

Neural Bases of Hypoactive Sexual Desire Disorder in Women: An Event-Related fMRI Study

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ABSTRACT

Introduction. Although there is an abundant debate regarding the mechanisms sustaining one of the most common sexual complaints among women, i.e., female hypoactive sexual desire disorder (HSDD), little remains known about the specific neural bases of this disorder.

Aim. The main goal of this study was to determine whether women with HSDD showed differential patterns of activation within the brain network that is active for sexual desire in subjects without HSDD.

Methods. A total of 28 right-handed women participated in this study (mean age 31.1 ± 7.02 years). Thirteen out of the 28 women had HSDD (HSDD participants), while 15 women reported no hypoactive sexual desire disorder (NHSDD participants). Using event-related functional magnetic resonance imaging (fMRI), we compared the regional cerebral blood flow responses between these two groups of participants, while they were looking at erotic vs. non-erotic stimuli.

Main Outcome Measure. Blood-oxygenation level dependent (BOLD) signal changes in response to erotic stimuli (compared with non-erotic stimuli). Statistical Parametric Mapping was used to identify brain regions that demonstrated significant differential activations between stimuli and between groups.

Results. As expected, behavioral results showed that NHSDD participants rated erotic stimuli significantly higher than HSDD participants did on a 10-point desirable scale. No rating difference was observed for the non-erotic stimuli between NHSDD and HSDD participants. Our functional neuroimaging results extended these data by demonstrating two distinct types of neural changes in participants with and without HSDD. In comparison with HSDD participants, participants without HSDD demonstrated more activation in brain areas involved in the processing of erotic stimuli, including intraparietal sulcus, dorsal anterior cingulate gyrus, and ento/perirhinal region. Interestingly, HSDD participants also showed additional activations in brain areas associated with higher order social and cognitive functions, such as inferior parietal lobule, inferior frontal gyrus, and posterior medial occipital gyrus.

Conclusion. Together, these findings indicate that HSDD participants do not only show a *hypo* activation in brain areas mediating sexual desire, but also a different brain network of *hyper* activation, which might reflect differences in subjective, social, and cognitive interpretations of erotic stimuli. Collectively, these data are in line with the incentive motivation model of sexual functioning. **Bianchi-Demicheli F, Cojan Y, Waber L, Recordon N, Vuilleumier P, and Ortigue S. Neural bases of hypoactive sexual desire disorder in women: An event-related fMRI study. J Sex Med 2011;8:2546–2559.**

Key Words. Sexual Desire; fMRI; Sexual Medicine; Social Neuroscience; Self Representation; Top-Down

Introduction

Hypoactive sexual desire disorder (HSDD) is highly prevalent in the population, notably among women. Because of its negative impact on quality of life, sexual health of individuals, and couples [1–5], there is a crucial need to better understand the foundation of this sexual disorder [6–10]. HSDD in women has many definitions, but the definition used here is that of the International Consensus Committee, as follows: “*During hypoactive sexual desire disorder there are absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to have sexual arousal are scarce or absent. The lack of interest is considered to be beyond the normative lessening with life cycle and relationship duration*” [11]. This definition has been established by an interdisciplinary consensus conference panel consisting of 19 experts in female sexual dysfunction selected from five countries, and is built on the existing framework of the classic Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) of the American Psychiatric Association. This definition is interesting because it goes beyond the definition of the DSM that is specifically limited to psychiatric disorders, and was not intended to be used for classification of organic causes of sexual dysfunction in women. According to the DSM IV, HSDD is defined by the following criterion “*‘persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity’*” that causes “*‘marked distress or interpersonal difficulty’*.” An essential element of the new diagnostic system is the “personal distress” criterion. Following the International Consensus Committee definition, the diagnosis of desire/interest disorder “*rests on an absence of desire at any stage during the sexual experience and comorbidity with combined and subjective arousal disorder is usual*” [11].

Epidemiologic studies report that about 40% of American women between 20 and 70 years of age have problems with low sexual desire [1,12–15]. This does not include women who report distress; prevalence for low desire and distress is much lower. For instance, in accord with Bancroft [6], the prevalence of HSDD, including the criterium of personal distress, concerns about the 24% of women between 20 and 65 years.

Despite the fact that HSDD in women affects a large number of the population, it is still very much misunderstood. HSDD in women is a multicausal medical issue that has psychological, relational,

environmental, and biological characteristics. For instance, life style factors, such as smoking, alcohol consumption, high cholesterol, cardiovascular health, and body mass index, may affect female sexual desire [15–19]. A recent study in premenopausal women shows that the most commonly cited contributing factors of female decreased sexual desire are the following: poor self-image (40.8%), stress or fatigue (60.0%), and other sexual difficulties (e.g., inability to reach orgasm; 33.5%) [20]. Along these lines, a broad variety of other psychological and hormonal factors may also interfere with sexual desire [17,21–24]. Because the psychologic and neuro-endocrinology components of desire have been addressed in depth previously [5,7,17,20,21,23,25–32], or is being currently investigated through larger scale longitudinal studies [33], we will not address them in details in the present article. Rather, our study aims to examine the cerebral bases of HSDD in women.

In the past, many hypotheses have been suggested regarding the role of the cerebral hemispheres in sexual desire, and notably HSDD [6,7,25,27,34–39]. The recent progress of neuroimaging techniques allows a better understanding of the brain regions mediating affective and motivational processes, including sexual desire. Although the neuroscience of sexual desire is a nascent field, recent neuroimaging data in healthy subjects [40–58] have already established that sexual desire involves not only emotion-related limbic areas, such as the amygdala, hypothalamus, hippocampus, ventral striatum, and insula, but also a distributed cortical network including (but not restricted to) three main areas: (i) anterior cingulate, (ii) parietal lobule, and (iii) middle temporal gyrus (MTG)/posterior superior temporal sulcus that extends to the temporo-parietal junction [10,58]. The distributed nature of this network in healthy subjects highlights how sexual desire involves brain areas that mediate different functions, such as reward mechanisms (e.g., ventral striatum), and also higher order cognitive processes (cortical network), associated with social cognition, self-representation, body-image, and attention [9,10]. Together, the functions of this brain network supports the view of desire as a phenomenon driven not only by bottom-up influences, but also top-down influences from past and integrated rewarding bodily self-related experiences, combined with sensory (e.g., visual) and emotional processing [9,10,58].

Here we tested the hypothesis that HSDD can be partly related to a different pattern of activation

within the sexual desire brain network [9,10,58]. Although HSDD is a common symptom in neurologic patients with epilepsy (in particular those with complex partial seizures) or after stroke [26,59,60], the lack of evidence of focal brain lesions associated with HSDD limits the detection of neural disturbances on the basis of neuropsychological examinations only. Neuroimaging studies in patients with HSDD constitute, nevertheless, a unique, non-invasive powerful technology and beneficial way to assess the neural bases of HSDD. To date, only two studies (one with male patients [50]; one with female patients [53]) have used functional neuroimaging techniques to investigate HSDD.

First, using positron emission tomography, Stoleru et al. [50] demonstrated differential brain activations between men with HSDD and healthy men, in response to visual erotic stimuli. HSDD men showed abnormally maintained activity of the medial orbito-frontal cortex, although control participants without HSDD displayed a deactivation of this brain region [50]. The authors interpreted this hyperactivation in HSDD men's medial orbito-frontal cortex as being due to a sustain mechanism of the inhibitory control of motivated behavior for erotic stimuli. In addition, HSDD men displayed abnormal deactivation in emotion-related brain regions (such as the anterior cingulate), and also in brain regions mediating motor imagery processes, somatic experiences, and self-representation (such as secondary somatosensory cortex) [50].

Arnow et al. studied the same question in women using functional magnetic resonance imaging (fMRI) [53]. Like Stoleru et al., they showed differences in brain activations between patients with HSDD and healthy participants, in response to visual erotic stimuli. In that study, participants included heterosexual women, aged 18–30. Participants with HSDD all met DSM IV criteria for HSDD, with no sexual aversion. Based on these criteria, it is difficult to know whether these participants suffered also from female sexual dysfunction (other than HSDD) or simply HSDD. Thus, further studies investigating participants with HSDD only need to be done. In contrast with Stoleru et al.'s study, Arnow et al.'s study used three types of stimuli (“erotic”, “sports”, and “relaxation”). Erotic segments depicted heterosexual couples engaging in various sexual activities and intercourse. Sports segments consisted in commercially available videos of female sports events and included basketball, soccer, and gymnastics.

Relaxation segments displayed nature scenes (e.g., flowers, mountains, ocean). In control participants (i.e., no hypoactive sexual desire disorder [NHSDD]), results showed that erotic video segments (compared with sport video segments) evoked a distributed cortico-limbic brain activity, including the anterior cingulate, the parietal lobule, the posterior MTG and the superior temporal sulcus [53]. In addition, NHSDD participants demonstrated greater activation than HSDD participants in the medial temporal lobes, notably in the entorhinal cortex (Brodmann areas [BAs] 28/34), a brain region at the interface between the hippocampus and the superior temporal gyrus, that is involved in emotion and memory [53]. According to Arnow et al., this specific activation of the entorhinal cortex could suggest a difference between HSDD and NHSDD participants in encoding erotic information and retrieving past erotic experiences [53].

Conversely, compared with NHSDD women, HSDD women showed higher activation in the medial frontal gyrus (BA 10) and the right inferior frontal gyrus (BA 47). The authors interpreted these activations in BA 10 and BA 47 as indicating that HSDD women allocated significantly more attention to monitoring and/or evaluating their responses to erotic stimuli than NHSDD women did, which may interfere with normal sexual response [53]. These results, if replicated, are important because they provide new insights into the possible processing anomalies associated with HSDD and may have direct implications for sexual medicine. Nonetheless, despite these compelling results, further fMRI studies are necessary to confirm (and refine) the brain network involved in HSDD in women. Because Arnow et al. used sport stimuli as a main control condition for the desire evoked by erotic stimuli, one cannot assert whether their results can be generalized with other types of control stimuli. Although their study included what they called “relaxation stimuli”, their main statistical analyses of interest focused on the comparison between the brain activation during erotic vs. sports video segments. Furthermore, because all the different video segments presented in Arnow et al.'s study did not have the same duration (erotic: 3 minutes; sports: 2 minutes; relaxation: 1 minute), it is difficult to ensure that comparable brain activation took place during all their video segments. Also, many different thoughts and brain mechanisms may occur during those 3 minutes of presentation of the erotic segments, other than those underlying

sexual desire per se. Thus, one needs to test shorter presentation of erotic stimuli.

Finally, there is one additional limitation in Arnov et al.'s study given the well-known effect of hormones on sexual desire and on brain mechanisms. The authors tested women on oral contraceptives and women off contraceptives during their luteal phase (which begins, after ovulation, with the formation of the corpus luteum and continues until menstruation begins, i.e., normally between 14 and 28 days from the beginning of the last menstrual cycle) and women on oral contraceptives between 7 and 20 days following the first day of last menses. To address these experimental limitations, one needs to test a more homogeneous group of cycling women (e.g., women off oral contraceptives), and use an experimental design that presents participants with similar categories of stimuli (e.g., pictures of erotic vs. non-erotic men) that vary as a function of their desirable levels (e.g., desirable vs. non-desirable) rather than as a function of their attributes (sports vs. human beings).

Here, we used such an experimental design in fMRI to test whether women with HSDD (compared with women without HSDD) showed distinctive patterns of brain activations in response to visual erotic male stimuli.

Materials and Methods

Participants

A total of 28 healthy heterosexual, sexually active women (mean age 31.1 ± 7.02 years) who were dating, engaged, or married, participated in the present study. All participants were recruited via flyers. The experimental procedure was then explained to eligible participants, including the use of erotic and non-erotic stimuli. All participants provided written informed consent to participate in the experiment, which was approved by the local University Institutional Review Board. All participants were right handed (Edinburgh Handedness Inventory [61]) with normal menstrual cycle, normal or corrected-to-normal vision, no medication, and no chemical dependency. None of the participants had prior or current neurologic or symptoms of psychiatric disorders, as ascertained by a detailed anamnesis and a structured clinical interview (including the Brief Psychiatric Rating Scale, BPRS 24 [62]; and the Hospital Anxiety and Depression scale, [63]). Moreover, the anamnesis did not reveal any history of psychiatric disorders, traumatic brain injury with loss of consciousness, epilepsy, neurologic impairment, gynecological

disorders or degenerative neurologic illness. None of the participants had any contra-indication for MRI scanning as assessed by the local University pre-scan screening form.

To ensure normal menstrual cycle functioning, a certified psychologist (NR), from the Psychosomatic Gynecology and Sexology Unit of the local University Hospital, performed a detailed structured interview with every participant. The exclusion criteria were the following: (i) the use of oral contraceptives within the previous 6 months; (ii) menstrual cycles that were longer than 30 days or shorter than 26 days or that were irregular; (iii) current treatment with anabolic steroids or psychoactive medications; (iv) or a history of neurologic or psychiatric disorders. The inclusion criteria were the following: (i) no use of oral contraceptives; (ii) normal menstrual cycles (between 23 and 29 days); (iii) no steroid or psychoactive medications; and (iv) no history of neurologic or psychiatric disorders.

In addition, we assessed the level of participants' sexual desire using a detailed structured interview on their sexual history and desire. This interview provided insights into the participants' feelings about their sexual desire, its intensity, frequency, and satisfaction. This interview was based on the DSM IV and on the International Consensus Committee criteria and was used to determine the diagnosis of HSDD [64]. Notably, the criterion of personal distress was clearly assessed in order to make the diagnosis of HSDD. To assess the women's subjective experience about sexual desire with their partner, we asked every participant to complete standard questions about whether (and to what degree) they felt sexual desire with their partner. For instance, we used questions that were part of the standardized Female Sexual Functioning Index (FSFI [28]), a self-report measure of sexual functioning that has been validated on a clinically diagnosed sample of 259 women with female arousal disorder [28,65]. Then, participants were scheduled for the fMRI scanning session (see below for further details). Because a growing number of studies has shown hormonal fluctuations, as evidenced by women's menstrual cycle, to influence sexual desire [66], cerebral laterality [67–75], and also the brain activations during the viewing of erotic stimuli [42], all participants had their fMRI scanning session at the same period of their menstrual cycle, i.e., within the first 10 days of their menstrual cycle (i.e., menses; a phase that occurs prior the phases of the menstrual cycle, such as the ovulatory phase, that are known to modulate sexual desire [42,66]).

Women with No HSDD (NHSDD Participants)

Fifteen women (aged 21–44; mean age: 30.4 ± 7.09 years) had no HSDD. From a phenomenologic viewpoint, all women with no HSDD defined their sexual desire with their partner as normal in comparison with their past personal sexual desire. FSFI and DSM IV criteria [64] for HSDD, as modified at the International Consensus Development Conference on Female Sexual Dysfunction [3], confirmed the absence of HSDD in these participants. Participant's FSFI desire scores were in the normal range (mean: 4.6 ± 0.7 standard deviation [SD]).

Women with HSDD (HSDD Participants)

Thirteen women (aged 26–47; mean age: 32 ± 7.13 years) who met the DSM IV criteria for HSDD [3,64] participated in this study. Initially, we had planned on having 15 participants per group. However, in the HSDD group, two participants who underwent the selection procedure dropped out prior to undergoing the fMRI scanning session. From a phenomenological viewpoint, all participants with HSDD described an absence (or a diminution) of feelings of sexual interest, an absence of sexual thoughts or fantasies, and/or a lack of responsive desire. In addition, they all described suffering from a marked personal distress related to the lack of sexual desire. Motivations for attempting to become sexually aroused were scarce (or absent) in all of them. On average, HSDD participant's FSFI desire scores were low (mean: 2.12 ± 0.8 [SD]). A *t*-test for independent samples showed significantly different FSFI desire scores between the two groups of participants (HSDD group vs. NHSDD group), $t(26) = 9.2$, $P < 0.0001$. No significant age difference was found between the two groups of participants, $t(26) = 0.59$, $P = 0.56$.

Procedure

Participants were tested in two main experimental conditions: "Erotic stimuli," i.e., stimuli eliciting sexual desire; and "Non-Erotic stimuli," i.e., stimuli non-eliciting sexual desire. Stimuli from these two different conditions were randomly presented during two experimental blocks during one fMRI scanning session. Before the fMRI scanning session, participants were told that the study was on sexual desire. Desire was defined here as the "presence of feelings of sexual interest, and of sexual thoughts or fantasies related to pictures." During this fMRI scanning session, all participants received explicit instructions to focus on the desir-

ability of the stimuli and to observe carefully the pictures for both the erotic and the non-erotic conditions. More precisely, participants were asked to look at the pictures and to focus on whether the pictures elicited specifically their sexual desire. In order to avoid any eye movements during scanning, participants were asked to fixate the central visual cross during the whole experiment. No reaction times were recorded during the fMRI session to avoid any motor interference. To make sure participants were paying attention to the pictures, all participants, nevertheless, performed a one-back task (button response after an immediate repetition of the image) during scanning. Only a few images ($N = 10$) were repeated during the whole fMRI session. Repeated images associated with reaction times were excluded from the analysis of the contrasts of interests. After the fMRI scanning session, a behavioral debriefing session, which required the rating of each picture, was performed with each participant.

Behavioral Debriefing Session

During the debriefing session, behavioral responses were collected by asking participants to write down their responses on a piece of paper. This information was collected for every stimulus. The participants were instructed to try to evaluate the level of sexual desirability of each picture on a 10-point desirable scale (from 1: not eliciting sexual desire at all, to 10: eliciting sexual desire very much).

Apparatus

The experiment was run using E-Prime (Psychology Software Tools Inc., Sharpsburg, PA, USA). During the scanning session, participants viewed the stimuli on a back projection screen mounted on the head coil of the MRI scanner. Each trial began with a 500 ms-fixation cross that was followed immediately by a 1,500 ms-target stimulus. A random 1,500–4,000 ms inter-stimulus interval separated each target presentation (Figure 1). All conditions were presented in two blocks of 85 trials each (in pseudorandomized order).

Stimuli

As described above, two different types of target stimuli were presented centrally: stimuli eliciting sexual desire (erotic stimuli), and stimuli non-eliciting sexual desire (non-erotic stimuli). All pictures represented models (i.e., 40 erotic stimuli and 40 non-erotic stimuli). No nude or pornographic pictures were presented. Stimuli were cat-

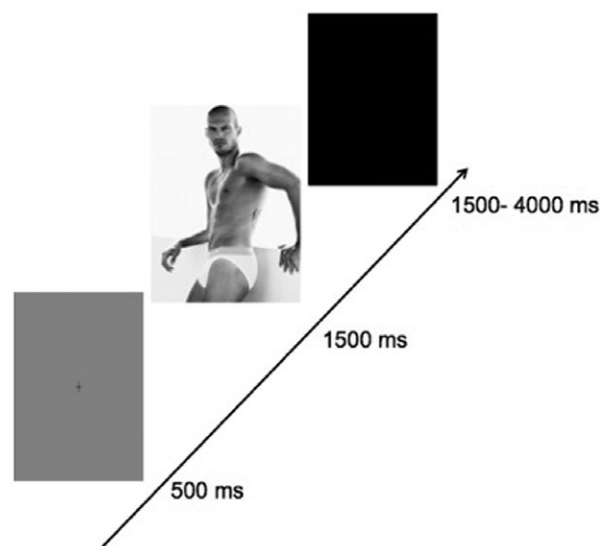


Figure 1 Experimental paradigm. Procedure: each trial consisted of the following sequence: a 500 ms-fixation cross was followed by a 1,500 ms-target stimulus (here an exemplar of the erotic condition is presented). A random 1,500–4,000 ms inter-stimulus interval separated each target presentation. Participants performed a one-back task requiring the detection of occasional immediate repetitions of the same picture.

egorized subjectively as being erotic or non-erotic by two heterosexual experimenters (one woman, one man) above 18 years of age who met NHSDD criteria according to the DSM IV criteria [3,64]. To control for visual features between stimuli, all the pictures of the male models were presented in black and white. Furthermore, all these male models were selected to be of the same age range as participants.

fMRI Acquisition and Analysis

MRI data were acquired on a 3T whole-body Trio system (Siemens, Erlangen, Germany), using the standard head coil configuration. For each participant, structural images were acquired with a 3 Dimension-Gradient Recalled Echo (3D-GRE) T1-weighted sequence (field of view [FOV] = 250 mm, TR/TE/Flip = 15 ms/5.0 ms/30°, matrix = 256 × 256, slice-thickness = 1.25 mm); and functional images with a GRE Echo Planar Imaging (EPI) sequence (relaxation time [TR]/echo time [TE]/Flip = 2,200 ms/40 ms/80°, FOV = 250 mm, matrix = 128 × 128). Each functional image comprised 36 contiguous 3.4 mm axial slices (TR = 2.2 s) oriented parallel to the inferior edge of the occipital and temporal lobes. For each of the two experimental blocks, a total of 195 functional images were acquired continuously.

Functional images were analyzed using the general linear model (Friston et al., 1998) for event-related designs in SPM5 (Wellcome Dept. of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). All images were realigned, corrected for slice timing, normalized to an EPI-template (resampled voxel-size of 3 mm), spatially smoothed (8 mm full width at half maximum [FWHM] Gaussian kernel), and high-pass filtered (cutoff 128 s).

Statistical analyses were performed on a voxel-wise basis across the whole-brain. Individual events were modeled by a standard synthetic hemodynamic response function (HRF). To account for residual movement artifacts after realignment, movement parameters derived from realignment corrections (three translations, three rotations) were entered as covariates of no interest. Trials with errors were not included in the analysis of fMRI data. The general linear model was then used to generate parameter estimates of activity at each voxel, for each experimental condition in each participant. Statistical parametric maps were generated from linear contrasts between the HRF parameter estimates for the different conditions.

A random-effect group analysis was then conducted on contrast images from the individual analyses, using one-sample *t*-tests. Only the maxima with a cluster size greater than 10, and a Z-value greater than 3 ($P < 0.001$) were reported. Bold brain coordinates were significant at $P < 0.05$ family-wise error corrected at the whole-brain level. Then, other significant brain coordinates at $P < 0.001$ uncorrected at the voxel level were also considered.

Accuracy of anatomical labeling was ascertained with the standard Talairach Daemon (available at, <http://www.talairach.org/>), and LONI Probabilistic Brain Atlas (LPBA40), which is “a series of maps of brain anatomic regions that were produced from a set of whole-head MRI of 40 human volunteers” [76].

Results

Behavioral Results

The post-scanning ratings of stimuli showed that NHSDD participants adequately identified the pictures eliciting sexual desire as being more highly desirable (mean score on a 1-to-10 scale: 6.57 ± 1.59 [SD]), and all the non-erotic stimuli as being significantly less desirable (mean score: 4.45 ± 1.43 [SD]). A paired *t*-test confirmed a significant difference between erotic stimuli and non-erotic stimuli for the NHSDD group of

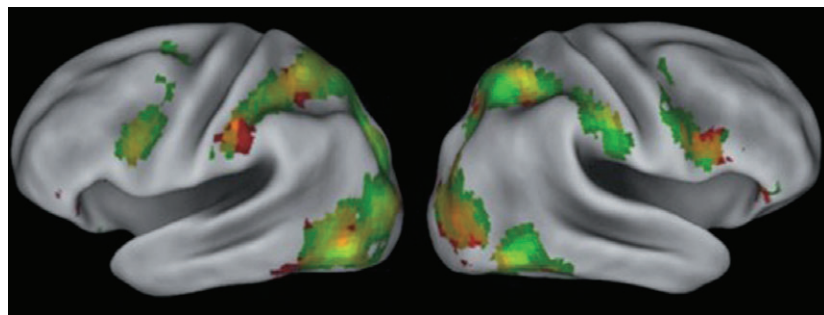


Figure 2 Surface rendering of NHSDD (green) and HSDD (red) group average brain activations for the Erotic stimuli > Non-Erotic stimuli contrast. BOLD responses are shown on lateral views of the flat PALS left and right of the human brain from Caret v.5.51 ($P < 0.01$ uncorrected). Overlap of activation appears for the two groups as yellow.

participants, $t(14) = 4.09$, $P = 0.001$. As expected, NHSDD participants rated stimuli eliciting sexual desire (mean score: 6.57) significantly higher on the 10-point desirable scale than HSDD participants did (mean score: 5.24, $t(26) = 2.23$, $P = 0.03$). Also, as expected, no rating difference was observed for the non-erotic stimuli between NHSDD participants (mean score: 4.45) and HSDD participants (mean score: 4.08, $t(26) = 0.67$, $P = 0.51$).

Neuroimaging Results

The main statistical analysis of interest was the contrast of brain activation when viewing erotic stimuli relative to non-erotic stimuli. For this analysis, we determined the patterns of brain activation for the NHSDD and HSDD participants separately, as well as the difference between these two groups. Figure 2 displays the surface rendering of brain activations in the NHSDD (in green) and HSDD (in red) group for the erotic > non-erotic comparison.

NHSDD Participants' fMRI Results

The analysis of blood-oxygenation level dependent (BOLD) signal changes from NHSDD participants in response to erotic stimuli (as compared with non-erotic stimuli) revealed activations in several areas (listed in Table 1). As expected, there was no significant increase in primary visual areas (BAs 17–18), suggesting that our non-erotic stimuli were adequately controlled for the basic visual features of pictures. On the other hand, activations in associative visual areas (BA 19) were observed, suggesting a greater recruitment of higher level visual processes for erotic stimuli (in comparison with non-erotic stimuli). Also consistent with previous studies [10,53,58], temporal lobe activations were found, notably in postero-inferior regions such as the ento/perirhinal region, bilateral fusiform gyrus, and lateral occipito-temporal cortex (BAs 37, 19). The latter brain

areas included the extrastriate body area (EBA) and extended to the MTG [77,78]. Frontal lobe activations were found bilaterally in the inferior frontal gyrus (BAs 44, 46, 47), left orbito-frontal area (BA 11) and right superior part of the precentral gyrus (BAs 6, 9). Within the parietal lobe, activations were found notably in the superior parietal lobule (local maximum: BA 7) extending slightly to the inferior parietal lobe. These activations are in accordance with previous studies on sexual desire [9,10,40,44,46,47,49,50,53,58,79,80]. Finally, an activation was also observed in the anterior cingulate gyrus, consistent with previous studies demonstrating its role in sexual response [40,44,47,53].

Table 1 Local maxima in MNI coordinates of cerebral activations peaks for erotic stimuli minus non-erotic stimuli for NHSDD participants

Brain regions	Erotic > non-erotic				Cluster size
	x	y	z	Z	
Temporal lobe					
Middle temporal gyrus (BA 37)	45	-60	-6	5.78	50
Fusiform gyrus (BA 19)	-33	-66	-15	5.69	25
	36	-69	-12	5.45	12
Ento/perirhinal region	-27	3	-30	4.39	33
Cingulate gyrus	-3	-15	36	4.12	59
Parietal lobe					
Superior parietal lobule (BA 7)	33	-60	60	5.36	59
Frontal lobe					
Inferior frontal gyrus (BAs 44, 46)	48	9	15	4.26	197
	-45	3	27	4.23	243
Inferior frontal gyrus (BAs 45, 47)	-39	30	6	3.86	18
Orbito-frontal area (BA 11)	-12	51	6	3.78	15
Superior frontal gyrus (BAs 6, 9)	33	0	42	3.82	19
Occipital lobe					
Medial occipital gyrus (BA 19)	-48	-72	-9	5.64	38

Local maxima in MNI coordinates. Only the maxima with a cluster size greater than 10, and a Z-value greater than 3 ($P < 0.001$) are provided in the present table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z-value. Bold brain coordinates are significant at $P < 0.05$ family-wise error (FWE) corrected at the whole-brain level. Other coordinates are significant at $P < 0.001$ uncorrected at the voxel level.

MNI = Montreal Neurological Institute; NHSDD = no hypoactive sexual desire disorder.

Table 2 Local maxima in MNI coordinates of cerebral activations peaks for erotic stimuli minus non-erotic stimuli for HSDD participants

Brain regions	Erotic > non-erotic				Cluster size
	x	y	z	Z	
Temporal lobe					
Fusiform gyrus (BAs 37, 19)	27	-66	-12	3.82	16
	-42	-72	-3	5.33	10
Parietal lobe					
Superior parietal lobule (BA 7)	36	-48	57	4.92	165
Post-central gyrus (BA 2)	-54	-27	36	5.29	1386
	45	-33	36	4.17	71
Inferior parietal lobule (BA 40)	39	-42	51	4.33	165
Frontal lobe					
Inferior frontal gyrus (BA 44)	48	6	27	4.64	103
	-48	6	27	4.31	86
Inferior frontal gyrus (BA 47, 45)	-39	27	6	3.84	20
Prefrontal gyrus (BAs 11, 47)	-24	27	-18	3.75	19
	42*	30	-3	3.71	24
Occipital lobe					
Medial occipital gyrus (BA 19)	-36	-96	9	5.37	10
	39	-84	6	4.81	555

Local maxima in MNI coordinates. Only the maxima with a cluster size greater than 10, and a Z-value greater than 3 ($P < 0.001$) are provided in the present table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z-value. Bold brain coordinates are significant at $P < 0.05$ family-wise error (FWE) corrected at the whole-brain level. Other brain coordinates are significant at $P < 0.001$ uncorrected at the voxel level. MNI = Montreal Neurological Institute; HSDD = hypoactive sexual desire disorder.

HSDD Participants' fMRI Results

Table 2 shows HSDD participants' results from the analysis of BOLD signal changes in response to erotic stimuli (as compared with non-erotic stimuli). Consistent with previous studies [53], HSDD participants showed, like NHSDD participants, activations in associative visual areas (BA 19) but no primary visual cortex (see above). In addition, HSDD participants showed greater activations in the right middle occipital gyrus, suggesting a greater recruitment of processes involved in visual feature extraction. Within the parietal lobe, HSDD participants (like NHSDD participants) showed activation of the superior parietal lobule (BA 7). However, the latter was less prominent in HSDD participants (in comparison with NHSDD participants), as ascertained by their Z score (Tables 1 and 2). Furthermore, unlike NHSDD, HSDD participants showed no significant activation in the right MTG, left fusiform gyrus, or ento/perirhinal area. Conversely, HSDD participants showed additional stronger parietal activations in the post-central gyrus (BA 2) and in the inferior parietal lobule (IPL; Table 3), which were not seen in NHSDD.

NHSDD Participants' vs. HSDD Participants' fMRI Results

To directly compare brain activation for erotic vs. non-erotic stimuli in the two groups of participants, this contrast was performed for each of the two groups, and differences between groups were analyzed using a two-sample *t*-test. These data analyses reinforced the results above and confirmed a selective difference of brain activation between HSDD and NHSDD participants in three main brain regions. NHSDD participants exhibited greater activation than HSDD participants in the following areas: (i) intraparietal sulcus/BA 7 (local maximum: 24, -54, 36 xyz mm, MNI coordinates), (ii) dorsal anterior cingulate gyrus (local maxima: 12, 12, 27 xyz mm, MNI coordinates; 12, -3, 42 xyz mm, MNI coordinates), and (iii) anterior ento/perirhinal region (local maximum: -24, 3, -27 xyz mm, MNI coordinates; $P < 0.01$ uncorrected; Table 3).

On the other hand, the reverse comparison (i.e., HSDD > NHSDD) revealed that HSDD participants showed greater activation than NHSDD participants in three other areas (see Table 3): (i) the extrastriate visual cortex in the posterior part of BA 19; (ii) the right inferior frontal gyrus (notably BAs 46, 47); and (iii) the left inferior parietal lobule (BA 40; $P < 0.01$ uncorrected).

Discussion

The present findings, which focus only on evoked desire (rather than spontaneous sexual desire),

Table 3 Local maxima in MNI coordinates of cerebral activations peaks for erotic stimuli minus non-erotic stimuli for HSDD participants vs. NHSDD participants

Brain regions	Erotic > non-erotic				Cluster size
	x	y	z	Z	
NHSDD > HSDD					
Intraparietal sulcus (BA 7)	24	-54	36	3.37	155
Dorsal anterior cingulate gyrus	12	12	27	3.1	18
	12	-3	42	4.61	23
Ento/perirhinal region	-24	3	-27	3.11	18
HSDD > NHSDD					
Inferior parietal lobule (BA 40)	-57	-45	42	2.80	21
Inferior frontal gyrus (BAs 46, 47)	54	15	45	2.99	15
Posterior medial occipital gyrus (BA 19)	-18	105	6	3.13	11
	18	-105	-3	3.26	11

Local maxima in MNI coordinates. Only the cluster size (in voxels) greater than 10 are provided in the table. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z-value. Brain coordinates are significant at $P < 0.01$ uncorrected.

MNI = Montreal Neurological Institute; HSDD = hypoactive sexual desire disorder; NHSDD = no hypoactive sexual desire disorder.

reinforce the hypothesis suggesting that exposure to erotic material show significant differences in both the subjective stimulus ratings and the brain activations among women meeting criteria for HSDD compared with women with NHSDD. As expected, subjective ratings were significantly different between the two groups of participants. NHSDD participants rated erotic stimuli significantly higher than HSDD participants did. By contrast, no rating difference was observed for the non-erotic stimuli. This accords with the clinical complaints of these patients and suggests that perceptual processing for erotic stimuli was specifically affected in women with HSDD.

Our functional neuroimaging results extended our behavioral results by demonstrating two distinct types of neural changes in participants with HSDD relative to those without. First, in comparison with NHSDD, participants with HSDD exhibited less activation in brain areas commonly observed in previous studies during the processing of erotic stimuli in healthy participants [9,10,40,44,46,47,49,50,53,58,79,80]. Specifically, women without HSDD demonstrated robust activations in cortical and emotional limbic-related brain areas. A direct comparison of brain activation patterns in NHSDD relative to HSDD revealed that NHSDD had a greater activation in the superior parietal cortex (notably in the intraparietal sulcus, BA 7), the anterior cingulate gyrus, and the ento/perirhinal region, a multimodal integration site, which indirectly reinforces the role of these brain regions in normal sexual desire. We therefore interpret the activations in the anterior cingulate gyrus and ento/perirhinal region as reflecting a greater recruitment of motivational and associative multimodal memory processes for emotional events, respectively, presumably because of a more attentive processing of erotic stimuli in healthy participants. These findings are consistent with previous findings on emotion perception and emotion regulation [81,82], as well as with findings demonstrating a greater involvement of medial temporal regions in sexual-related processes [53,58,82]. The activation of the ento/perirhinal region is also in line with evidence suggesting that this area, through interaction with other emotion-related areas (such as the adjacent amygdala), is strongly activated during the processing of emotional events (as opposed to neutral events), as well as during the encoding and retrieving of self-relevant past experiences [83]. Thus, the present activation in the ento/perirhinal region among NHSDD participants, while

viewing erotic stimuli, suggests differences between the two groups of participants in processing erotic material in relation to affectively relevant past experiences.

Similarly, the present involvement of BA 7 in NHSDD participants suggests a greater recruitment of attentional and appraisal processes elicited by erotic stimuli in this group [44,84]. This result is in line with other studies that showed an early and sustained activation of the superior parietal lobule during erotic stimulus presentation [44,85]. Thus, together, these results reinforce the hypothesis that there may be significant changes in information processing within the neural systems mediating erotic desire in participants with HSDD, as compared with NHSDD [10,50,53]. Most importantly, these between-group differences cannot be explained by menstrual cycle differences because all participants in the present study were tested in the same time period of their cycle (within the first 10 days of their menstrual cycle). Similarly, these differences cannot be explained by visual differences in face/body content between stimulus categories because both the erotic and the non-erotic stimuli included similar face/body features (as directly demonstrated here by the lack of effects in primary visual cortex). Moreover, the EBA was also activated by erotic stimuli more than non-erotic stimuli, consistent with previous findings of emotional modulation of this area [86], but we found no difference between groups.

This finding that there may be differences in information processing and motivation between the two groups lends support for the Incentive Motivation model of sexual functioning [87], which suggests that sexual desire results from confronting sexual stimuli or thinking about these cues [88,89]. Further studies using high temporal resolution technique (such as electroencephalography) [79,90] are needed to better understand the temporal dynamics of how incentives and cues impinge on the brain areas mediating sexual desire.

Interestingly, the present study shows that participants with HSDD exhibit not only *hypo* activations in brain areas mediating sexual desire in healthy participants, but also *hyper* brain activations in three specific brain regions: i.e., inferior parietal lobule, inferior frontal gyrus, and extrastriate visual cortex. This distinct pattern of neural changes in HSDD participants might potentially reflect different subjective interpretations (e.g., different scenario) during the processing of

stimuli. Indeed, our results show that participants with HSDD differentially recruit brain areas mediating high-level cognitive functions such as social perception (BAs 40, 46,47) and visual analysis (BA 19). Increased activation in the inferior frontal areas is consistent with previous findings in HSDD patients that also suggested greater activity in brain areas mediating inhibitory executive control, self-focus attention, and judgments about one's own subjective experience [50,53,91,92]. This is in line with current hypotheses about reduced sexual desire [6,27], which suggest that: "*Hypoactive sexual desire disorder (HSDD) may result from hypofunctional excitation, hyperfunctional inhibition, or some mix of the two*" [27]. Furthermore, the present findings converge with Arnow et al.'s results suggesting that HSDD women allocate significantly more efforts to monitoring and/or evaluating their responses to erotic stimuli than NHSDD women, which may interfere with normal sexual response [53]. One might also hypothesize that these findings accord with Masters and Johnson's, Kaplan's, and Barlow's clinical concept of "spectatoring" [93–95], which assumes that deficits in sexual functioning may be (at least partly) associated with inhibited excitement that are because of a disruption in the processing of erotic stimuli and a shift in attentional focus from erotic stimuli to self-monitoring of sexual response (i.e., self-focus attention) [93,95].

Based on these findings, it would be interesting, as a future perspective, to test whether individual differences can be exhibited with respect to the increased activations in the inferior parietal lobule, inferior frontal gyrus, and extrastriate visual cortex. Along these lines, future studies could investigate whether these brain activations vary as a function of the desirability level of every participant. To do so, further studies might want to use visual-auditory stimuli (rather than visual stimuli only), which in women are associated with higher levels of evoked sexual arousal [96], and measure brain responses in conjunction with peripheral response (e.g., blood flow in the vagina, lubrication).

In addition, our results show that HSDD participants have increased task-related activity in the posterior part of the extrastriate areas (right BA 19), which suggests they perform a different visual analysis for erotic stimuli than NHSDD. These findings further point to a propensity of patients with HSDD for processing and analyzing visual stimuli that might interfere with their ability to experience these visual stimuli as being erotic. Accordingly, we hypothesize that HSDD partici-

pants' perception of erotic stimuli may involve a "hyper-visual" evaluation of stimuli. By analogy, we note that persons with autism also typically demonstrate highly efficient complex visual task processing with poor social cognitive interactions [97]. Hence, we metaphorically suggest that erotic stimuli might constitute for HSDD individuals what social interactions represent for individuals with autism and propose that heightened visual processing mechanisms might play a role in the exaggerated reasoning and reduced feeling states elicited by visual erotic stimuli in participants with HSDD. In light of the findings by McCall and Meston showing that women with sexual dysfunction have fewer "cues" that elicit sexual desire, another interpretation may be that the different mechanisms proposed for a visual analysis relate more to fewer stimuli being perceived as erotic among women with HSDD [17]. Further studies need to be done to clarify this mechanism.

Finally, our results show a greater involvement of the inferior parietal lobule in HSDD participants than in NHSDD, which reinforces the critical role of higher order cognitive brain areas in sexual desire beyond the limbic system [32,35,58,98,99].

Although several brain areas mediating cognitive functions (such as self-representation, body image, attention, social cognition, and multimodal integration of past self-experiences) are activated in participants with or without HSDD, the fact that the inferior parietal lobule is more activated in HSDD suggests a critical role of this associative brain region and its functions in mediating distorted sexual desire. This finding suggests that cortical areas sustaining higher order cognitive functions (e.g., social cognition, body image) play a role in sexual desire, which reinforces the Ortigue and Bianchi-Demicheli's neurofunctional theory of sexual desire proposing top-down influences from associative cognitive areas to areas involved in more basic visual and emotional processes [58]. This assumption is in accordance with current psychosocial models suggesting an interaction between self-representation, body image, and sexual function, as people often apprehend a novel sexual partnered-experience (or a novel sexual stimulus) based on previous sexual experiences [9,10,58,97–99]. That said, further studies, using high-density electroencephalogram recordings, need to be done to further investigate the temporal dynamics between bottom-up and top-down effects within these brain areas in patients with HSDD.

Together, these findings raise the question of self-awareness and aspects of consciousness during

sexual desire. In line with this, one may wonder: (i) whether the speed of cognitive processing may influence the awareness of sexual desire (in conjunction with feelings of arousal or not), and (ii) whether the awareness of sexual desire may vary as a function of the types of erotic stimuli (e.g., visual vs. visuo-auditory). Based on the specific pattern of brain activation of the women with HSDD in response to visual stimuli, one may also wonder whether women with HSDD could need other types of erotic stimuli (e.g, auditive or tactile stimuli) than visual stimuli to feel desire. In light of this, it would be interesting to test whether their response system is different but not their general processing pattern to other types of erotic stimulation. To elucidate these questions, further studies need to be done. Future studies combining peripheral and central measurement, with high spatio-temporal resolution [58,81], in response to various types of stimuli (i.e., visual, tactile, and auditory) would be helpful: (i) to disentangle the contribution and interaction of sexual desire and arousal in patients with or without HSDD; (ii) to better understand the correlations between incentives, past self-experiences, body image, sexual desire, and modulations in the inferior parietal activation; and (iii) to better understand the causal relationship between self-awareness, sexual desire, arousal and the temporal dynamics of bottom-up and top-down influences in patients with various degrees of intensity of disorders on the spectrum of sexual desire and different types of body dysmorphic disorders.

Conclusion

The present study demonstrates a differential recruitment of higher-order cognitive brain areas (inferior parietal lobule, inferior frontal gyrus) in HSDD (compared with healthy participants) when viewing erotic pictures, which was not seen for non-erotic pictures. These regions may in turn modulate perceptual analysis and visual cortex activation in a distorted way (compared with normal sexual desire in NHSDD). This would, in essence, instruct the eyes and the emotional brain centers on how to respond to men who look sexually desirable or not. The integration of these new neuroscientific data in our understanding of HSDD will provide physicians with new conceptual and therapeutic tools to apprehend these disorders in sexual medicine.

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