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ORIGINAL PAPER

Brain responses to pictures of children in men with pedophilic disorder: a functional magnetic resonance imaging study

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Abstract
Structural and functional neuroimaging techniques have recently been used to investigate the mechanisms of sexual attraction to children, a hallmark of pedophilic disorder, and have reported many contradictory or non-replicated findings. Here, our purpose was to identify through functional magnetic resonance imaging the brain responses of 25 male outpatients with pedophilic disorder to visual stimuli depicting children (VSc) and to compare them with 24 male healthy controls matched on sexual orientation (to female or male adults), age, and handedness. No region was differentially activated across the two groups in response to VSc. However, as shown by a random-effects statistical analysis (cluster-level p_{FWE}-corrected < 0.05), in patients with pedophilia, but not in controls, the presentation of VSc induced a bilateral activation in the lateral occipital and temporal cortices, in particular in the right inferior temporal gyrus, as well as an activation in the declive of the cerebellar vermis. In addition, in patients the level of bilateral activation in the above-mentioned regions was positively correlated with ratings of perceived sexual arousal elicited by VSc. These results implicate these regions as possible candidate areas mediating sexual arousal in patients with pedophilic disorder.

Keywords Pedophilic disorder · Functional magnetic resonance imaging · Visual sexual stimuli · Occipital cortex · Temporal cortex · Cerebellar declive

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Introduction

Child sexual abuse (CSA) is considered to be a public health problem. Based on 55 studies from 24 countries, Barth et al. [1] showed that sexual abuse of children under 18 years of age ranged from 8 to 31% for females and from 3 to 17% for males. Several studies of the consequences of CSA on the victims' mental health show that a history of CSA is associated with a substantially higher prevalence of various psychiatric disorders in adulthood [2–4].

At least half of the perpetrators of CSA are men with pedophilic disorder [5]. Diagnostic criteria [6] include persistent or recurrent sexual fantasies, desires, or behaviors directed towards prepubescent children. Some patients have acted on these sexual urges, or the sexual urges or fantasies cause marked distress or interpersonal difficulty. Patients are at least 16 years old and at least 5 years older than the target child or children.

Although its causes are poorly known, pedophilic orientation has repeatedly been found associated with a history of being a victim of CSA [5]. In addition, relatively strong evidence supports a neurodevelopmental etiology. Compared with controls, patients are more likely to report head injuries before the age of 13 [7], obtain lower IQ scores on average [8, 9], show an increased rate of non-right-handedness [8] and alterations in fronto-executive and/or verbal skills [10, 11].

Given the major role of the brain in sexual arousal (SA) [12] and the case reports of brain pathology associated with attraction to children [13, 14], several studies have investigated the functional and/or structural cerebral correlates of pedophilic disorder. Although the majority of patients with pedophilic disorder have no macroscopic brain abnormalities, widely different results have been reported about more limited structural differences. As reviewed by Mohnke et al. [15], the only replicated finding is a reduction in amygdalar volume [16, 17], which still requires further confirmation since it would not have survived statistical correction for multiple testing in one study [17]. Gerwinn et al. [18] did not find any significant gray or white matter differences between patients and teleiophilic subjects, i.e., controls attracted to adults.

Although there may not be any consistent structural brain abnormality in pedophilia, sexual attraction to children may have functional neural correlates. In seven functional magnetic resonance imaging (fMRI) studies, brain responses to erotic pictures were compared across patients and teleiophilic controls [for a review, see 15]. Restricting their analyses to the bilateral amygdala, Sartorius et al. [19] found significantly stronger activity in pedophiles than in controls in response to visual sexual stimuli representing children (VSSc). They also showed that amygdala activity was higher in response to VSSc compared to visual sexual stimuli representing adults (VSSa) in pedophiles while the opposite pattern was found for controls. In response to VSSc, whole-brain studies have repeatedly shown a greater activation in the right medial frontal gyrus [20, 21], the hippocampus, and the thalamus [20, 22] in pedophiles than in teleiophiles. However, the locations of maximal activation of these clusters diverged widely across studies, except for the hippocampus. In addition, Habermeyer et al. [23] found that pedophiles attracted to girls showed a higher response in the right middle frontal gyrus [Brodmann area (BA) 10] than heterosexual teleiophiles.

Although no consistent differential activation was found in pedophiles in response to VSSc compared with teleiophiles in response to VSSa, the pattern of activation was similar in the two groups [20–22]. According to the meta-analysis by Polisois-Keating and Joyal [24], the regions activated in both groups in response to their respective preferred sexual stimuli were the fusiform gyrus, occipital cortex, cerebellum, anterior cingulate cortex, and substantia nigra. Activated regions were distributed over the four components of the neurophenomenological model of SA, i.e., the cognitive, motivational, emotional and bodily components [12].

Finally, Ponseti et al. [25] investigated whether it was possible to diagnose pedophilic attraction on the sole basis of fMRI responses to child versus adult stimuli. They reliably discriminated teleiophilic from pedophilic participants, and found preference-specific brain activity in brain areas demonstrated to be involved in processing sexually arousing stimuli, such as the caudate nucleus, cingulate cortex, insula, fusiform gyrus, temporal and occipital cortices, thalamus, amygdala, and cerebellum [12].

Reviews of the literature have suggested some methodological improvements, including larger sample sizes, differentiation between pedophiles whether they have committed CSA or not, control for the recruitment setting (inpatient versus outpatient status), stricter inclusion/exclusion criteria to better limit potential confounds, control of sexual orientation (gender orientation and/or exclusivity of pedophilic preference), control for pharmacological treatment and validation of stimulus sets [15, 26]. In the present study, we incorporated several of these recommendations. In addition, we used penile plethysmography as an objective index of SA in response to visual sexual stimuli (VSS).

Our objective was to study male outpatients with pedophilic disorder and acknowledging sexual attraction to prepubescent girls and/or boys, in order (1) to identify through functional magnetic resonance imaging (fMRI) their brain responses to validated VSS, and (2) to compare them with healthy controls matched on sexual orientation (to female or male adults), age, and handedness.

Our main hypothesis was that brain activation in pedophilic patients in response to VSSc would belong to the cognitive component of SA that is activated in response to VSSa in teleiophilic men [for a review, see 12], including the lateral part of the orbitofrontal cortex and the caudal part of the fusiform gyri. Conversely, we hypothesized that images of children would not elicit activation in these regions—or would elicit lower activation—in healthy controls. In addition, as our proposed model of SA posits that the activation of the right lateral orbitofrontal cortex is the starting point of "downstream" components, we hypothesized that a higher activation would be found in patients than in controls in the insula bilaterally (emotional component), the left anterior cingulate gyrus (motivational component), and the hypothalamus (bodily component).

As regards the regions less activated in patients than in healthy controls in response to the presentation of VSSc, we hypothesized they would include: (1) several lateral temporal areas that are considered to exert a tonic inhibitory action on SA [27]; (2) the ventromedial prefrontal cortex bilaterally and (3) other areas found deactivated in healthy volunteers in response to VSS representing women [27], i.e., in the left hemisphere, the middle occipital gyrus and the calcarine sulci, the posterior cingulate gyrus, the precuneus and the caudate nucleus. All the above-mentioned hypotheses do not exclude the possibility that exploratory analyses reveal responses in unexpected regions.

Finally, we hypothesized that the level of plasma testosterone would be correlated with the activation of regions whose responses to VSSa were found to be dependent on testosterone, including the right claustrum/insula (positive correlation) and the right middle temporal gyrus (negative correlation) [28]. Such correlations would potentially offer a better insight into the effectiveness of antihormonal therapy.

Materials and methods

Participants

25 patients were recruited through psychiatrists of centers specialized in the assessment and treatment of sexual offenders. 24 controls were recruited through a web platform dedicated to informing potential participants about current investigations in psychology and neuroscience in the Parisian region. Importantly, to avoid recruitment bias the information posted on the web only mentioned that we purported to study the brain bases of human motivation, but did not specify that the project was focused on sexuality. The latter information was communicated on the first telephone interview.

Inclusion criteria common to the two groups were male gender and age between 18 and 65. Specific inclusion criteria for patients were: (1) meeting the criteria for pedophilia according to the DSM-IV-TR [29] and/or according to the International Classification of Diseases [30]; (2) to admit sexual attraction to prepubescent or early pubescent children; (3) willingness to participate in treatment to prevent first, or further, sexual offenses. As a specific inclusion criterion, each control had to match an already recruited patient on age (± 13 years), on the Edinburgh Handedness Inventory score (± 50 points), and on sexual orientation (to adult women, to men, or to women and men for controls matching patients attracted to girls, to boys, or to children of both genders, respectively).

Exclusionary criteria common to both groups were: (1) IQ < 70; (2) brain disorders; (3) contraindication to MRI examination, and (4) current detention. Specific exclusionary criteria for patients were: (1) current treatment with antihormonal therapy or with antidepressant drug of the selective serotonin reuptake inhibitor family; (2) endocrine disorder affecting the hypophysis, the hypothalamo–pituitary–gonadal axis or the adrenal glands. Comorbid psychiatric disorders and other psychotropic medications were not exclusionary criteria. Specific exclusionary criteria for controls were: (1) psychiatric disorders, including sexual and substance-related disorders; (2) psychotropic medication; (3) drug treatment with potential sexual side-effects.

Protection of subjects' intimacy was ensured following specific guidelines [31]. Subjects received financial compensation for participating.

Assessment of participants

Participant inclusion comprised a psychiatric, a psychological and a biomedical assessment. A psychiatrist interviewed each patient to confirm the diagnosis of pedophilia, collect psychiatric history and check his eligibility. Controls were also interviewed by a psychiatrist to assess potential psychiatric disorders or medication. A psychologist conducted a standardized psychological assessment with all participants. Handedness was assessed with the Edinburgh Handedness Inventory [32], and IQ was evaluated with a seven-subtest short form of the Wechsler Adult Intelligence Scale-III [33]. Sexual function was assessed as follows in all participants, unless otherwise specified: (1) to further characterize the sexual orientation of all participants and identify potential interest in children in controls, all subjects were presented with standardized questions, redacted by our team, on the age and sex of persons to whom they felt attracted; (2) to assess the severity of pedophilic disorder and identify potential comorbidity of several paraphilias [34], patients were presented with the Sex History Questionnaire Revised (SHQ-R) [35]; (3) to obtain a quantitative assessment of the current level of sexual interest, two instruments were used: (i) the Sexual Fantasies, Desires and Activity Interview

Schedule (SFDAIS) [36], which focuses on the last 30 days; while its first part assesses the levels of fantasies, of desires and of sexual activity whatever their targets (adults, adolescents and/or children), the second focuses on the level of fantasies, of desires and of sexual activity exclusively directed to prepubescent or early pubescent children; (ii) the Sexual Interest Score (SIS) [37], which does not specify the targets of sexual interest; (4) in order to assess sexual function directed to adults during the last month, all participants were presented with the Brief Sexual Function Questionnaire (BSFQ) [38]; (5) finally, in order to compare the controls with those of previously published studies, control subjects were presented with the Sexual Arousal Inventory (SAI) [39], adapted to men.

Other aspects of psychopathology were assessed using the Symptom Checklist-90-Revised (SCL-90R) [40], the 21-item Beck Depression Inventory (BDI) version [41], and the Barratt Impulsiveness Scale (BIS-10) [42].

A physician performed a medical examination and screened participants for exclusionary criteria. A blood sample was obtained for hormonal investigation. Testosterone, sex-hormone binding globulin (SHBG), bioavailable testosterone (not bound to SHBG), and estradiol were measured by using previously reported methods [43] and commercially available kits were used for routine measurements of LH, FSH, prolactin, and cortisol.

All the above-mentioned assessments were distributed over 2–3 sessions in patients and over one or two sessions in controls. On the next session, functional images were acquired (see below). At the end of each fMRI run, subjects were presented with a series of rating scales, ranging from 1 (null or extremely low) to 9 (extremely high), to assess seven kinds of subjective responses to each of the picture categories: desire for sexual activity, perceived erection, beauty of presented characters, pleasure, displeasure, attention, tenderness. Participants selected their answers through a keypad connected to a PC through an optic fiber. The functional imaging acquisitions were coupled with penile response measurements performed by using a volumetric penile plethysmograph [described in 44].

Functional MRI

Stimuli and design

We presented to each subject eight different categories of pictures, which varied according to: (1) the dressing style (undressed or lightly dressed, versus ordinarily dressed); (2) the gender (male or female); (3) the age category of the single character depicted (adult or child). Most pictures were downloaded free of rights from the Internet; in addition, some pictures representing children were obtained from a photographic agency. Most photographs of undressed or lightly dressed children showed children in swimming suits, with two back-view photographs showing a nude boy and two back-view photographs a nude girl. Pictures representing adult women were the same as those used in our previous studies [e.g., 44]. Pictures representing children and those showing adult males were selected out of a large series of photographs by 15 control subjects and 11 child sexual offenders not otherwise involved in the experiment. They rated the level of SA and of negative emotion induced by each picture on scales ranging from 1 to 9. Then, the sets of selected pictures of undressed or lightly dressed children were matched with the pictures of adults on the average SA ratings, level of nudity and view of the portrayed person (front, back, profile or three-quarter front views). Pictures of dressed children and adults were also matched in the same manner, except for nudity degree. Pictures retained as stimuli did not induce negative emotions.

Functional imaging was performed according to a block design and in two separate runs. One run presented pictures of female characters, and pictures of males were presented in the other run, regardless of the age category. Each run consisted of 12 blocks of pictures presented in a pseudorandom order across participants (5 pictures per block, each displayed during 7.5 s, yielding 37.5-s blocks) and alternating with 17.5-s fixation-cross blocks. For each run, there were three blocks of a given category (in one run: pictures of prepubescent girls, dressed or undressed, and pictures of adult women, dressed or undressed; in the other run: pictures of prepubescent boys, dressed or undressed, and pictures of adult men, dressed or undressed) and two blocks of the same category could not follow each other. Each patient and his matched control had the same assigned order. Finally, to ensure that participants paid attention to the stimuli, they were asked to press a button of the keypad placed on their abdomen when a brief orange screen (0.5 s) randomly appeared, once for each category within a run.

MRI data acquisition

Acquisitions were performed on a 3.0 T Verio MRI scanner (Siemens, Erlangen, Germany) in the following order: (1) a 3D spoiled gradient-echo sequence with sagittal excitation acquired a structural T1-weighted image with the following parameters: 176 contiguous 1.0-mm-thick slices, TR = 2300 ms, TE = 2.96 ms, field of view (FOV) = 256 × 256 mm, matrix size = 256*256 voxels, flip angle = 9°, NEX = 1, bandwidth = 24 Hz/pixel; (2) functional images were acquired in two 11-min 25-s-long runs, using a T2*-weighted echoplanar (EPI) gradient-echo sequence (37 2-mm-thick slices, acquired in ascending order, with 1-mm interslice gap; TE = 30 ms; TR = 2500 ms; flip angle = 90°; FOV = 204 × 204 mm; matrix size = 68 × 68). To allow for T_1 equilibrium, each run started with 4 dummy scans which were later discarded before analysis. To reduce image distortions and signal losses caused by susceptibility gradients near air/tissue interfaces, in particular in the orbitofrontal cortex, a z-shimming gradient prepulse was applied (duration: 1 ms; amplitude: − 2.5 mT/m) and the plane of acquisition was tilted by 30° relative to the bicommissural plane, with the anterior part of the brain higher than the posterior part [45].

MRI data preprocessing

Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) was used for image preprocessing and subsequent analysis. All functional volumes were realigned to the first volume of the first run to compensate for subject's motion, and coregistered with the 3D structural image, using the mean functional image as reference; then, 3D-structural and functional images were spatially normalized to a standard space (Montreal Neurological Institute, MNI), using a nonlinear deformation field from SPM8 unified segmentation and normalization procedure. Data were finally smoothed with a 3D isotropic Gaussian kernel (FWHM = 6 × 6 × 6 mm).

For the subsequent individual statistical analyses, a binary explicit mask of each subject's brain was computed. To do so, the native structural image was segmented into gray and white matter volumes, which were added together. The resulting image was normalized to the MNI space, binarized, smoothed (FWHM = 6 × 6 × 6 mm) and intersected with the mean functional image to restrict analyses to voxels where functional data were actually available.

FMRI data contrast analyses

First-level fixed-effects individual analyses including the two runs were conducted in the framework of the general linear model. The design matrix comprised eight regressors related to adult and child stimuli (four per run), two regressors associated with the orange screen (one per run), two regressors associated with the fixation-cross condition (one per run), and 12 motion parameters (six parameters per run). Stimuli were modeled as blocks convolved with the canonical hemodynamic response function. Time series were high-pass filtered (cut-off period: 512 s). For each participant, regional responses to the condition factor (Undressed versus Dressed) were analyzed on a voxel-wise basis for pictures showing prepubescent girls (i.e., $\text{Girls}_{\text{response}} = \text{Girls}_{\text{undressed}} - \text{Girls}_{\text{dressed}}$), prepubescent boys, adult females and adult males.

In second-level analyses, within- and between-groups effects of the condition factor were entered into a random-effects model. Firstly, for each of the subgroups (heterosexual and homosexual patients, heterosexual and homosexual controls), we performed one-sample t-tests using the individual contrast images (e.g., $\text{Girls}_{\text{response}}$) to investigate at the group level the neural response to the condition factor for pictures showing prepubescent girls, prepubescent boys, adult females and adult males.

In order to increase statistical power, we further pooled heterosexual and homosexual patients on the one hand, and heterosexual and homosexual controls on the other hand. Pooling was conducted as heterosexual and homosexual patients did not show any differential responses to the pictures of their respective preferred gender $[(\text{Girls}_{\text{response}})_{\text{heterosexual patients}} - (\text{Boys}_{\text{response}})_{\text{homosexual patients}}]$. Finally, between-groups effects comparing patients with controls were investigated using paired t-tests, thus taking into account the matching of each patient to one control.

Contrasts are listed in Table 1. As planned before acquiring the data, we compared patients and controls on both their behavioral and brain responses (1) to pictures of children (Ch) of the patients' preferred (Pref) gender: $[(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{ChPref}_{\text{response}})_{\text{controls}}]$ (for this contrast and the following ones, its opposite was also tested); (2) to pictures of adults (Ad) of the patients' preferred gender: $[(\text{AdPref}_{\text{response}})_{\text{controls}} - (\text{AdPref}_{\text{response}})_{\text{patients}}]$. For patients, the preferred adult gender could be different from their preferred child gender: for instance, a patient might be preferentially attracted to prepubescent boys and to adult women; for such patients, the preference for adult women would differ from his matched control's preference for men (patients attracted to male children were systematically matched with controls attracted to men); (3) to pictures of characters with both the age and the gender preferred by each group: $[(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{AdPref}_{\text{response}})_{\text{controls}}]$.

Other analyses were performed post hoc. Two analyzes aimed to compare our results with those of related studies. (4) First, we compared patients' responses to images of prepubescent children with their responses to images of adults: (a) $(\text{ChPref}_{\text{undressed}} - \text{AdPref}_{\text{undressed}})_{\text{patients}}$,

Table 1 Contrasts tested both for behavioral variables and BOLD signal

No.	Meaning
C1	$(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{ChPref}_{\text{response}})_{\text{controls}}$
C2	$(\text{AdPref}_{\text{response}})_{\text{controls}} - (\text{AdPref}_{\text{response}})_{\text{patients}}$
C3	$(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{AdPref}_{\text{response}})_{\text{controls}}$
C4a	$(\text{ChPref}_{\text{undressed}} - \text{AdPref}_{\text{undressed}})_{\text{patients}}$
C4b	$(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{AdPref}_{\text{response}})_{\text{patients}}$
C5	$(\text{ChPref}_{\text{Undressed}} - \text{AdPref}_{\text{Undressed}})_{\text{patients}} - (\text{ChPref}_{\text{Undressed}} - \text{AdPref}_{\text{Undressed}})_{\text{controls}}$
C6	$(\text{ChPref}_{\text{response}})_{\text{offender\_patients}} - (\text{ChPref}_{\text{response}})_{\text{non-offender\_patients}}$

Ch children, *Pref* preferred gender; "Response" refers to the effect of dressing style (undressed or lightly dressed, versus ordinarily dressed). For every "(*X*−*Y*)" contrast, its opposite, "(*Y*−*X*)", was also tested as performed by Poeppl et al. [20], and (b) [$(ChPref_{response})_{patients}-(AdPref_{response})_{patients}$]. (5) Second, in line with Ponseti et al. [25], we subtracted in each group the responses to undressed female (resp., male) VSSc from the responses to undressed female (resp., male) VSSa and then compared patients with controls on the obtained differences. (6) Finally, we compared patients who had committed a sexual offense with non-offender patients on their responses to the nudity of preferred children.

FMRI data correlational analyses

Plethysmographic data In order to study the correlation between the erectile responses and the BOLD signal, each participant's plethysmography data were preprocessed as follows: (1) plethysmographic values corresponding to the first four discarded functional volumes were also discarded; (2) as the sampling frequency of the plethysmograph was higher than that of the MRI scanner (20 versus 0.4 Hz), plethysmographic data were downsampled by replacing each set of 50 consecutive values by its mean value, yielding a time series referred to as the plethysmographic regressor, with as many plethysmographic values as functional volumes; (3) this time series was then standardized using a *z* transformation.

To identify brain regions where the BOLD signal was correlated with the erectile response, we conducted regression analyses on the patients and controls who presented an erectile response. At the individual level, the model included the plethysmographic regressor and six motion parameters. As in Mouras et al. [44], variations of the BOLD signal potentially leading to erection were hypothesized to precede those of the plethysmographic signal. The time lag between the two signals was hypothesized to be equal to the delay between the start of stimulus presentation and the start of the erectile response. The plethysmographic regressor was thus shifted backwards in time by a lag equal to the interval between the start of the VSS and the beginning of erection, and the correlation between this shifted regressor and the recorded BOLD signal was analyzed. Then, the resulting correlation maps were entered into a random-effects group analysis, which allowed us to study the correlation between the plethysmographic and the BOLD signals within each group and to evaluate whether this correlation differed across groups.

Behavioral and endocrine data We conducted regression analyses to identify regions where the level of activation in response to preferred stimuli (undressed versus dressed) was correlated with three types of variables: the subjective ratings of stimuli, the testosterone levels (both total and bioavailable testosterone) and the psychological scores of each individual. In the case of subjective ratings (e.g., Perception of Erection), one rating per picture category was available, i.e., 8 ratings per subject; therefore, the correlational analysis was based, at the first level, on the model used in the contrast analyses, with an additional regressor which associated each category of pictures with its mean rating over the three blocks of its presentation. Each analysis yielded a correlation map for each subject; these maps were used in second-level analyses based on a random-effects model to assess within-group correlations and a differential correlation across groups. In the case of testosterone levels and psychological scores, where we had only one measure per participant, this measure was used, at the second level only, as a covariate of interest to assess its correlation with the level of activation in response to preferred stimuli (undressed versus dressed). Again, within- and between-groups analyses were performed.

FMRI data exploratory and hypothesis-driven analyses

Regarding statistical significance, for all second-level analyses, inferences were made based either on cluster-wise significance ($p < 0.05$ FWE-corrected, cluster-forming threshold $p < 0.001$ uncorrected) and/or on peak height significance ($p < 0.05$ FWE-corrected).

Exploratory analyses We performed traditional exploratory between-groups comparisons on the whole set of voxels contained in the explicit brain mask.

Hypothesis-driven analyses We also used a set of regions previously found to show activation or deactivation in response to VSS in healthy adult males [12, 46]. Those regions were hypothesized to respond to images of children in pedophiles. In order to use SPM8 small-volume correction procedure, one single volume of activated regions and one single volume of deactivated regions were constructed using WFU PickAtlas software [47] for contrast analyses. Similarly, one volume of regions positively correlated with indices of SA and one volume of negatively correlated regions were constructed for correlational analyses.

T-tests or Chi-square tests were performed to compare patients and controls on sociodemographic, clinical and behavioral variables. On the other hand, repeated measures analyses of variance of subjective ratings and of erectile responses were performed using SPSS® 19 software (Armonk, NY). Regarding erectile responses, the dependent measure was the mean area under the three curves obtained for each category of pictures (mean of the three blocks presented in the run).

Results

Sociodemographic and clinical characteristics

Sociodemographic and sexological characteristics of participants are presented in Table 2. Among the 25 patients, 10 were attracted to prepubescent girls and 12 to prepubescent boys. Hereafter, these patients are called heterosexual and homosexual patients, respectively. Three were attracted to children of both genders; for analytic purposes, these patients were assigned to the subgroup corresponding to the children of their preferred gender, which was the heterosexual subgroup for all three. All patients were non-exclusive, i.e., were also attracted to adults. All heterosexual patients, five homosexual patients, and all bisexual patients were attracted to adult women, so that 18 patients overall were attracted to women and seven patients to men. 15 patients were extra-familial pedophiles, 3 were incestuous, and 7 belonged to both categories. 18 patients had sexually offended children, while 7 had used child pornography or remained totally abstinent.

Patients and controls did not differ significantly on intelligence quotient, age, and handedness (Table 2 and Online Resource 1, Table 1). On the Sexual Fantasies, Desires and Activities Interview Schedule, for the section related to persons whatever their age category (from children to adults), patients and controls had similar scores for sexual fantasies, activities and overall mean, but the score on sexual desire was lower in patients. Conversely, for the child section, all three scores (fantasies, desires, and activity) and their mean were higher in patients, as no controls declared any fantasies, desires or activities related to children. On this questionnaire, patients' self-declared sexual activity referred only to masturbation accompanied by fantasies and desires about children, not to actual sexual behavior with children. On the BSFQ, patients had lower scores than controls on Sexual Activity, Sexual Satisfaction, and Physiological Component, while Sexual Interest did not differ significantly

Table 2 Sociodemographic and sexological characteristics of subjects

Variable	Patients $n=25$	Controls $n=24$	p
Age	42.2 ± 12.0	37.8 ± 12.8	NS
Years of education	16.0 ± 4.8	16.2 ± 3.2	NS
Sexual partnership with adult (M/PS/PNS/NP)	3/2/2/18	13/3/4/4	< 0.001[a]
SHQ-R			
Female child frequency (heterosexual patients)	62.1 ± 28.9	Not presented	NA
Male child frequency (homosexual patients)	67.1 ± 25.9	Not presented	NA
SAI	Not presented	90.2 ± 19.8	NA
SFDAIS			
Fantasies, any target	6.2 ± 5.6	6.2 ± 5.6	NS
Desires, any target	13.6 ± 5.7	16.3 ± 3.3	< 0.05
Sexual activity, any target	10.2 ± 5.7	9.6 ± 3.8	NS
Mean score, any target	10.0 ± 3.9	10.7 ± 3.1	NS
Fantasies, children	4.8 ± 4.5	1.0 ± 0.0	< 0.001
Desires, children	7.0 ± 7.3	1.0 ± 0.0	< 0.001
Sexual activity, children	6.1 ± 4.4	1.0 ± 0.0	< 0.00001
Mean score, children	5.9 ± 4.5	1.0 ± 0.0	< 0.0001
SEXUAL INTEREST SCORE	3.0 ± 1.0	3.2 ± 0.8	NS
BSFQ factors			
Sexual activity	33.8 ± 24.0	83.4 ± 19.5	< 0.00001
Sexual interest	38.1 ± 34.8	51.4 ± 31.6	NS
Sexual satisfaction	3.0 ± 2.2	7.3 ± 1.8	< 0.00001
Physiological component	11.0 ± 6.2	22.1 ± 7.7	< 0.00001

Figures are means ± SDs, except for sexual partnership where figures are frequencies; *BSFQ* Brief Sexual Function Questionnaire; *M* married or living together; *NA* not applicable; *NP* no current adult partner; *NS* not significant; *PNS* partner, not stable; *PS* lasting relationship, same partner, not living together; *SFDAIS* Sexual Fantasies, Desires and Activities Interview Schedule; *SAI* Sexual Arousal Inventory; *SHQ-R* Sex History Questionnaire-revised; figures are percentiles referring to a sample of sexual offenders gathered by the SHQ-R developers

[a]"No current adult partner" versus "current adult partner"

across groups. On the BDI and on the SCL-90R, patients had significantly higher scores than controls (Online Resource 1, online table 1). 18 patients were receiving some form of psychological treatment at the time of the study, mostly individual supportive psychotherapy ($n = 15$), for their pedophilic disorder.

Regarding hormonal measurements (Online Resource 2, online table 2), the plasma level of bioavailable testosterone, i.e., testosterone unbound to the sex-hormone binding globulin, was lower in patients. In addition, cortisol and FSH levels were higher in patients.

Measures of sexual arousal during fMRI scans

Before pooling into one group heterosexual and homosexual patients on the one hand, and heterosexual and homosexual controls on the other hand, we compared the subgroups on the effects of interest (both for behavioral and for fMRI data). Pooling proceeded as the comparisons did not reveal any statistically significant differential responses. Hence, we report analyses on the pooled subgroups of heterosexual and homosexual patients and controls. Hereunder, we first provide the results of the analyses of the behavioral indexes of SA, based on the same contrasts as those subsequently used for the neural responses (Table 1).

Ratings of stimuli

Here we detail the results of analyses focused on two rating scales, Desire for Sexual Activity (DSA) and Perceived Erection (PE) (Table 3). Analyses related to the other scales are presented in Online Resource 3 (online table 3).

Contrast 1 We first compared patients' and controls' ratings of pictures showing children of the patients' preferred gender (Table 1, C1). For the DSA rating, there was a Group by Condition interaction: compared with controls, patients showed a higher difference between ratings for undressed children and for normally dressed children. This Group by Condition interaction is important as it represents the behavioral correlate of the C1 contrast tested on fMRI data. The same statistically significant interaction was found for the rating of PE (Table 3).

Contrast 2 We compared patients and controls on their ratings of pictures of adults of their preferred gender. For DSA, but not for PE ratings, we found a Group by Condition interaction, with a lower difference between the conditions in patients (Table 3).

Contrast 3 We compared patients and controls on their ratings of the pictures of characters with both the age and the gender preferred by each group. Again, we found a Group by Condition interaction only for DSA, with a lower difference between the conditions in patients (Table 3).

Contrast 4 Patients' responses to children's versus adults' nudity. Regarding the fourth contrast [$(\text{ChPref}_{\text{undressed}} - \text{AdPref}_{\text{undressed}})_{\text{patients}}$; C4a, Table 1], both for DSA and for PE, ratings were not significantly different. When the Dressed condition was introduced into the contrast (C4b, Table 1), the interaction Condition by Age of Character was not significant for both rating scales. These negative findings are very likely related to the fact that, although patients were preferentially attracted to children, they were also attracted to adults.

Contrast 5 Comparison of patients and controls on their responses to adults' versus children's nudity. For both rating scales, there was an Age of Character by Group interaction,

Table 3 Comparison of patients and controls on ratings of stimuli of their preferred gender

Variable	Patients $n = 25$	Controls $n = 24$	Group effect	Condition effect	Group by condition
Desire for sexual activity					
Children, undressed	5.4 ± 2.3	1.2 ± 0.5	< 0.000001	< 0.000001	< 0.00001
Children, normally dressed	3.3 ± 1.6	1.0 ± 0.2			
Adults, undressed	4.6 ± 2.1	6.3 ± 2.0	NS	< 0.000001	< 0.001
Adults, normally dressed	2.4 ± 2.0	1.6 ± 1.1			
Characters with preferred age, undressed	5.4 ± 2.3	6.3 ± 2.0	NS	< 0.000001	< 0.001
Characters with preferred age, dressed	3.3 ± 1.6	1.6 ± 1.1			
Perception of erection					
Children, undressed	2.9 ± 1.6	1.1 ± 0.3	< 0.00001	< 0.0001	< 0.001
Children, normally dressed	1.9 ± 1.2	1.0 ± 0.0			
Adults, undressed	2.7 ± 1.8	2.0 ± 1.6	NS	< 0.0001	NS
Adults, normally dressed	1.6 ± 1.1	1.2 ± 0.6			
Characters with preferred age, undressed	2.9 ± 1.6	2.0 ± 1.6	NS	< 0.00001	NS
Characters with preferred age, dressed	1.9 ± 1.2	1.2 ± 0.6			

Figures are means ± SDs on scales ranging from 1 to 9. Condition effect: pictures of undressed versus dressed characters with a lower difference in patients [Table 3; $F(1, 47) = 69.1$, $p < 0.01E-11$]. Again, this effect was related to the fact that patients were attracted both to children and adults, whereas controls were attracted only to adults.

Contrast 6 Comparison of offender with non-offender patients. Finally, the comparison of patients who had committed a sexual offense with non-offender patients on their ratings of pictures of preferred children did not reveal any significant differences.

Penile plethysmography

Due to technical reasons, data were missing for two patients. Thus, the findings were based on 23 patients and 24 controls (Online Resource 4, Table 4).

Contrast 1 We first compared the two groups' responses to pictures showing children of the patients' preferred gender. The Group by Condition interaction was not significant, which was related to the fact that only 16 patients showed an erectile response to the pictures of undressed children, with wide individual differences in penile responses. There were a Group effect with higher responses in patients, and a Condition effect, with higher responses for undressed children.

Contrast 2 The analysis of erectile responses of patients and controls to pictures of adults showed higher responses to pictures of undressed adults; by contrast, neither the Group effect nor the Group by Condition interaction was significant.

Contrast 3 The comparison of the two groups in response to pictures of characters with both the age and the gender preferred by each group revealed the same pattern of results as in Contrast 2, i.e., only the condition effect was significant.

Contrast 4 Patients' responses to children's versus adults' nudity. Contrast 4a. Although the patients were not exclusively attracted to children, they showed higher penile responses to pictures of undressed children ($p < 0.01$) than to pictures of undressed adults. Contrast 4b: After including the Dressed Condition into the contrast $[(\text{ChPref}_{\text{response}})_{\text{patients}} - (\text{AdPref}_{\text{response}})_{\text{patients}}]$, the Condition by Age of Character interaction was not significant. However, the analysis revealed higher responses to pictures of undressed characters ($p < 0.01$) and an Age of Character effect, with higher responses to pictures of children than to pictures of adults ($p < 0.0001$).

Contrast 5 Comparison of patients and controls on their responses to adults' versus children's nudity. There was an Age of Character by Group interaction, with higher responses to pictures of children than to pictures of adults in patients and the reverse pattern in controls (Online Resource 4, Table 4; $p < 0.05$).

Contrast 6 The comparison of patients who had committed a sexual offense with non-offenders on their responses to pictures of preferred children did not reveal any significant differences.

Within the group of patients, those presenting an erectile response ($n = 16$) had higher levels of plasma total testosterone by comparison with non-responders [mean (SD): 16.5 (6.6) versus 10.4 (3.5) nmol/l; $t(21) = 2.4$, $p < 0.05$]. There was a significant correlation between the level of total testosterone and the penile response to pictures of undressed children of the preferred gender ($r = 0.72$, $p < 0.0001$, $n = 23$).

Functional magnetic resonance imaging

Contrast analyses

Contrast 1 Responses to images of children of the preferred gender.

Regarding within-group analyses, in response to preferred VSSc, patients showed a bilateral activation in the lateral occipital and temporal cortices, fusiform gyri, left temporal pole, and in the cerebellar declive (a part of the vermis) (Table 4; Fig. 1). After masking (exclusive mask) the previous contrast with activations observed in patients in response to VSSa, the activation in the left fusiform gyrus, right middle temporal gyrus (a part of the large cluster with a maximum in the right inferior temporal gyrus), left superior temporal gyrus (temporal pole) and cerebellar declive survived. Thus, in patients these clusters showed activation in response to VSSc, but not to VSSa. Regarding controls, analysis showed an activation in the left cerebellar pyramis and the cerebellar declive as well as in both thalami in response to VSSc (Online Resource 5, online table 5). Bilateral activation was also found in the inferior frontal gyri (BA 44) and in the anterior cingulate cortex (ACC). Most of these clusters persisted after exclusive masking with activations observed in controls in response to preferred VSSa.

Both in patients and controls, no regions were more activated in response to images of dressed than undressed children. Finally, the between-groups analysis did not show any differentially activated regions.

Contrast 2 Responses to pictures of undressed adults of the preferred gender.

Regarding the within-group analyses, in response to VSSa, patients showed a significant activation in the lateral occipital and temporal cortices bilaterally, in the right fusiform gyrus, the right postcentral gyrus and the medial thalamus (Table 5). When this contrast was masked with activations of patients in response to VSSc, activation in the right postcentral gyrus and the medial thalamus persisted (Table 5). Thus, these two regions responded to images of adults' nudity, and not to children's nudity. Regarding controls, analysis showed bilateral activations in the lateral occipital and temporal cortices, the fusiform gyri, the postcentral gyri, the orbitofrontal cortices, and right medial

Table 4 Brain responses of patients to pictures of undressed children of their preferred gender

Brain region	BA	k	Side	MNI coordinates			T	$p_{corrected}$
				x	y	z		
Inf. temporal gyr.[(SVC+),a]	**37**	**759**	**R**	**45**	**−67**	**−2**	**7.90**	**<0.001**
Inf. temporal gyr.[(SVC+)]	**37**	**727**	**L**	**−42**	**−70**	**−8**	**6.21**	**<0.001**
Middle occipital gyr.[SVC+]	18		L	−30	−85	−2	6.09	<0.01
Inferior occipital gyr.[SVC+]	19		L	−39	−79	−11	5.46	<0.05
Fusiform gyr.[SVC+, a]	19		L	−33	−76	−17	5.39	<0.05
Cerebellum declive[a,b]	**–**	**364**	**R**	**0**	**−61**	**−23**	**6.17**	**<0.001**
Sup. temporal gyr. (pole)[a,b]	**38**	**47**	**L**	**−30**	**5**	**−20**	**4.76**	**<0.05**
Inferior occipital gyr.[SVC+]	**19**	**94**	**R**	**39**	**−76**	**−8**	**5.48**	**<0.001**
Fusiform gyr.[SVC+]	**37**	**49**	**R**	**36**	**−55**	**−20**	**5.23**	**<0.01**
Inferior frontal gyr.[SVC+,b]	**47**	**26**	**L**	**−45**	**17**	**−8**	**4.31**	**<0.05**

Contrast: $ChPref_{Undressed}-ChPref_{Dressed}$. All probabilities are corrected for multiple comparisons, based on the Family-Wise Error (FWE) rate control. $p_{corrected}$ in bold characters refers to cluster-wise significance (cluster-forming threshold: 0.001, unc.; cluster-extent threshold: FWEc = 47 voxels for binary explicit mask); $p_{corrected}$ in light characters refers to peak height significance. k, cluster extent; [SVC+], small-volume correction procedure, based on areas showing activation in response to VSSa in healthy males; [(SVC+)], region identified both within whole mask and with small-volume correction based on areas showing activation in response to VSSa in healthy males; for these regions, $p_{corrected}$ refers to analysis in whole mask. [a]Cluster that survives exclusive masking by regions activated in patients in response to images of nude adults. BA, Brodmann area; gyr., gyrus; MNI, Montreal Neurological Institute. [b]Region identified only by cluster-extent thresholding. Although peak MNI coordinates and T-values are reported, it can only be inferred that there is signal somewhere within each cluster and no inferences can be made about the statistical significance of specific locations within the cluster [48]

frontal gyrus (Online Resource 6, online table 6). When masked with activations of controls in response to VSSc, most clusters persisted. Thus, these clusters showed activation in response to images of adults' nudity, and not to children's nudity.

Regarding the opposite contrast ($AdPref_{Dressed}-AdPref_{Undressed}$), while patients showed a higher activation only in the right calcarine sulcus, no regions were more activated in controls. Finally, the between-groups analysis did not show any differential responses to pictures of undressed adults.

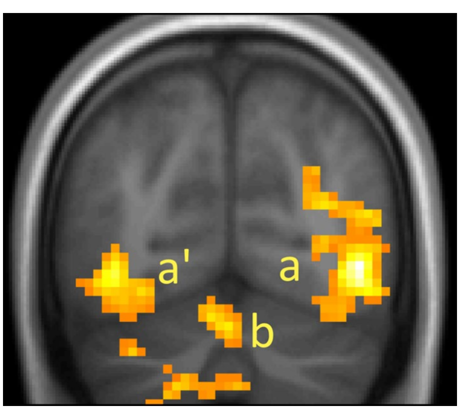

Fig. 1 Coronal section (67 mm caudal to anterior commissure) showing patients' brain responses to pictures of undressed children of their preferred gender in the bilateral inferior temporal gyri (a and a') and in the cerebellar declive (b). Height threshold: $T = 3.50$; extent threshold: $k = 30$. Right hemisphere is on the right. The clusters of activation are overlaid on the mean structural MRI scan of the 25 patients. Figures were produced by using SPM software

Contrast 3 Responses to preferred pictures.

The between-groups analysis showed that in response to their respective age- and gender-preferred stimuli, the right inferior temporal gyrus (BA 37) was more activated in controls than in patients. By contrast, no region was significantly more activated in patients compared to controls, in response to their respective preferred stimuli.

Contrast 4 Patients' responses to children's versus adults' nudity.

Contrast 4a Within-group analyses conducted in patients showed a greater activation in the right middle temporal gyrus in response to VSSc compared to VSSa. *Contrast 4b*. However, when the Dressed condition was introduced into the contrast to control for the morphological differences between images of adults and children, the within-group analysis did not show any differential activation to VSSc compared to VSSa. Regarding controls, no clusters were more activated in response to VSSc than to VSSa; similarly, no clusters were found more activated in response to VSSa.

Contrast 5 Comparison of patients and controls on their responses to VSSa versus VSSc.

Contrast 5 (Table 1) can be rewritten $(AdPref_{Undressed}-ChPref_{Undressed})_{controls}-(AdPref_{Undressed}-ChPref_{Undressed})_{patients}$. Between-groups analysis showed a higher differential activation in the left middle

Table 5 Brain responses of patients to pictures of undressed adults of preferred gender

Brain regions	BA	*k*	Side	MNI coordinates			*T*	p_{corr}
				x	*y*	*z*		
Middle occipital gyr.	**37**	**888**	**L**	**−39**	**−67**	**−5**	**8.26**	**<0.001**
Middle occipital gyr.[(SVC+)]	19		L	−48	−79	−11	7.95	<0.01
Middle occipital gyr.	18		L	−39	−88	4	7.52	<0.01
Middle temporal gyr.[SVC+]	37		L	−42	−64	−2	6.60	<0.01
Inferior occipital gyr.[SVC+]	19		L	−39	−70	−8	6.51	<0.01
Inferior occipital gyr.[SVC+]	18		L	−39	−85	−17	5.81	<0.05
Inferior temporal gyr.	**37**	**863**	**R**	**39**	**−61**	**−8**	**7.83**	**<0.001**
Middle occipital gyr.	19		R	42	−79	−2	7.58	<0.01
Inferior temporal gyr.	37		R	48	−70	−8	6.92	<0.05
Fusiform gyr. [SVC+]	37		R	42	−64	−20	5.82	<0.05
Middle temporal gyr.[SVC+]	**37**	**36**	**R**	**48**	**−64**	**-8**	**6.03**	**<0.05**
Postcentral gyr.[a,b]	**3**	**67**	**R**	**60**	**−22**	**46**	**5.36**	**<0.05**
Thalamus[a] [(SVC+)]	**–**	**57**	**R/L**	**0**	**−7**	**4**	**5.76**	**<0.05**
Thalamus [SVC+]	–		L	−3	−10	10	5.35	<0.05

Contrast: $AdPref_{Undressed}-AdPref_{Dressed}$. $p_{corrected}$ in bold characters refers to cluster-wise significance (cluster-forming threshold: 0.001, unc.; cluster-extent threshold: FWEc = 57 for binary explicit mask); $p_{corrected}$ in light characters refers to peak height significance

[a] Cluster that survives exclusive masking by regions activated in patients in response to images of nude children

[b] Region identified only by cluster-extent thresholding. See legend of Table 4 for additional information

occipital gyrus, consistent with a higher activation of that region in controls in response to images of undressed adults.

Contrast 6 Comparison between offenders and non-offenders.

Analysis did not show any brain regions responding differentially to VSSc in patients who had committed a sexual offense ($n = 18$) compared with non-offender patients ($n = 7$). The same was true for the comparisons between each subgroup of patients with the controls.

Correlational analyses

Within-group analyses did not show statistically significant correlations between the magnitude of erectile responses and the level of the BOLD signal, both in the 16 patients and the 12 controls who presented an erectile response. Similarly, between-groups analyses did not show differential correlation across patients and controls.

In patients, the ratings of DSA (whatever the age and gender of characters in pictures) was positively correlated with the level of activation in widespread areas including: (1) two clusters in the right middle temporal gyrus, (2) two clusters located bilaterally in the inferior frontal gyri, (3) the left precentral gyrus, (4) the left orbitofrontal cortex, (5) the left medial frontal gyrus and (6) the declive of cerebellar vermis (Table 6; Fig. 2). Conversely, the ratings were negatively correlated with activation in the right superior temporal gyrus. In controls, we found a positive correlation between DSA ratings (whatever the age and gender of characters in pictures) and bilateral activation in the lateral occipital, temporal cortices, and lingual gyri (Online Resource 7, online table 7). The between-groups analysis showed a higher correlation in patients than in controls between DSA ratings and activation in the left calcarine sulcus, extending to the left lingual gyrus.

Regarding ratings of PE, the correlational analysis yielded results similar to those obtained for DSA, as the two ratings were themselves correlated. Notably, there was in both groups a negative correlation between PE ratings and the BOLD signal in the right middle temporal gyrus (BA 21). The corresponding between-groups analysis showed that in a cluster in the left posterior cingulate and extending to the calcarine sulcus, the correlation was higher in patients than in controls. This was related to a positive correlation found only in patients ($t = 5.05$; $p_{uncorr.} < 0.001$).

As regards psychological scores, on the Sexual Fantasies, Desires and Activity Interview Schedule, we found in patients a negative correlation between the score of sexual desire directed to children and the level of activation in the left parahippocampal gyrus (BA35; *x, y, z*: −27, −25, −29; cluster size: 56 voxels, $p_{FWE} < 0.05$, corrected both at the cluster and the peak levels).

Finally, in patients, the higher the total testosterone level as measured a few days before the neuroimaging session, the higher the BOLD signal in the right middle occipital gyrus.

Table 6 Positive and negative correlations between rating of Desire for Sexual Activity and BOLD signal in patients

Brain region	BA	*k*	Side	MNI coordinates			*T*	p_{corr}
				x	*y*	*z*		
Positive correlation								
Middle temporal gyr.	37	7416	R	48	−64	7	11.57	< 0.001
Middle temporal gyr.[SVC−]	39	45	R	45	−76	16	7.4	< 0.01
Inferior frontal gyr.	9	774	R	48	11	31	7.65	< 0.001
Inferior frontal gyr., OFC	47	235	L	−27	32	−11	7.11	< 0.001
Inferior frontal gyr.[a]	9	101	L	−42	2	31	6.23	< 0.01
Medial frontal gyr.[a]	10	191	L	−3	59	25	5.82	< 0.001
Precentral gyr.[a]	6	77	L	−42	−4	46	5.55	< 0.01
Superior frontal gyr.[a]	6	60	R	3	11	55	4.83	< 0.05
Declive of vermis[SVC+]	-	78	L	−3	−73	−17	6.43	< 0.001
Fusiform gyr.[SVC+]	37	23	L	−42	−55	−20	5.42	< 0.05
Inferior frontal gyr.[SVC+]	45	30	L	−39	23	4	5.27	< 0.05
Lingual gyr.[SVC−]	17	80	L	−15	−88	−5	10.66	< 0.001
Inferior occipital gyr.[SVC−]	18	97	R	33	−85	−8	10.64	< 0.001
Fusiform gyr.[SVC−]	37	144	L	−30	−52	−8	7.93	< 0.001
Lingual gyr.[SVC−]	18	49	L	−3	−79	−2	6.01	< 0.01
Negative correlation								
Superior temporal gyrus[a]	22	136	R	66	−31	4	5.39	< 0.001

p_{corr} refers to cluster-wise significance: $p_{FWE\ corrected}$ (cluster-forming threshold: 0.001 unc.; cluster-extent threshold: FWEc = 60 and FWEc = 136 for positive and negative correlations, respectively, for binary explicit mask). *k*: cluster extent; [SVC+], small-volume correction procedure, based on areas showing positive correlation with neural response to VSSa in healthy males; [SVC−], small-volume correction procedure, based on areas showing negative correlation with neural response to VSSa in healthy males. BA, Brodmann area; gyr., gyrus; OFC, orbitofrontal cortex. [a]Region identified only by cluster-extent thresholding. See legend of Table 4 for additional information

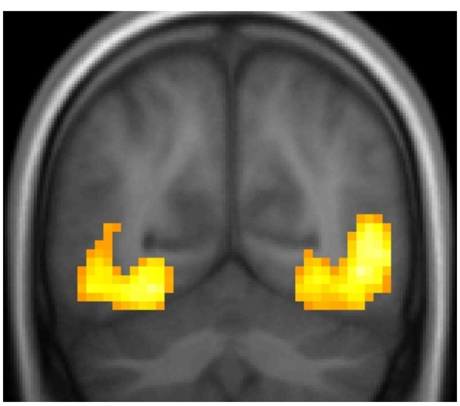

Fig. 2 Coronal section (61 mm caudal to anterior commissure) showing the positive correlation in patients between the Desire for Sexual Activity rating and the BOLD signal in a bilateral extended area including the right middle temporal gyrus and the left fusiform gyrus. Height threshold: $T = 5.50$; extent threshold: $k = 70$. Right hemisphere is on the right. The clusters showing correlation are overlaid on the mean structural MRI scan of the 25 patients. Figures were produced by using SPM software

Discussion

Visual stimuli induced the behavioral effects that we intended and whose correlates were investigated through fMRI analyses. For instance, compared with controls, patients showed a higher difference between DSA ratings for undressed and for normally dressed children. On the whole, these effects were more frequently observed for ratings than for erectile responses. This is likely due to the high frequency of participants with no erectile response to their preferred stimuli ($n = 7$ patients with no erectile response, i.e., 30.4% of all patients with available plethysmographic data; $n = 12$ controls, i.e., 50.0% of controls with available plethysmographic data).

The mean testosterone levels were significantly lower in the group of pedophilic patients than in the control group. In normal circumstances, aging males show a progressive decrease in testosterone levels with some increase in SHBG that contributes to lower the bioavailable testosterone as reported by several groups, including ours [43]. Lower testosterone levels in pedophilic patients have rarely been reported [49] and are likely to be associated with the age of the pedophilic group that was higher, although not significantly, than that of the control group. Indeed, when age was included as a covariate in the comparison, the between-groups difference of testosterone levels became non-significant ($p = 0.07$). Importantly, the pedophilic subjects were not taking antihormonal therapy at the time of inclusion in the study and were eligible since their testosterone was not pathological, although in the low normal range.

Subtractive analyses

In line with our hypothesis, most activations found in patients in response to their preferred VSSc were located in areas that respond to VSSa in healthy males [12]. Consistent with previous reports on heterosexual and homosexual patients [20–22], the regions involved included the lateral occipital and temporal areas, as well as the fusiform gyri.

In addition, patients presented a large cluster of activation in the cerebellar declive, an area where activation was found to be positively correlated with markers of SA in a study on nonclinical heterosexual males [27]. A greater activation in the declive in response to VSSc than to VSSa was also reported by Poeppl et al. [20]. Conversely, the activation in the cerebellar declive in response to VSSc was decreased by gonadotropin-agonist therapy in a patient with pedophilia [50]. By contrast with Poeppl et al.'s study [20], we did not observe any significant activation in the right middle frontal gyrus, the posterior cingulate gyrus, the right hippocampus-amygdala complex, the right postcentral gyrus, the right precentral gyrus and the right calcarine sulcus. However, the comparability of analyses is limited as Poeppl et al. [20] used neutral scrambled images as reference conditions whereas we used images of dressed characters.

Compared with patients, controls showed a much less extended activation in lateral occipital and temporal areas in response to pictures of undressed children. This is consistent with the non-significant difference between their ratings of pictures of undressed and normally dressed children (Table 3). Importantly, among these areas, the right inferior temporal gyrus and the middle occipital gyri bilaterally showed activation only in patients.

What is the functional significance of the widespread activation in lateral occipital and temporal areas in pedophiles in response to pictures of undressed children? In patients those areas may process images of children's nudity and participate in assigning to it a sexually stimulating valence. The activated clusters lie in temporal regions considered to mediate SA (BA 37, BA 19), by contrast with more anterior temporal areas (BA 20, 21 and 22) that are deemed to inhibit SA [12]. Alternatively, this temporal activation may result from top-down influences that would enhance attention to these stimuli, once a sexual valence has been assigned to the pictures by the orbitofrontal cortex, as posited in our neurophenomenological model [12]. Investigations with a higher time resolution should help to test the latter interpretation.

Whatever the answers, the lateral occipital and temporal areas responding to images of children's nudity in the patients appear to be partly similar to areas responding to images of adults' nudity in healthy controls both in the present study and in previous ones [12].

Surprisingly, we did not find any significant differences between patients and controls in response to VSSc despite the significant Condition by Group interaction on ratings of both DSA and PE. This is in line with results reported by Poeppl et al. [20] when, like in the present study, they used a corrected probability threshold. By contrast, our results were not consistent with those of Poeppl et al. [20] when they used an uncorrected probability threshold ($p < 0.001$, cluster extent $k > 10$ voxels) and reported higher activation in pedophiles in various regions (right middle temporal gyrus, right medial temporal lobe, right hippocampus, right posterior cingulate gyrus, left thalamus, and right culmen), which we did not find even with the same probability and cluster extent thresholds. However, the comparability of the studies is again limited as the controls in Poeppl et al.'s study were nonsexual offenders.

Regarding the responses to preferred VSSa, only controls showed activation in the right fusiform gyrus, the right orbitofrontal cortex and the left pregenual anterior cingulate gyrus. The bilateral activation in areas of the lateral occipital and temporal cortices and in the right postcentral gyrus observed in patients is consistent with previous findings in heterosexual and/or homosexual patients [21, 22]. These regions are also activated in healthy males in response to VSSa [12]. Conversely, the higher activation observed in patients in the right calcarine sulcus in response to dressed compared with undressed characters is consistent with findings in healthy males who showed a negative correlation between markers of SA and the level of activation in this area [27]. These findings are likely to be related with the fact that all our patients were non-exclusive, i.e., were also attracted to adults.

Despite these results of the within-groups analysis, the between-groups analysis did not find any differential responses to undressed adults, which contrasts with the significant Condition by Group interaction on the DSA rating, but is consistent with the lack of significant Group by Condition interaction on PE and on erectile responses. In contrast with Walter et al. [51], using the same threshold as in their study ($p < 0.005$, uncorrected, $k > 10$ voxels) we did not find a higher activation in healthy males in the dorsal midbrain, the left dorsolateral prefrontal cortex, the right parietal cortex, the right ventrolateral frontal cortex, the right occipital cortex and the left insula. However, the comparability of analyses is again limited as Walter et al. [51] compared groups on the contrast "sexual arousal > emotional arousal".

Whereas Poeppl et al. [20] reported that several regions showed higher activation (using an uncorrected threshold) in pedophiles than in controls in response to their respective age-preferred VSS, we found no such region (also using an uncorrected threshold). By contrast, whereas Poeppl et al. [20] did not find any areas that responded more in controls than in pedophiles to their age-preferred VSS, our study found such a higher activation in the right inferior temporal gyrus. A meta-analysis comparing pedophilic to non-pedophilic men failed to reveal any significant differences in either direction (pedophiles > non-pedophiles or non-pedophiles > pedophiles) when comparing groups on their responses to their age-preferred VSS [24].

When focusing on the patients' group, we found a higher activation in the right middle temporal gyrus in response to VSSc compared with VSSa. Based on the analysis of a comparable contrast, Poeppl et al. [20] found that several brain areas showed a higher responses to VSSc. However, the small-volume correction analysis based on the coordinates of the peaks reported in Poeppl et al. [20] replicated only the activation reported in the left middle occipital gyrus. This is likely related to the fact that in Poeppl et al.'s study [20] patients were exclusively attracted to prepubescent children, whereas all of our patients were non-exclusive. The latter feature was reflected in the non-significant differences of behavioral variables: for DSA, PE and erectile responses, the interaction Condition (undressed, dressed) by Age of Character (child, adult) was not significant.

Ponseti et al. [25] showed that it was possible to discriminate with high accuracy pedophilic patients from teleiophilic controls based on their brain responses to adult and child VSS. We performed a similar analysis with the purpose of identifying areas that responded differentially to these stimuli [$(\text{AdPref}_{\text{undressed}} - \text{ChPref}_{\text{undressed}})_{\text{Controls}} - (\text{AdPref}_{\text{undressed}} - \text{ChPref}_{\text{undressed}})_{\text{Patients}}$, and opposite contrast]. As in Ponseti et al. [25], an area with a differential response across groups was located in the left middle occipital gyrus. Results of within-group analyses showed that the above finding was related to the higher activation shown by controls in this area in response to pictures of undressed adults than to pictures of undressed children. These neuroimaging findings are consistent with the results of analyses of ratings and of penile responses, which showed an Age of Character by Group interaction.

Correlational analyses

In our study, the lack of correlation between the erectile response and brain activations in patients and in controls contrasts sharply with results reported by Arnow et al. [52] who performed a similar analysis in nonclinical heterosexual subjects. This discrepancy may be related to the difference in stimuli, as Arnow et al. [52] used video clips, which were presented for a longer time and are known to induce higher erectile responses than static pictures [e.g., 27].

As regards ratings of stimuli, in patients, in keeping with the findings of two reviews of the neural correlates of SA in healthy males [12, 46], the rating of DSA elicited by viewing the characters appearing in the pictures was positively correlated with the level of activation in clusters located (1) in the right middle temporal gyrus; (2) in the inferior frontal gyri; (3) in the precentral gyri; and (4) in the left medial frontal gyrus. The latter finding regarding the dorsomedial prefrontal cortex is consistent with a result reported by Walter et al. [53]. Like Schiffer et al. [22], we also found a positive correlation between the BOLD signal in the left fusiform gyrus and the DSA rating (Table 6). As indicated in Table 6 with the abbreviation "SVC-", whereas previous work in healthy subjects suggested that in some temporal regions (BA 39) the correlation with the level of SA would be negative [27, 54], the correlation was instead found positive in patients. As a negative correlation with a marker of SA suggests that a region inhibits SA [12], our results could be related to a failure of these regions to get deactivated by VSS, i.e., inhibitory regions would remain activated in patients with pedophilia. This is consistent with the embarrassment felt and reported by some patients in response to pictures of undressed children. However, it should be noted that regions deactivated by VSS are poorly known and have been reported by only one meta-analysis [46].

The greater correlation in patients than in controls between the left posterior cingulate activation and the ratings of PE was related to the high correlation found only in patients. In healthy subjects, this region has been reported to be deactivated in response to VSS [46] and negatively correlated with objectively measured penile erection [27, 54]. Thus, as mentioned for DSA, in patients with pedophilia the level of activation of a potentially inhibitory region was positively, instead of negatively, correlated with an indicator of SA.

Regarding scores on psychological questionnaires, the negative correlation found in patients between the BOLD signal in the left parahippocampal gyrus and the score of sexual desire directed to children on the Sexual Fantasies, Desires and Activity Interview Schedule is consistent with the negative correlation found in healthy males between the left parahippocampal regional cerebral blood flow and the markers of SA [27].

Finally, the positive correlation found in patients between the total testosterone level and the BOLD signal in the right middle occipital gyrus is consistent with the positive correlation reported in healthy men between plasma testosterone and the cerebral blood flow in that region in response to VSSa [55].

The regions reported in the "Results" section include some of the areas associated with attention to erotic stimuli and/or with the wanting or liking components of reward processing [56, 57], e.g., the orbitofrontal and the cingulate cortices; however, the regions we report do not comprise some other areas of these putative networks, e.g., the ventral striatum (including the nucleus accumbens), the anterior insula, the amygdala, the midbrain, the lateral hypothalamus, the ventral pallidum, the frontal operculum, and the inferior parietal lobule.

The lack of clear-cut differential responses between patients and controls to pictures presented in this study may be related to a true lack of differential responses or to methodological limitations. Regarding the limitations, some patients reported embarrassment while watching pictures of undressed children. Many of them (72.0%) were engaged in psychotherapy and may have had ambivalent feelings during these presentations, including the fear of potential relapse because of sexual stimulation. In addition, it is also possible that the moderate level of SA induced by pictures of children in swimming suits (only four photographs presented naked children) limited the level of activation. While the level of DSA induced by their preferred stimuli in the undressed condition was similar in patients and controls, the difference between ratings induced by undressed and dressed characters was higher in controls, with a significant Condition by Group interaction. Here, the experimental need to induce strong SA in patients was conflicting with the ethical and clinical concerns to limit such arousal. Furthermore, using pictures of dressed characters as a control condition may be less adequate in patients than in control subjects, as the latter showed higher responses to the Dressing condition for pictures of adults than did patients in response to pictures of children (Table 4). Another limitation, from a technical standpoint, was that the explicit mask did not cover the entire brain, as it left the upper part of the parietal lobe unexplored due to the initial 30° tilt of the acquisition plane, which limited the field of view in that region. Finally, from a statistical point of view, the sizes of the samples, although reasonable regarding the pooled groups, may be insufficient to demonstrate limited effect sizes and to investigate subgroups of patients, e.g., patients attracted to girls versus those attracted to boys.

Conclusion

Several lines of evidence implicate the right and left occipital and temporal gyri, in particular the right inferior temporal gyrus (BA 37), as possible candidate areas mediating SA in patients with pedophilic disorder in response to pictures of undressed children. Firstly, these regions were more activated in response to preferred VSSc. Secondly, in patients the BOLD level in these areas was positively correlated with the ratings of DSA and of PE. Thirdly, the right inferior temporal cortex (1) was more activated in response to pictures of undressed children than to those of undressed adults in patients and (2) was activated by pictures of undressed children in patients but not in controls. These activated temporal areas were distinct from other temporal areas, also located in the right temporal lobe but more rostrally (BA 20, 21, 22), which are thought to exert an inhibitory function on SA in healthy males [12] and whose BOLD level was found in the present study to be negatively correlated with the level of PE. Finally, the cerebellar declive is likely to be implicated in the cognitive processing of children's nudity as (1) in the present study, it showed activation in response to images of nude children in both groups; (2) gonadotropin-releasing hormone agonist therapy in a patient with severe pedophilia induced a decrease of both sexual desire and declive activation in response to these pictures [50]; and (3) a greater activation in the declive in response to pictures of children than to those of adults was also reported by Poeppl et al. [20].

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study was approved by the local ethics committee (CPP Sud-Est: No. A00451-56) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from all subjects after complete description of the study.

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