicate onset of erection and Button C was pressed to indicate loss of interest. The onset and durations of the three different video conditions, erotic, sports and relaxation (R), are indicated below the turgidity trace.

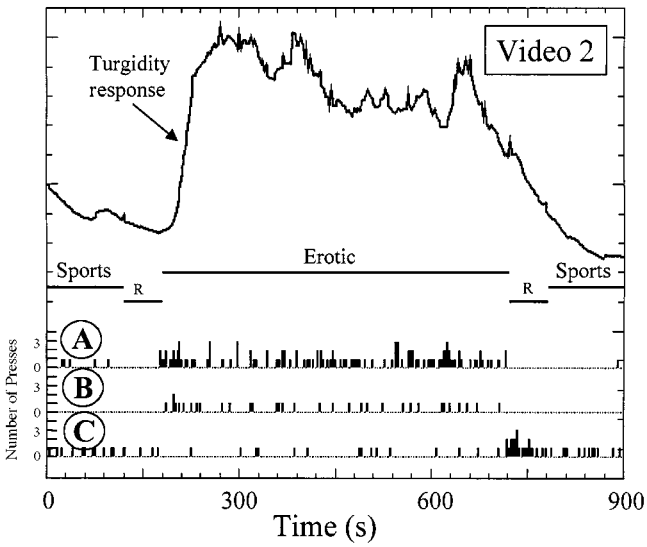

Fig. 2 Average penile turgidity and button presses for 11 subjects for video 2. Button responses A, B and C were as described in Fig. 1.

video 1: (i) turgidity/respiration: $r = 0.295$, (ii) heart rate/respiration: $r = 0.023$, (iii) turgidity/turgidity: $r = -0.176$. For video 2, the correlations were: (i) turgidity/respiration: $r = 0.455$, (ii) respiration/respiration: $r = 0.1$, (iii) turgidity/turgidity: $r = 0.177$. To test the statistical significance of these correlations, the r-value between two measures was computed for each subject and converted to a Z score using the Fisher r to Z transformation. A one-sample t-test was then performed with one value per subject to test whether the mean

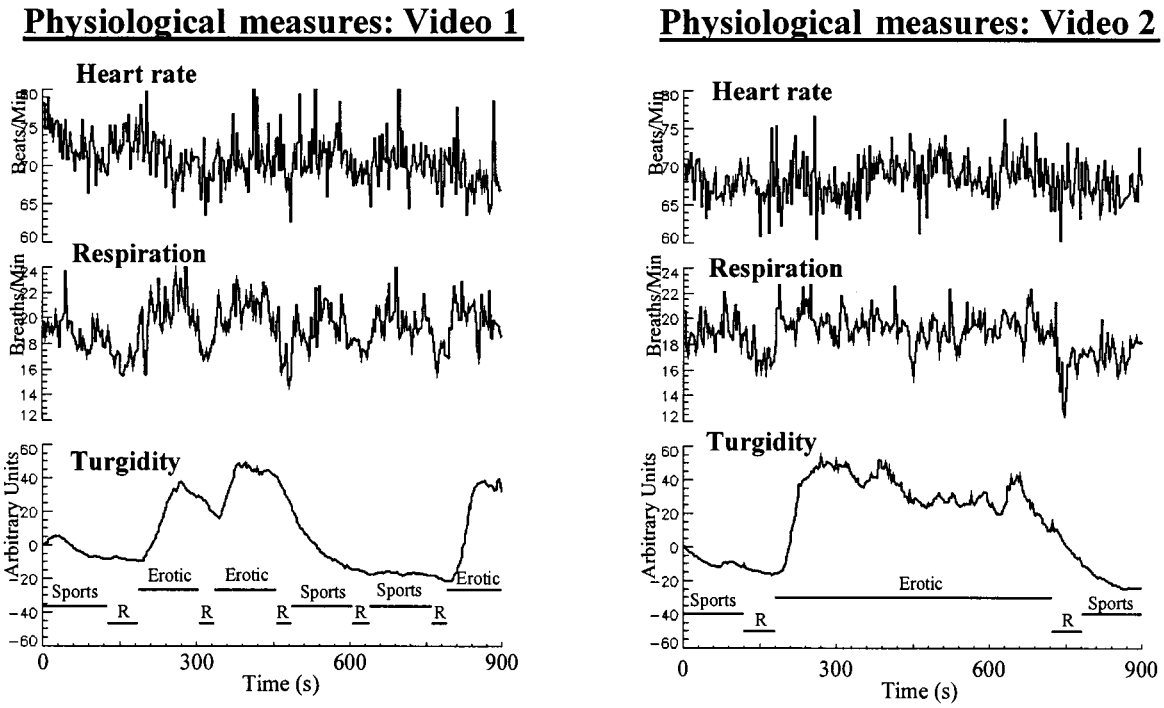

Fig. 3 Heart rate, respiration rate and penile turgidity measures for videos 1 and 2, averaged over 11 subjects. The onset and durations of the three different video conditions [erotic, sports and relaxation (R)] are indicated below the turgidity trace.

of those scores was significantly different from zero. This analysis revealed that the turgidity/respiration correlation was significant for both video 1 ($P < 0.035$) and video 2 ($P < 0.013$), and no other correlations were significant.

Brain activations

Block analysis

Because the sports video segments were separated in time from the erotic segments to a greater degree than the relaxation segments (see Figs 1 and 2) and were more closely matched to the erotic segments with respect to duration of the segments, block analyses focused on the contrast between erotic and sports segments. Very few activations were observed for this analysis. Erotic video elicited greater activation than sports segments only in visual areas. Sports video elicited greater activation relative to erotic video in the cerebellum and in the posterior portion of the right middle temporal gyrus.

Penile turgidity regression analysis

In contrast to the results obtained for the block analysis, strong activations were revealed when penile turgidity was used as a regressor. Activation foci revealed from this analysis are listed in Table 1, while Fig. 4 illustrates major activation foci superimposed on the average T_2-weighted and stereotaxically normalized anatomical images. As is evident from Fig. 4A and B, the largest and most significant region of activation was the right subinsular/insula region, including the claustrum. Fig. 5 illustrates the close correspondence between the average time course of penile turgidity across all subjects and the time course of brain activation obtained from this region during video 1.

Additional large activations, surviving the more stringent multiple comparison correction criterion, are also illustrated in Fig. 4. These include the right middle occipital/middle temporal gyri (Fig. 4A and C). Note that a slightly smaller activation near the same location was also observed on the left side, with x, y, z coordinates –45.5, –67.7, 5.2 in Table 1; left caudate and putamen (Fig. 4C), bilaterally in the cingulate gyrus (Fig. 4D) and in the right sensorimotor and pre-motor regions (observed as the faint red activations superior to the insular/claustrum activation in Fig. 4A).

Of the smaller activations observed using the less stringent criterion (but still at $P < 0.001$), one of particular relevance to this report was observed in the right hypothalamus, as illustrated in the coronal section (Fig. 4E). Additional small foci listed in Table 1 were observed mostly on the left side. These include the anterior medial prefrontal regions (with one small activation in the inferior frontal gyrus), anterior insula/claustrum, cuneus and putamen.

Discussion

Our two aims were: (i) to develop an experimental paradigm including an objective measure of tumescence and erotic visual stimuli, as well as neutral and visually stimulating

Table 1 *Turgidity-correlated activations: positive correlations*

Hemisphere	*x*	*y*	*z*	SPM{*Z*}	N Vox	Brain structures
Left	**–21.8**	**13.8**	**4.8**	**4.64**	**274**	**Putamen**
Left	**–28.0**	**10.0**	**2.0**	**4.51**		**Putamen**
Left	**–20.0**	**24.0**	**6.0**	**4.33**		**Caudate**
Left	**–7.9**	**29.5**	**7.7**	**4.75**	**134**	**GC, BA 24**
Left	–19.8	44.8	1.4	4.50	77	GC, BA 32
Left	–33.7	4.8	18.2	3.95	52	Ant insula/claustrum
Left	–21.8	21.0	–7.8	4.04	21	Putamen
Right	**41.6**	**5.7**	**–2.0**	**4.81**	**1494**	**Insula**
Right	**34.0**	**10.0**	**–4.0**	**4.13**		**Claustrum, putamen**
Right	**28.0**	**–10.0**	**18.0**	**4.13**		**Claustrum/insula**
Right	**38.0**	**–10.0**	**–4.0**	**4.12**		**Claustrum/insula**
Right	**26.0**	**–20.0**	**18.0**	**4.06**		**Claustrum**
Right	**40.0**	**–8.0**	**–12.0**	**4.04**		**Insula**
Right	**4.0**	**30.8**	**33.5**	**4.65**	**435**	**GC, BA 32**
Right	**12.0**	**20.0**	**28.0**	**4.58**		**GC, BA 32**
Right	**16.0**	**34.0**	**40.0**	**4.31**		**GFm, BA 8**
Right	**0.0**	**18.0**	**32.0**	**4.25**		**GC, BA 32**
Right	**41.6**	**5.8**	**38.4**	**4.03**	**168**	**GPrC, BA 6**
Right	**52.0**	**–4.0**	**24.0**	**3.98**		**GPrC, BA 4**
Right	**45.5**	**–65.6**	**8.8**	**4.54**	**133**	**GTm/GOm, BA 37/19**
Right	5.9	–6.4	–11.5	3.72	43	Hypothalamus

Brain activations that were significantly positively correlated with penile turgidity measurements taken during the fMRI scanning session, based on a random effects analysis of 11 subjects. No significant negative correlations were observed. Activations in bold type were observed using a whole-brain corrected P value < 0.05. The remaining activations were observed using an uncorrected P threshold of 0.001 and a small volume correction for $P < 0.05$. The coordinate system of Talairach and Tournoux's stereotaxic atlas was used to express the x, y and z coordinates. Abbreviations for brain regions were also derived from this atlas. Ant = anterior; GC = cingulate gyrus; GFm = middle frontal gyrus; GOm = middle occipital gyrus; GPrC = precentral gyrus; GTm = middle temporal gyrus; N Vox = Number of voxels in the cluster (if blank then the coordinate is a local maximum or minimum for the first coordinate above it that contains a value for N Vox); SPM{Z} = statistical parametric map maximum Z score value for the cluster; Sup = superior.

control segments using fMRI technology to evaluate regional brain activation during sexual arousal; and (ii) to use the superior resolution of fMRI to identify which regions of the brain exhibit changes in activation that correlate with physiological changes in sexual arousal in young, healthy heterosexual males.

With respect to aim (i), requiring that subjects be immobile within an enclosed, magnetized space did not present a significant impediment to examining the phenomena of interest. The experimental protocols operated as planned, with subjects reliably reporting sexual interest and erection during the erotic segments but not during the two comparison segments. In addition, the erection monitoring device designed for this study proved suitable in the fMRI environment with substantial evidence of subjects' engorgement during the erotic sequences, no engorgement during the control segments, and extremely high correlation between time of subjects' self-report of erection and mercury changes in the monitoring device. Thus, our study establishes the feasibility of fMRI to study brain activation and objective sexual arousal.

Regarding aim (ii), our findings may be summarized as follows. First, evidence of unique brain activation associated with sexual stimuli and response was strongest in the turgidity-correlated analyses; the block analyses revealed few significant differences. Secondly, the major areas of activation associated with tumescence were: (i) the right insula/subinsular region, including the claustrum; (ii) hypothalamus; (iii) caudate nucleus; (iv) putamen; (v) Brodmann area (BA) BA 24 and BA 32; and (vi) BA 37/19.

The large and significant activation in the right insula/subinsular region (including the claustrum) is strikingly similar to findings reported in PET studies of male sexual arousal (Stoleru *et al*., 1999; Redoute *et al*., 2000). While the insula has been linked to motor, vestibular and language functions (Augustine, 1985), it also lies in close proximity to the secondary somatosensory cortex, and both projects to and receives projections from the latter (Augustine, 1996). Evidence from a number of studies suggests that the insula is involved in visceral sensory processing including studies of taste (Scott *et al*., 1991; Smith-Swintosky *et al*., 1991) and oesophageal stimulation via balloon distention (Aziz *et al*., 1995). In addition, evidence including increased rCBF in the insula following vibrotactile stimulation (Burton *et al*., 1993) has led to the conclusion that the insula functions as a somatosensory processing area (for a review, see Augustine,

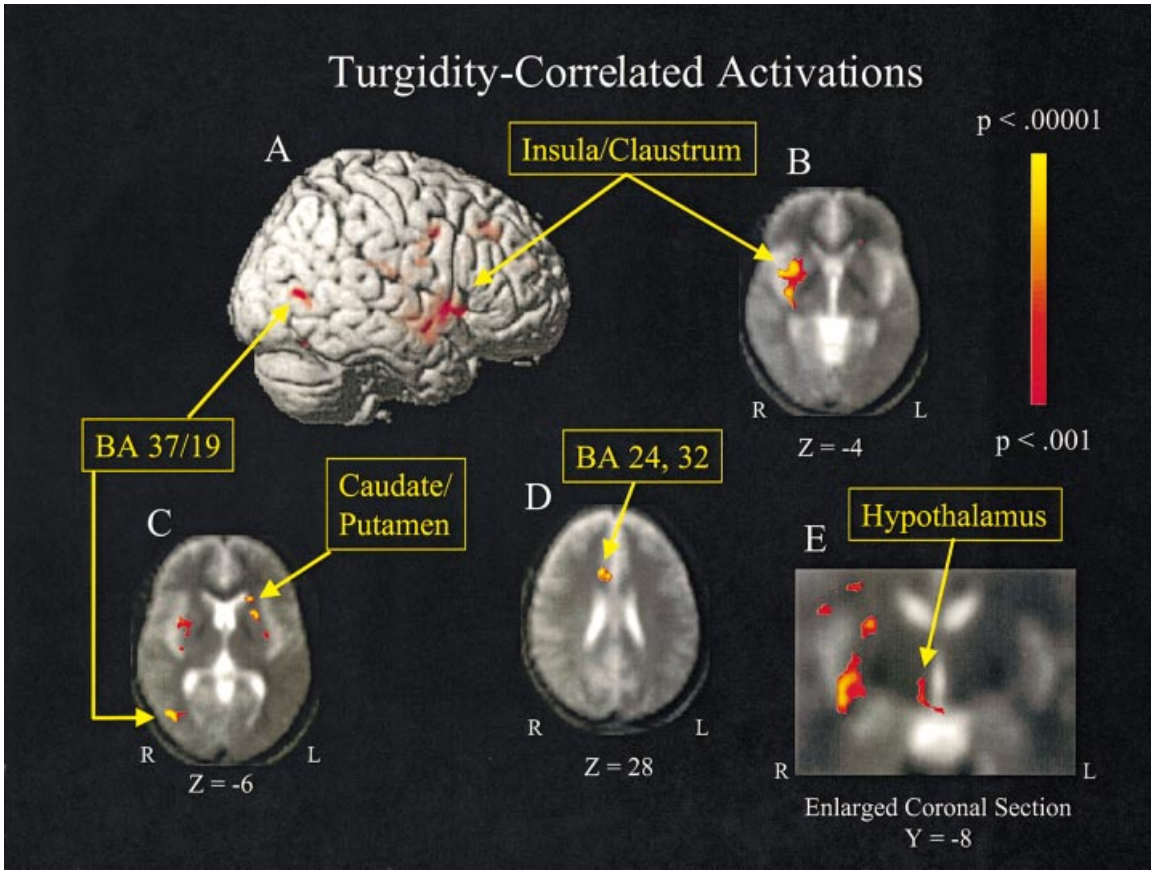

Fig. 4 Turgidity-correlated brain activations obtained from a random effects analysis of 11 subjects. Red–yellow colour scale indicates regions that exhibit significant correlations with behavioural measures of penile turgidity. These colour maps have been superimposed on the average T_2-weighted and stereotaxically normalized brain volume. (**A**) SPM99 surface reconstruction depicting projections of activations on the right side of the brain. (**B**) Axial section depicting the largest brain activation observed in this experiment in the right insula and claustrum. (**C**) Axial section illustrating activation in left caudate/putamen and right middle temporal/middle occipital gyri (BA 37/19). (**D**) Axial section depicting cingulate gyrus activation. (**E**) Coronal section illustrating activation in the right hypothalamus.

1996). Thus, activation observed in the insula in the present study may reflect somatosensory processing and recognition of erection.

Moreover, additional evidence suggests involvement of the right insula/claustrum in cross-modal information transfer. In a PET study investigating the regional neuroanatomic basis of sensory information transfer between different modalities (i.e. tactile and visual), young adult males were exposed to tactile–tactile, visual–visual and tactile–visual conditions in addition to a control condition using ellipsoids (Hadjikhani and Roland, 1998). Consistent with earlier findings (Horster *et al*., 1989; Ettlinger and Wilson, 1990), the results revealed that the right insula–claustrum region was uniquely involved in cross-modal matching, i.e. in tasks requiring subjects to visually identify objects that had been perceived by touching. Thus, our findings and those of others (Stoleru *et al*., 1999; Redoute *et al*., 2000) of claustrum/subinsular activation during arousal while watching erotic videos may reflect cross-modal transfer of visual input to imagined tactile stimulation. Other evidence consistent with this hypothesis comes from data gathered from traumatic brain injury patients with diminished sexual arousal indicating that impairment is associated with difficulties forming and manipulating sexually arousing imagery (Crowe and Ponsford, 1999) and from individuals with claustrum lesions who demonstrated abnormal somatosensory evoked potentials (Morys *et al*., 1988).

Other areas activated during tumescence were the hypothalamus and in the basal ganglia, the striatum (i.e. the caudate nucleus and the putamen). A large number of animal studies have linked the hypothalamus to sexual response. Evidence includes studies demonstrating that lesions in the medial preoptic area impair male copulatory behaviour in all species tested (for a review, see Meisel and Sachs, 1994) and that electrical stimulation of the paraventricular nucleus of the hypothalamus is associated with erection in rats (Chen *et al*., 1997; McKenna *et al*., 1997). In studies of humans, pituitary secretion of oxytocin from the paraventricular nucleus has been shown to increase during sexual arousal in males and females (Carmichael *et al*., 1987, 1994).

Moreover, dopamine is projected to both the hypothalamus and the striatum from the incertohypothalamic area and the substantia nigra, respectively. Evidence that dopamine facilitates male sexual behavior is substantial. For instance, dopamine agonists such as apomorphine have been shown to

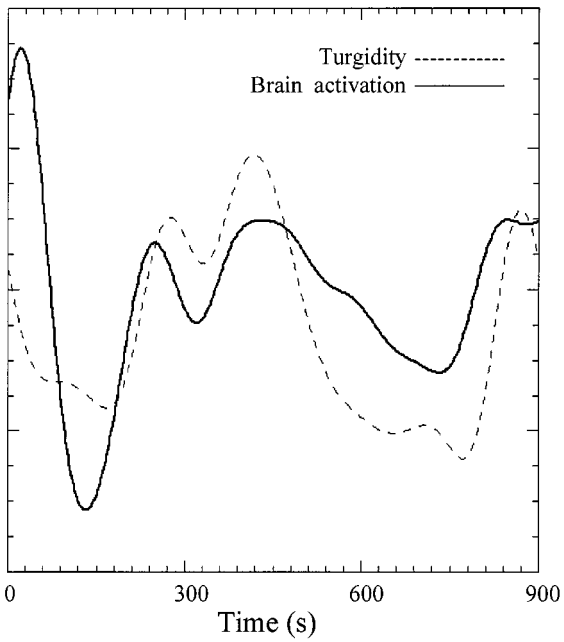

Fig. 5 Concordance of the temporal fluctuations observed for penile turgidity and brain activation of the right insular cortex/claustrum. Brain activation waveform was obtained by extracting from each subject the average time series data from voxels within a 5 mm radius of the $x = 41.6$, $y = 5.7$, $z = -2$ coordinate, where the maximum claustrum/insula activation was found, using the SPM99 volume of interest function. The resulting waveform for each subject, as well as that subject's penile turgidity measurements, were filtered with a Butterworth lowpass filter with cut-off frequency of 0.008 and then averaged across subjects.

induce erection in men with both normal and impaired erectile function (Lal *et al*., 1989), while antipsychotics which decrease dopaminergic activity are associated with erectile impairment (Marder and Meibach, 1994; Aizenberg *et al*., 1995). Another dopamine agonist, L-dopa, a medication for Parkinson's disease which itself is associated with 80–90% dopamine reductions in the striatum, has been shown to produce erection in men (Hyppa *et al*., 1970; Bowers *et al*., 1971; O'Brien *et al*., 1971). While there are several dopamine systems in the central nervous system, animal studies have linked both the nigrostriatal and the incertohypothalamic dopamine systems to sexual behavior (Hull *et al*., 1986; Eaton *et al*., 1991).

Activation in the anterior cingulate cortex, specifically BA 24 and BA 32, was also associated with tumescence. The anterior cingulate is known to be linked to attentional processes. More specifically, Devinsky and colleagues (Devinsky *et al*., 1995) suggested that BA 24 and BA 32 may guide responsiveness to new environmental stimuli. Abnormalities in anterior cingulate function have been reported in patients with obsessive–compulsive disorder (Rauch *et al*., 1994), autism (Ohnishi *et al*., 2000), and autism spectrum disorders (Haznedar *et al*., 2000), all of which are characterized by repetitive behaviour and difficulties shifting attention. However, contributions of the anterior cingulate to sexual response may also be more direct. BA 24 and BA 32 are involved in modulating autonomic and endocrine functions including gonadal and adrenal secretion (Devinsky *et al*., 1995). Electrical stimulation to BA 24 has been shown to bring about erection in monkeys (Robinson and Mishkin, 1968).

Activation during erection was also observed in the right middle temporal and middle occipital gyri (BA 37/19). Considerable evidence suggests that visual processing is a major function in this area. In a PET study focused on novel and familiar word and face stimuli, significant right hemisphere activation was reported in areas 37 and 19 in the novel and familiar face conditions, but not in either word condition (Kim *et al*., 1999). Other data suggest that BA 37/19 may be specifically involved in processing novel visual stimuli. In an fMRI investigation comparing face perception and memory using a repeated face, unrepeated novel faces, nonsense scrambled faces and a blank screen, areas 37 and 19 were significantly activated during the novel face condition but not during the comparison conditions (Clark *et al*., 1998). Similar to face processing, the visual focus of our participants is likely to have involved considerable feature abstraction.

Unlike recent PET studies of sexual arousal (Stoleru *et al*., 1999; Redoute *et al*., 2000), block analyses of the data revealed relatively few activations. Differences in experimental design may explain this discrepancy. First, compared with our investigation, the latter studies incorporated substantially longer temporal separation between erotic and non-erotic conditions (i.e. 15 min versus 30–60 s). Secondly, the sports comparison condition in our study may have been a more effective control compared with the humour conditions in the PET studies. Although there were some areas of overlap, on the whole we found substantially different regions of activation compared with the one published fMRI study of male arousal (Park *et al*., 2001). This may be attributable to the absence of objective measurement of tumescence in the study by Park and colleagues (Park *et al*., 2001), as well as the absence of non-neutral visual segments (e.g. sports) to control for general arousal.

It should be noted that neuroimaging studies of respiratory control have revealed insular, hypothalamic and paralimbic activations in studies of humans who underwent breathlessness induction (Brannan *et al*., 2001; Liotti *et al*., 2001; Parsons *et al*., 2001). The modest but significant correlations we observed between turgidity and respiration (0.295 for video 1, 0.45 for video 2) introduce the possibility that some of the observed relationships between brain activation and sexual response in our study may be respiratory-related. However, given the complexity of brain functions associated with sexual response and the correlational nature of the data, we are unable to state with certainty which activations are primarily or specifically sexual and which relate to other autonomic functions.

Although we cannot draw causal conclusions regarding brain–behaviour relationships, the regions of activation do provide hypotheses about which regions of the brain, if damaged, might produce changes in sexual function. Further

studies of brain-damaged patients reporting such changes may shed additional light on the precise roles of activated regions in sexual arousal. In addition, the potential contribution of hormonal influences (e.g. testosterone) as mediators of sexual response were beyond the scope of the present study, but could also contribute significantly to the activations.

The present study specifically investigated the neural correlates of sexual arousal in young healthy males. Of significant interest for future studies is how these activations might change as a function of age, and how male and female brain activations might differ. With respect to such differences, a recent 1.5 T fMRI study of six females reported activation sites in areas of the thalamus, amygdala, anterior temporal cortex, fusiform gyrus, inferior frontal gyrus and posterior temporal regions (Maravilla *et al*., 2000). These activations do not overlap with the large insular/sub-insular, cingulate and basal ganglia activations observed in the present study. Further studies will be needed to determine if such discrepancies reflect gender or paradigm differences in sexual arousal related brain activation.

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