Brain activation during human male ejaculation revisited

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In a prior [^{15}O]-H_2O positron emission tomographic study we reported brain regions involved in human male ejaculation. Here, we used another, more recently acquired data set to evaluate the methodological approach of this previous study, and discovered that part of the reported activation pattern was not related to ejaculation. With a new analysis of these ejaculation data, we now demonstrate ejaculation-related activations in the deep cerebellar nuclei (dentate nucleus), anterior vermis, pons, and ventrolateral thalamus, and, most importantly, ejaculation-related deactivations throughout the prefrontal cortex. This revision offers a new and more accurate insight into the brain regions involved in human male ejaculation. *NeuroReport* 18:553–557 © 2007 Lippincott Williams & Wilkins.

Keywords: deep cerebellar nuclei, methodology, orgasm, positron emission tomography, prefrontal cortex, sexual behaviour

Introduction

In 2003, we reported on ejaculation-related brain regions, identified with [^{15}O]-H_2O positron emission tomography (PET) [1]. Single, short-lasting, more or less randomly occurring events like ejaculation, however, are not commonly investigated with [^{15}O]-H_2O PET and provide a methodological challenge [2,3].

In conventional [^{15}O]-H_2O PET, data are usually integrated over a 90–120 s-period, during which an experimental task is performed continuously. With single, short-lasting events the task is less homogenous over the course of the scan, which reduces the statistical power [2,3]. In addition, it puts constraints on the timing of the event, because of different sensitivities within the scan owing to radiotracer dynamics [2,3].

Therefore, we used a customized methodological approach to investigate ejaculation-related brain activity: we ensured that ejaculations occurred within a fixed time window and, to enhance the specificity, we selected only 20 s of data around the moment of ejaculation. Following this approach we found abundant activation, primarily in the midbrain, the thalamus, the striatum, and the cerebellum, but also in parts of the neocortex [1]. This methodological approach, however, could not be validated at the time.

The acquisition of a new data set enabled us to evaluate our previous methodology. Here, we present the results of this evaluation. In addition, we reanalysed the ejaculation data using a different strategy. Through this combined effort we put forward a new view on the neurobiology of the sexual climax in men.

Materials and methods

Figure 1 gives an overview of the data analysis flow. In our previous paper, we essentially compared 20-s images of ejaculation scans (EJAC) with 120-s images of stimulation of the erect penis scans (STIp) [1]. Here, we report the results of two types of analysis:

(1) *Evaluation*. To validate our previous methodological approach [1], we performed three analyses comparing 20-s and 120-s images of the same condition.
(2) *Reanalysis*. We compared equal 120-s images of EJAC and STIp.

Participants and conditions

Two data sets were used, both of which were approved by the institution's internal medical ethics committee and complied with the national laws on the use of human participants and the declaration of Helsinki.

Data set I: data set of previous paper [1]

Eleven heterosexual male volunteers were included. The experiment consisted of eight scans and four conditions, including EJAC and STIp. A more detailed description of the participants and conditions was given earlier [1]. Here, this data set was used for evaluation and reanalysis (Fig. 1).

Data set II: evaluation data set

This data set was acquired more recently than data set I. Eleven healthy, right-handed heterosexual female

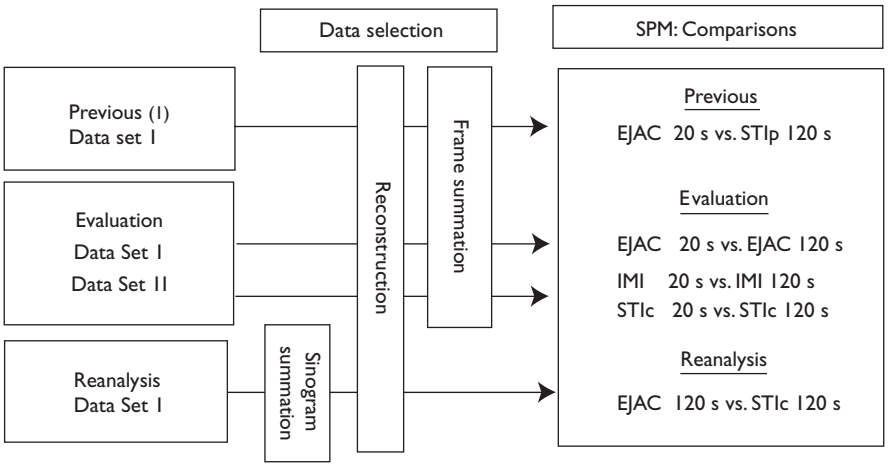

Fig. 1 Data analysis flow. The previous analysis of data set I [I] (top row) was evaluated using data set I proper and the more recently acquired data set II (middle row). Finally, data set I was reanalysed (bottom row). EJAC, ejaculation; IMI, imitation (motor task); SPM, Statistical Parametric Mapping; STI_c, clitoral stimulation; STI_p, stimulation of the erect penis.

volunteers (mean age 35 years; range 21–47) were included. The experiment, designed to investigate the neurobiology of orgasm in women, consisted of eight scans and four conditions:

(1) *Rest*: passive, nonsexual resting state.
(2) *Imitation (IMI)*: voluntary, repetitive contractions of hip, buttock, abdominal, and pelvic floor muscles in a rhythmic 'orgasm-like' fashion.
(3) *Stimulation (STIc)*: receiving clitoral stimulation without executing bodily movements.
(4) *Orgasm*: orgasm induced by clitoral stimulation.

A separate paper describes brain regions related to orgasm in women [4]. Here, this data set was used only for evaluation (IMI and STIc, see Fig. 1).

Data acquisition

General acquisition protocol

The volunteer was positioned supine in the PET scanner (Siemens Ecat HR+, Siemens AG, Erlangen, Germany; 4–5 mm full width at half maximum spatial resolution in all three directions). PET scans were made in 3D-mode (63 planes; axial field of view of 15.5 cm) and the radiotracer [^{15}O]-H_2O was used to measure regional cerebral blood flow (rCBF). Per scan, 500 MBq of activity was dissolved in 32 ml of sterile saline (0.9%), and administered intravenously at 8 ml/s. After injection of the radiotracer, data were collected for 120 s. Consecutive scans were made with intervals of approximately 8 min. This protocol was the same for data sets I and II.

Multiple frame acquisition

There was an important difference was observed in the acquisition of data sets I and II (Fig. 1):

Data set I: EJAC was acquired in eight data frames (7×10 and 1×50 s), the other scans in one data frame of 120 s.
Data set II: all scans were acquired in eight data frames (7×10 and 1×50 s).

Image reconstruction

Image reconstruction was the same for both data sets. The emission scans were reconstructed using the filtered back-projection reconstruction algorithm. Attenuation correction was performed using manually drawn ellipses on the images, thereby preventing artifacts induced by inter-scan displacement [5].

Data selection

Evaluation

After image reconstruction, 20-s and 120-s images of the same condition were selected and summed, making sure that the 20-s selections corresponded with those for ejaculation in our previous paper [1]. This 20-s and 120-s selection was performed for one condition from data set I, EJAC, and two from data set II, STIc (sensory task) and IMI (motor task). In comparison to STIc and IMI, which were performed for the full duration of the scan, the 120-s images of EJAC represented an heterogenous condition.

Reanalysis

From data set I all data frames were summed for EJAC to obtain 120-s images. To optimize the signal-to-noise ratio, the data frames were summed before image reconstruction (Fig. 1: sinogram summation) [6].

Spatial preprocessing

Spatial preprocessing was the same for both data sets. Using Statistical Parametric Mapping (SPM99) software [7], the data were realigned, spatially normalized ($7 \times 8 \times 7$ non-linear basis functions; 12 iterations; heavy regularization), and smoothed (Gaussian filter of 10 mm full width at half maximum).

Statistical analysis

For both data sets, 11 participants and eight conditions were added as factors to the general linear model in SPM99 [8]. Global blood flow differences were corrected for by proportional scaling (analysis threshold 1.2). This procedure also normalized the large difference in global count rate between a 20-s and a 120-s image.

Table 1 Artefactual (de)activations from comparing 20 s and 120 s-[^{15}O]-H_2O-PET-images

Previous result [1]	Evaluation analyses		
Data set I	Data set I	Data set II	Data set II
EJAC 20 s *STIp 120 s*	*EJAC 20 s* *EJAC 120 s*	*IMI 20 s* *IMI 120 s*	*STIc 20 s* *STIc 120 s*
Activated Clusters			
Dorsal medulla	–	–	–
Pontine tegmentum	–	+[a]	–
Midbrain and thalamus	+	+	+
Putamen/claustrum	+	+	+
Cerebellar hemisphere	+	+	+
Vermis	+	+	+
Deep cerebellar nuclei	–	–	–
Lingual gyrus (BA 18)	+	+	+
Inferior parietal lobule (BA 39/40)	+	+	+
Precuneus (BA 7)	+	+	–
Superior parietal lobule (BA 7/19)	+	+	+
Inferior temporal gyrus (BA 20)	+	–	–
Superior temporal gyrus (BA 42)	+	+	+
Superior frontal gyrus/ Precentral gyrus (BA 4/6)	+	+	+[b]
Inferior frontal gyrus (BA 47)	+	+	+
Deactivated Clusters			
Entorhinal cortex/extracerebral	–	+	+

The previous results [1] are listed in the left column. The three columns on the right indicate whether these clusters were (+) or were not (–) found with the evaluation analyses. Clusters with a '+' in all three columns can no longer be attributed to ejaculation.
[a]Midline, while bilateral in [1].
[b]Left, while bilateral in [1].
BA, Brodmann's area; EJAC, ejaculation; IMI, imitation (motor task); PET, positron emission tomography; STIc, clitoral stimulation (sensory task); STIp, stimulation of erect penis; 120 s, 120 s-image; 20 s, 20 s-image.

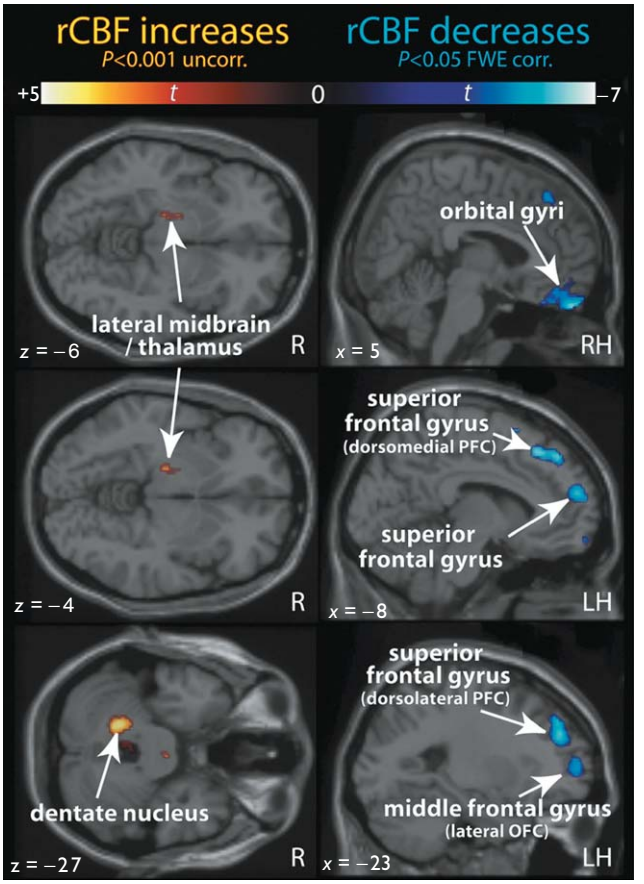

Fig. 2 Ejaculation-related rCBF changes, comparing 120s-images of ejaculation and stimulation of the erect penis. rCBF Increases are depicted in the left column ($P<0.001$, uncorrected), rCBF decreases in the right column ($P<0.05$, corrected). LH, left hemisphere; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; R, right; RH, right hemisphere; *t*, *t*-value; *x*, distance (mm) relative to midsagittal plane (+right; –left); *z*, distance (mm) relative to intercommisural line (+dorsal; –ventral).

Evaluation

Three separate statistical designs were built (Fig. 1), containing both the 20-s and 120-s images of: (i) EJAC, (ii) IMI, or (iii) STIc. In each design, the normalized 20-s and 120-s images of the same condition were treated as activation and baseline conditions, respectively. Differences in rCBF between activation and baseline conditions were tested by performing a two-tailed *t*-test on each voxel of the brain (Fig. 1). As in [1], the significance threshold was set to $P<0.01$, family-wise error corrected for multiple comparisons, for rCBF increases, and to an uncorrected $P<0.001$ for rCBF decreases.

Reanalysis

From data set I, 120-s images of EJAC and STIp were compared (Fig. 1). Differences in rCBF were tested by performing a two-tailed *t*-test on each voxel of the brain ($P<0.05$, family-wise error corrected). In the event that no rCBF differences could be detected, the threshold was lowered to an uncorrected $P<0.001$. The stereotaxic atlases of Talairach and Tournoux [9] and Schmahmann *et al.* [10] were used for localization of regions in the cerebral cortex and the cerebellum, respectively.

Results

Evaluation

Table 1 demonstrates that the striatum, the midbrain, the thalamus, the cerebellar hemispheres, and parts of the neocortex were found with all three evaluation analyses and that these brain regions comprise the bulk of the result previously reported as ejaculation related [1]. Therefore, these regions can no longer be ascribed to ejaculation. The only brain regions from our previous study [1] that were not found by any of the evaluation analyses are the caudal medulla and the deep cerebellar nuclei. These regions might still be related to ejaculation. Inconsistencies were observed in the precuneus and the region of the left entorhinal cortex (found by two of the evaluation analyses), as well as in the right inferior temporal gyrus and the pontine tegmentum (found by one evaluation analysis).

Reanalysis

Comparing equal 120-s images of EJAC and STIp at corrected $P<0.05$ ($t>5.00$) resulted in significant rCBF decreases only. As can be observed in Fig. 2 (right column) and Table 2, these deactivations were present throughout the prefrontal cortex. To a much lesser extent, there was also decreased rCBF in the posterior parietal cortex (Table 2). Increases of rCBF were observed when the significance

Table 2 Ejaculation-related rCBF changes

K		Clusters	*x*	*y*	*z*	*Z*
rCBF increases						
158	L	Deep cerebellar nuclei	−18	−50	−28	4.43
38	L	Deep cerebellar nuclei	−2	−42	−28	3.52
31	L	Lateral rostral midbrain	−18	−18	−4	3.45
23	R	Cerebellar vermis	2	−56	−12	3.3
8	R	Pons	2	−18	−28	3.24
rCBF decreases						
106	R	Middle frontal gyrus (BA 11)	32	38	−18	5.78
478	R	Orbital gyri (BA 11)	4	54	−28	5.70
883	L	Superior frontal gyrus (BA 8)	−8	30	48	5.67
267	L	Inferior frontal gyrus (BA 44)	−44	8	32	5.54
521	L	Superior frontal gyrus (BA 9/10	−6	58	20	5.42
77	L	Inferior parietal lobule (BA 40)	−60	−40	32	5.24
184	R	Superior frontal gyrus (BA 10)	16	64	12	5.22
51	L	Middle frontal gyrus (BA 8/9)	−34	30	44	5.15
51	L	Inferior/middle frontal gyrus (BA 45/46)	−50	34	18	5.14
59	M	Medial frontal gyrus (BA 6)	0	12	62	5.06
60	L	Inferior frontal gyrus (BA 47)	−36	38	−18	5.01
54	R	Middle/superior frontal gyrus (BA 10)	26	64	−8	4.99
47	L	Inferior parietal lobule (BA 40)	−36	−74	42	4.97
21	R	Medial frontal gyrus (BA 8)	2	42	26	4.77

Equal 120 s-images of ejaculation and stimulation of the erect penis were compared. At $P < 0.05$, corrected, only rCBF decreases were found. Increased rCBF was found at an uncorrected $P < 0.001$.

BA, Brodmann's area; k, number of voxels; L, left; M, positron emission tomography, midline; R, right; *x*, distance (mm) relative to midsagittal plane (+right; −left); *y*, distance (mm) relative to anterior commisure (+anterior; −posterior); *z*, distance (mm) relative to intercommisural line (+dorsal; −ventral).

threshold was lowered to an uncorrected $P < 0.001$ ($t > 3.21$: Table 2; Fig. 2). The primary cluster of increased rCBF was in the deep cerebellar nuclei, centred on the dentate nucleus. Another activated cluster was found on the border of the left lateral rostral midbrain, internal segment of the globus pallidus, and lateral ventral thalamus. Smaller activations were found in the medial anterior lobe of the cerebellar vermis and the pons.

Discussion

We evaluated the methodological approach that was used in a previous paper on human male ejaculation [1] and performed a new analysis of the data. Together, these analyses revealed a new and more accurate concept of the brain mechanisms underlying sexual climax in men.

The evaluation consisted of three separate analyses, each comparing 20-s and 120-s data selections within a condition. All three analyses essentially reproduced the (de)activation pattern previously ascribed to ejaculation [1], although in the evaluation each condition was compared with itself (EJAC vs. EJAC; IMI vs. IMI; STIc vs. STIc: see Table 1). This means that our previous result was largely artefactual. As a consequence, the reported clusters in the cerebellar hemispheres, striatum, midbrain, thalamus, and parts of the neocortex [1] can no longer be attributed to ejaculation.

Subsequently, we reanalysed the original data set comparing 120-s images of EJAC and STIp. As the results show, this analysis sheds new light on the ejaculation-related brain regions in men.

The main result was a pronounced rCBF decrease in the prefrontal cortex (PFC) during EJAC compared with STIp. Within the PFC, the deactivation was bilateral, in dorsal as well as in ventral (orbitofrontal) subregions. The PFC plays a well-documented role in higher-order functions, including moral judgement, self-control, attention, working memory, and language [11,12] and damage to it is associated with disinhibited behaviour, including sexual disinhibition [13,14]. Indeed, decreased activity in the PFC has been demonstrated with increased sexual arousal in men [15] and orgasm in women [4]. The present results confirm the idea that the PFC has inhibitory control over sexual behaviour.

Ejaculation-related increased rCBF was most prominent in the left dentate nucleus (DN). This was one of the few clusters reported in our previous paper [1] that did not become activated by any of the evaluation analyses, indicating that activation of the left DN is a true feature of ejaculation. Recently, in women who experienced orgasm, we demonstrated a positive correlation between rCBF in the left DN and pelvic muscular contractions [4]. Possibly, in men activation of the left DN is related to ejaculatory muscular contractions.

Interestingly, the DN is functionally associated with the PFC [16,17]. One way for these regions to interact is that decreased activity of the PFC would provide the cerebellar hemispheres with less input, resulting in disinhibition (activation) of the DN [18]. During orgasm this might reflect a temporary reduction of higher-order functioning, coinciding in sexual disinhibition and muscular contractions.

The primary finding presented in our previous paper was the involvement of the transition zone of midbrain and thalamus, mainly because it contains reward-related areas [1]. Here, the evaluation analyses indicated that this activation was artefactual. With the reanalysis, however, increased rCBF was still found in the lateral part of the left transition zone of midbrain and thalamus, which strongly suggests that at least this part is related to ejaculation. This is confirmed by studies in rodents, which have linked a corresponding area to the sensory processing of ejaculation [19,20].

For the reanalysis we improved the signal-to-noise ratio of the ejaculation images by summing data frames before image reconstruction [5]. On the other hand, these summed 120-s images contained more than the ejaculation *per se*. This means that brain regions resulting from this reanalysis might also have been the result of events occurring immediately before and/or after ejaculation, such as high sexual arousal or sexual satiety. Therefore, brain regions reported in this paper are considered ejaculation-related rather than ejaculation-specific. The decreased signal-to-noise ratio resulting from this heterogenous condition would likely lead to underestimation of the effect size.

Conclusion

This revision offers a new and more accurate concept of the brain regions involved in human male ejaculation. Increased rCBF was primarily in the left DN, but also in the ventrolateral part of the transition zone of midbrain and thalamus. On the other hand, decreased rCBF was found throughout the PFC. We hope that these results will benefit the growing field of neurosexology.

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