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Apomorphine-induced brain modulation during sexual stimulation: a new look at central phenomena related to erectile dysfunction

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It is well recognized that sexual stimulation leading to penile erection is controlled by different areas in the brain. Animal erection studies have shown that apomorphine (a D2>D1 dopamine receptors nonselective agonist) seems to act on neurons located within the paraventricular nucleus and the medial preoptic area of the hypothalamus. Yet, only recently, was a centrally acting agent, apomorphine sublingual, approved for the treatment of erectile dysfunction. The present functional magnetic resonance imaging placebo-controlled study presents the first *in vivo* demonstration of the apomorphine-induced modulation of cortical and subcortical brain structures in patients with psychogenic erectile dysfunction. Noteworthy, patients in comparison with potent controls, showed an increased activity in frontal limbic areas that was downregulated by apomorphine. This suggests that psychogenic impotence may be associated with previously unrecognized underlying functional abnormalities of the brain.
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Introduction

Apomorphine sublingual (sl) is the first centrally acting agent officially approved for the treatment of erectile dysfunction (ED). Animal studies have clarified the role of apomorphine in initiating the erectile process.[1] Apomorphine has been shown to be a mixed D1/D2 dopamine receptor agonist with more potent D2-like effects. Selective postsynaptic D2 receptor activation seems to promote dopamine agonist-induced stretching–yawning and penile erection. The paraventricular nucleus (PVN) of the hypothalamus have been identified in rats as the brain site where apomorphine acts to induce the erectile response, whereas it modulates sexual behavior (and hence penile erection in mating tests) by acting on the medial preoptic area (MPOA).[2–4] Dopamine-containing nerve endings seem to impinge on oxytocinergic cell bodies in PVN which, in turn, project to extrahypothalamic brain areas (eg hippocampus, the medulla oblongata and the spinal cord) activating proerectile central neurological pathways involving nitric oxide signaling, finally resulting in penile erection.[4–10] These neurons directly or through interconnections reach the spinal cord where they synapse with neurons located at the sacral level. The latter neurons reach the smooth muscle cells of the corpora cavernosa through the cavernous nerves fibers. Additional actions within the spinal cord may also contribute to the overall profile of apomorphine on sexual function.[11] To date, the mechanisms for comparable effects induced by apomorphine in humans have not been reported. Functional magnetic resonance imaging (fMRI) is a technique that has been recently used for the evaluation of functional neuroanatomy related to various processes including sexual responses.[12,13] The aim of this study was to evaluate in the brain the functional effect of apomorphine sl versus placebo in patients with psychogenic ED by using fMRI.

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Materials and methods

We identified eight consecutive patients seen at our outpatient clinic with a diagnosis of psychogenic ED. The diagnosis was based on the following: absence of any organic comorbidities or risk factors for ED, reported normal morning erections, normal penile hemodynamics according to color Doppler sonography, normal nocturnal erections as evaluated by the RigiScan™ device during three consecutive nights in the sleep laboratory of our institute. The mean duration of ED was 11.4 months (range: 6–17 months). Mean patient age was 43 y (range: 25–58 y). All patients had been previously enrolled in a home trial with apomorphine sl 4 mg and had responded to the drug.

All patients underwent two separate fMRI sessions, which were scheduled 7 days apart. Each fMRI session started 15 min after the double-blinded administration of placebo or apomorphine sl 4 mg, following a randomized, crossover design. During fMRI acquisition, each patient was shown 24 consecutive neutral (NVS) and erotic (EVS) videosequences of 40 s each in a alternated block-study fashion. The selected scenes were comparable except for the erotic content, the neutral sequences showing people speaking or walking.

Four potent volunteers (mean age 25 y; range: 22–28 y) with no history of physical, psychiatric or neurological diseases and in whom nocturnal penile tumescence and rigidity testing was normal were enrolled in this study as controls. These four fully potent controls did not receive placebo.

The study received the approval of our Ethics Committee and all patients and controls signed an informed consent.

Functional-MRI data were acquired using a 1.5 T Signa Horizon GE (General Electric Medical Systems, Milwaukee, WI, USA) scanner equipped with echo speed gradients using a standard quadrature head coil. The functional images were acquired using a gradient echo EPI pulse sequence ($TR = 3000$ ms, $TE = 60$ ms, 64×64, 280×280 mm^2). The 24 slices, 4 mm thick, were positioned to cover the Talairach space from -24 to $+68$ with respect to the AC–PC line. Data analysis was performed with ANALYZE-5 (BRU, Mayo Foundation, Rochester, MN, USA) in Matlab 7.2 (Math Works, Natick, MA, USA) using Statistical Parametric Mapping software (SPM-99, Wellcome Department of Cognitive Neurology, London, UK). A factorial design enabled the comparison of patients and normal participants in terms of the activations engendered by the experimental tasks and the pharmacological challenge and the interaction of the two.[14] In detail, we performed *direct comparisons* between the experimental condition (EVS) and the baseline condition (NVS) in patients and in normal participants:

1. EVS – NVS in patients during placebo condition,
2. EVS – NVS in patients during apomorphine condition,
3. EVS – NVS in controls.

In patients, statistical *interactions* between visual tasks during apomorphine or placebo condition were also calculated, masking for the condition of interest:

A. $(EVS–NVS)^{\text{in apomorphine}}$-$(EVS–NVS)^{\text{in placebo}}$ masked for $(EVS–NVS)^{\text{in apomorphine}}$,

B. $(EVS–NVS)^{\text{in placebo}}$-$(EVS–NVS)^{\text{in apomorphine}}$ masked for $(EVS–NVS)^{\text{in placebo}}$.

These provide the significant activation increases for apomorphine during EVS (A) and the significant decreases induced by drug administration (B).

Results

At the end of both the first and second fMRI session, each patient has been investigated by means of some general assessment questions concerning physical and emotional sensation during the projection of neutral and erotic videosequences. Six out of the eight (75%) patients reported penile erection following the intake of apomorphine sl. On the other hand, two out of the four (50%) healthy volunteers reported a penile erection during the erotic videosequences projection.

The direct comparisons between the experimental condition and the baseline condition in patients and in normal participants demonstrated:

Direct comparisons 1 *and* 3: Viewing EVS, in comparison to NVS, elicited a common activation pattern in patients and controls. This was characterized by bilateral brain activations in prefrontal and premotor cortex, in associative occipital and parietal areas, in the temporal polar cortex and in the pons. At difference, the frontal mesial and frontal basal cortex, the cingulate cortex, hippocampus, the thalamus and hypothalamus were activated only in patients with psychogenic ED (see Table 1).

Direct comparisons 1 and 2: In the patients, apomorphine sl induced a downregulation of the frontomesial and frontobasal cortex, thus making the functional pattern similar to the normal one. Noteworthy, the drug induced also significant activations in the pallidum and midbrain (see Table 1).

In patients with psychogenic ED viewing EVS, we found an increase in the extension of the above-described activated networks during apomorphine sl in comparison to the placebo condition. Indeed, sl administration of a therapeutic dose of apomorphine elicited a brain response in areas known to be associated with erection,[15–17] but quantitatively

Table 1 Comparisons between erotic and neutral sequences (T: 3.09, $P \leq 0.001$)

	Controls				*Patients in placebo*				*Patients in apomorphine*			
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
(L) Posterior occipital cortex (18)	−22	−90	20	>8	−26	−86	12	>8	−32	−90	−8	>8
Lateral occipital cortex (18, 19)	−44	−82	−8	>8	−40	−88	−4	>8	−48	−78	−8	>8
Inferior temporal cortex (37)	−44	−82	−16	>8	−48	−78	−16	>8	−48	−78	−8	>8
Inferior parietal cortex (40)	−48	−38	40	>8	−34	−46	44	>8	−38	−48	44	>8
Superior parietal cortex (7)	−30	−60	52	>8	−30	−64	52	>8	−30	−60	52	>8
(R) posterior occipital cortex (18)	26	−28	16	>8	32	−82	16	>8	34	−80	8	>8
Lateral occipital cortex (18, 19)	34	−80	8	>8	36	−78	8	>8	46	−78	−8	>8
Inferior temporal cortex (37)	44	−74	16	>8	56	−66	16	>8	56	−66	−16	>8
Inferior parietal cortex (40)	46	−38	40	>8	40	−40	44	>8	44	−40	44	>8
Superior parietal cortex (7)	30	−64	52	>8	24	−64	56	>8	34	−56	56	>8
(L) Lateral premotor cortex (6)	−50	2	32	>8	−54	6	32	>8	−54	6	32	>8
Prefrontal cortex (44, 45)	−58	10	16	>8	−46	10	20	6.3	−48	8	20	>8
(R) Lateral premotor cortex (6)	58	4	36	>8	46	0	48	>8	38	2	56	>8
Prefrontal cortex (44, 45)	56	8	12	>8	62	18	12	>8	52	16	28	>8
(L) Temporal anterior cortex (38)	−56	18	−12	4.2	—	—	—	NS	−54	18	−16	4.7
(R) Temporal anterior cortex (38)	44	0	−16	5.0	46	2	−8	3.8	56	8	0	3.4
(L) Thalamus	—	—	—	NS	−16	−6	8	6.3	−14	−4	4	>8
(R) Thalamus	—	—	—	NS	14	−6	12	6.6	2	−16	8	5.3
(L) Frontal mesial cortex (10)	—	—	—	NS	−6	66	12	6.9	—	—	—	NS
(R) Frontal mesial cortex (10)	—	—	—	NS	2	66	20	4.3	—	—	—	NS
(L) Frontal basal cortex (11)	—	—	—	NS	−8	28	−12	>8	—	—	—	NS
(R) Frontal basal cortex (11)	—	—	—	NS	10	30	−12	>8	—	—	—	NS
(L) Cingulate cortex (24)	—	—	—	NS	−2	26	−4	4.8	—	—	—	NS
(R) Cingulate cortex (24)	—	—	—	NS	2	26	−4	4.8	—	—	—	NS
(R) Hippocampus	—	—	—	NS	32	−36	−8	4.3	—	—	—	NS
(L) Pallidum	—	—	—	NS	—	—	—	NS	−14	−4	4	>8
(R) Pallidum	—	—	—	NS	—	—	—	NS	16	−4	4	7.4
(L) Putamen	—	—	—	NS	−18	−4	8	5.5	—	—	—	NS
(R) Putamen	—	—	—	NS	20	−8	8	4.1	—	—	—	NS
(R) Midbrain	—	—	—	NS	—	—	—	NS	12	−16	−4	5.4
(L) Midbrain	—	—	—	NS	—	—	—	NS	−4	−20	−4	>8
Hypothalamus	—	—	—	NS	0	−12	−8	4.0	−8	2	−8	6.5
Pons	12	−38	−20	4.6	6	−34	−20	5.7	10	−34	−20	6.7

L: left; R: right; *xyz*: stereotactic coordinates according to the Talairach atlas; Z scores: level of significance. In brackets the Brodmann areas; NS: not significant ($P > 0.001$).

greater than in placebo (extent of voxel cluster level in left and right occipito-temporo-parietal cortex from 3701 to 5498, in frontal cortex from 556 to 1484, $P < 0.001$).

Interactions: The interactions between task conditions (EVS and NVS) confirmed these findings by showing the activated bilateral network during apomorphine (Figure 1a, Table 2):

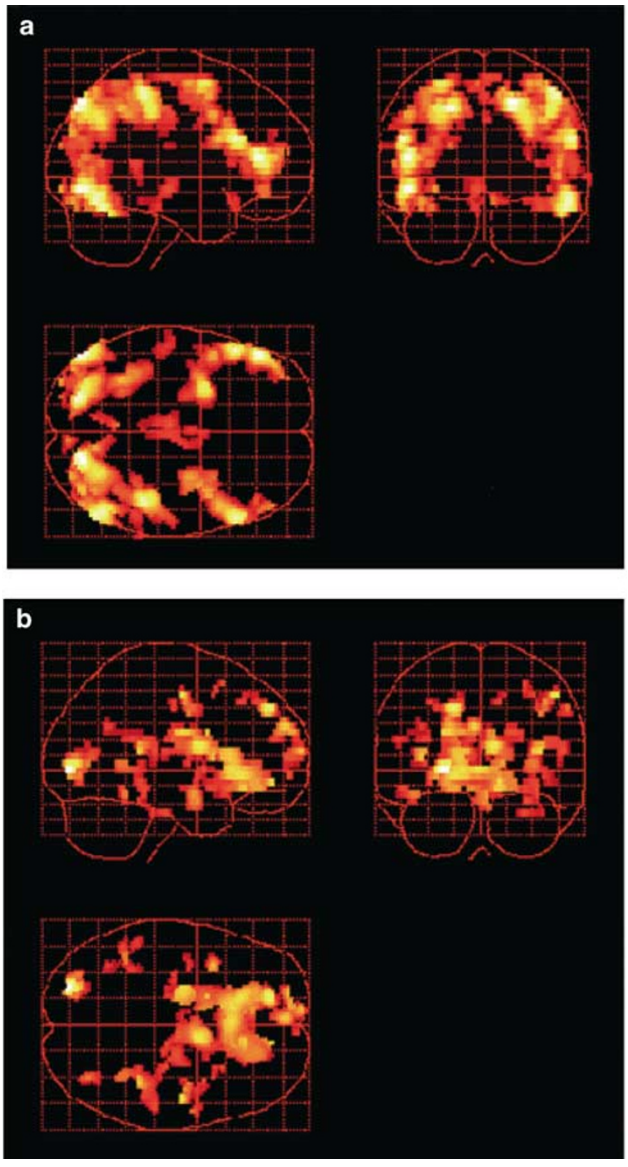

Figure 1 The functional modulation induced by apomorphine sl in psychogenic ED patients. See Table 2 and text for details. (**a**) Activations and (**b**) deactivations during apomorphine sl in patients as obtained by interaction analysis. The colors (red to white) are proportional to statistical significance, from suprathreshold values ($Z = 3.09$, red) to maximum ($Z > 8$, white).

extrastriate occipital regions, superior and inferior parietal lobules, prefrontal and premotor cortex, midbrain and the pons. A downregulation as identified by the decrease of fMRI signal reflecting the deactivation of specific brain regions was found in (Figure 1b, Table 2): the frontal basal, frontal polar, frontal mesial cortex, the cingulate gyrus, insula, caudate nucleus, hippocampus and hypothalamus.

Discussion

Apomorphine sl has been recently approved in Europe as the second oral treatment for ED and the postmarketing experience will better define its precise role within the therapeutic algorithm for impotent patients. Apomorphine, a small molecule derived by acid modification of morphine, has key structural similarities to dopamine. It has nonselective dopamine receptor (D2 > D1) agonist activity and has been extensively studied in animals, primarily rodents as a prototypical dopaminergic initiator of erectile pathways in the brain.[9] Apomorphine has PVN selective action at doses relevant to erectile response, as verified by c-fos labeling techniques.[2] Several studies have also emphasized the role of the medial amygdala and MPOA in sexual behavior. Dopamine (DA) in the MPOA results especially important for copulation; indeed, microinjections of apomorphine into the MPOA facilitated copulation.[3] Available data suggest that the hypothalamic–hippocampal oxytocinergic pathways may mediate apomorphine-induced penile erection,[5] as clearly stated when bilateral electrolytic lesions of the PVN prevent yawning and penile erection induced by oxytocin.[18] On the other hand, oxytocin seems to be involved at different levels of the central nervous system (CNS) in the regulation of these responses. Nitric oxide (NO), which has a well-known role in the peripheral mediation of erection,[19] has also been implicated in the central initiation of erection.[20] *In vivo* studies on rats have shown that oxytocin may increase NO production in the PVN[21,22] and the oxytocinergic system may be influenced by the NO synthase signal transduction pathway. The activation of these pathways, through a hierarchical control of sexual reflexes, leads to a cascade of events ultimately causing smooth muscle relaxation and a penile erection.[23] The brainstem inputs onto the spinal cord circuits regulating sexual reflexes are primarily inhibitor with the neurons located in the nucleus paragigantocellularis (nPGi) being responsible for this inhibition. Excitatory pathways may relay through the midbrain periaqueductal gray (PAG) to the spinal cord or via dis-inhibition of nPGi neurons. Sympathetic, parasympathetic and somatic systems are interconnected by spinal interneurones, which regulate spinal motor output and, ultimately, penile erectile function.

In our fMRI study, we evaluated *in vivo*, the action of apomorphine on brain systems, in humans during both neutral and erotic visual stimulation. The brain activations seen in our study were exclusively because of the erotic stimulation since all the basic visual processes operating during observation of video sequences were subtracted out by the baseline condition.

Table 2 Interactions for the patient group (T: 3.09, $P>0.001$) (A) (erotic sequences versus neutral sequences) in apomorphine versus (erotic sequences versus neutral sequences) in placebo, (B) (erotic sequences versus neutral sequences) in placebo versus (erotic sequences versus neutral sequences) in apomorphine. Masked for condition of interest

	(A) activations				*(B) deactivations*			
	x	y	z	*Z*	x	y	z	*Z*
(L) Precuneus (7)	−20	−80	44	>8	—	—	—	NS
Inferior occipital gyrus (18)	−32	−90	−8	7.2	−22	−84	0	>8
Lateral occipital cortex (18,19)	−48	−78	−8	>8	—	—	—	NS
Inferior parietal cortex (40)	−32	−52	44	7.8	—	—	—	NS
Superior parietal cortex (7)	−4	−54	60	6.0	—	—	—	NS
(R) Precuneus (7)	20	−76	48	>8	—	—	—	NS
Inferior occipital cortex (18)	6	−86	−16	6.2	—	—	—	NS
Inferior parietal cortex (40)	44	−38	56	>8	—	—	—	NS
(L) Premotor cortex (6)	0	−6	52	4.2	—	—	—	NS
Prefrontal cortex (46)	−50	38	12	>8	—	—	—	NS
Cingulate cortex	—	—	—	NS	−10	4	12	5.7
Cingulate cortex	—	—	—	NS	−8	−6	12	3.4
Frontal polar cortex (8)	—	—	—	NS	−18	46	40	>8
Frontal polar cortex (9, 10)	—	—	—	NS	−4	56	28	6.7
Frontal basal cortex (11)	—	—	—	NS	−16	26	−4	7.1
(R) Premotor cortex (6)	42	4	52	7.7	—	—	—	NS
Prefrontal cortex (44, 45 46)	56	22	24	>8	—	—	—	NS
Cingulate cortex	—	—	—	NS	8	2	16	7.5
Cingulate cortex	—	—	—	NS	8	−12	16	4.9
Frontal mesial cortex (10)	—	—	—	NS	12	48	−8	6.8
Frontal basal cortex (11)	—	—	—	NS	12	30	−12	6.7
(L) Superior temporal gyrus (22)	—	—	—	NS	−34	−42	20	4.5
(R) Superior temporal gyrus (22)	—	—	—	NS	38	−38	12	6.9
(R) Fusiform gyrus	54	−68	−16	>8	—	—	—	NS
(L) Insula	—	—	—	NS	−36	−6	4	4.4
(R) Insula	—	—	—	NS	36	4	0	4.7
(L) Caudate	—	—	—	NS	−12	22	0	7.1
(R) Caudate	—	—	—	NS	10	22	0	5.8
(L) Hippocampus	—	—	—	NS	−28	−20	28	4.6
(R) Hippocampus	—	—	—	NS	30	−38	−20	4.6
Hypothalamus	—	—	—	NS	4	−2	−16	5.7
Midbrain	−4	−20	−8	5.6	—	—	—	NS
Pons	−6	−28	−20	4.7	—	—	—	NS

L: left; R: right; *xyz*: stereotactic coordinates; Z scores: level of significance. In brackets the Brodmann areas; NS: not significant ($P>0.001$).

In normal controls, as well as in patients with ED, viewing erotic films activated a bilateral network in the dorsolateral and premotor frontal cortex, the occipital, parietal and temporal anterior regions. These results are in agreement with other reports in literature of visually evoked sexual arousal in males showing bilateral activation of prefrontal areas, parietal lobes and, mainly, the occipital and inferior temporal, vision related, regions.[15–17,24–25] It has been proposed that human sexual arousal is a multifactor process comprising inter-related components. Among these there are the cognitive, emotional, motivational and physiological components, which concern different and specific cortical and

subcortical brain structures. For instance, the physiological component is related to autonomic and endocrinological responses, and it has been referred to activation of hypothalamus and cingulated cortex.[15] Activation of associative cortices endows the cognitive and emotional contents.[15,16,24] A SPECT study during orgasm in healthy males also showed a right prefrontal rCBF increase.[26]

PET studies in normal volunteers on the effects of apomorphine alone contributed to the *in vivo* demonstration of the systems involved in dopamine regulation.[27,28] The rCBF increases were found in the brain regions, that receive dopaminergic projections.[29] Our data complement the results of these studies since, for the first time, they report the effects of the erotic visual stimulation in a selected series of patients during apomorphine.

A striking difference was found in patients in comparison to the normal participants, since they demonstrated significant and extended activations in the frontal mesial and frontal basal cortex, and in the cingulate gyrus, bilaterally (Table 1). These additional activations seen in psychogenic impotent patients and not in potent controls may suggest the presence of an underlying biologic factor for ED at the brain level. An alternative explanation might be on a functional basis: the activated brain regions, belonging to a limbic orbitofrontal network, might have been activated by a specific emotional reaction in the patients and not in controls. Noteworthy, a modulation of this neural system was induced by apomorphine sl administration in the patients, leading to an fMRI picture comparable to the one seen in potent controls (Table 1). This modulatory effect was also exerted through activation of subcortical and deep structures, namely the pallidum, hypothalamus, midbrain and pons structures (Table 1 and 2, Figure 1). During fMRI, the majority of patients demonstrated penile erection following apomorphine sl suggesting a correlation between these drug-induced brain activations and the observed erectile events.

The fMRI activations recorded in associative areas (occipital–temporal, frontal), in paralimbic areas (anterior cingulate gyrus, mesial and orbito-frontal cortex), in the striatum (pallidum) and in the posterior hypothalamus provide the brain functional correlates in mediating the emotional, motivational and autonomic components of human male sexual arousal in pathological condition (ED) and its modulation during pharmacological challenge (Tables 1 and 2, Figure 1). We suggest that these findings appear both to support current concepts regarding the erectogenic activity of the drug and to stimulate further neurophysiological research in the area of 'psychogenic' ED.

The fMRI interaction studies between task conditions (EVS and NVS) demonstrated the bilateral activation of the thalamus during apomorphine absorption. A few *in vivo* data of the literature reported an action of apomorphine also in the thalamus. Beck *et al*,[30] for instance, have studied the dose-dependent changes in behavioral patterns and in local cerebral glucose utilization (LCGU) following subcutaneous application of apomorphine in conscious, unrestrained rats by means of a scoring system and autoradiographic [^{14}C]-2-deoxyglucose technique. Maximal scores for yawning and penile erections were obtained after 0.07 mg/kg. After subcutaneous apomorphine (0.07 mg/kg) LCGU was not significantly changed except for decreases in the cingulate cortex and hypothalamus. Apomorphine 0.5 mg/kg decreased LCGU in the cingulate, parietal and occipital cortex, antero-medial and lateral thalamus and lateral habenula but increased it in laminae IV and VI of the sensori-motor cortex, in the parafascicular nucleus of the thalamus, and in some parts of the basal ganglia and related nuclei. However, the data obtained with LCGU did not support the idea that behavioral effects after low doses of apomorphine (ie doses relevant to erectile response) could be elicited by activation of dopamine autoreceptors at the thalamic level.

A recent study performed in rats (ie unilaterally lesioned with intranigral 6-hydroxydopamine rats) using magnetic resonance imaging to detect dopaminergic supersensitivity and hemodynamic time course reflective of this fact in different brain regions did also show that intranigral apomorphine injections lead to a large increase in hemodynamic response (cerebral blood volume) in the striato-thalamo-cortico circuit on the lesioned side but had little effect on the intact side and did not exert a penile erection *per se*.[31] On the contrary, Schwarting and Huston supported findings on the behavioral and neurochemical effects of apomorphine in the neostriatum and ventral mesencephalon, and added new evidence for an action on the septal area, thalamus and fronto-parietal cortex.[32] It must be underlined that this last study was performed with 0.5 mg/kg apomorphine dosing and it was therefore out of range of dosing relevant to penile erection. Thus, further studies are surely needed to verify that apomorphine may also activate thalamus as an important target for penile erection in humans. Functional-MRI could provide an important new tool in evaluating the cerebral areas of the penile erection functionally activated during stimulation by means of different neurochemical agonists.

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