Expectation of sexual images of adults and children elicits differential dorsal anterior cingulate cortex activation in pedophilic sexual offenders and healthy controls

Inka Ristow[a,b], Jens Foell[c], Christian Kärgel[d], Viola Borchardt[a,b], Shijia Li[e,f], Dominik Denzel[a,b], Joachim Witzel[g], Krasimira Drumkova[g], Klaus Beier[h], Tillmann H.C. Kruger[i], Jorge Ponseti[j], Boris Schiffer[d], Kolja Schiltz[k,l], Henrik Walter[m], Martin Walter[a,b,l,n,o,*]

[a] Clinical Affective Neuroimaging Laboratory (CANLAB), Magdeburg, Germany
[b] Leibniz Institute for Neurobiology, Department for Behavioral Neurology, Magdeburg, Germany
[c] Department of Psychology, Florida State University, Tallahassee, FL, USA
[d] Division of Forensic Psychiatry, LWL-University Hospital, Ruhr University Bochum, Bochum, Germany
[e] Key Laboratory of Brain Functional Genomics (MOE&STCSM), Shanghai Changning-ECNU Mental Health Center, School of Psychology and Cognitive Science, East China Normal University, Shanghai, China
[f] Shanghai Key Laboratory of Magnetic Resonance, East China Normal University, Shanghai, China
[g] Forensic Psychiatric State Hospital of Saxony-Anhalt, Stendal-Uchtspringe, Germany
[h] Institute of Sexology and Sexual Medicine, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
[i] Department of Psychiatry, Social Psychiatry and Psychotherapy, Section of Clinical Psychology and Sexual Medicine, Hannover Medical School, Hannover, Germany
[j] Institute of Sexual Medicine and Forensic Psychiatry and Psychotherapy, Kiel University, Medical School, Kiel, Germany
[k] Section of Forensic Psychiatry, Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Munich, Germany
[l] Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Magdeburg, Germany
[m] Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy CCM, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Univesität zu Berlin and Berlin Institute of Health, Berlin, Germany
[n] Department of Psychiatry, Eberhard Karls University, Tübingen, Germany
[o] Max Planck Institute for Biological Cybernetics Tübingen, Germany

ABSTRACT

Background: Pedophilic disorder is characterized by increased sexual interest towards children, with comparatively lesser interest towards adults. In real life, the behavior of subjects with pedophilic disorder is shaped by evaluative processes in response to sexually relevant cues. Therefore, brain activation during anticipation of sexually relevant cues is of potential interest. Whereas previous research demonstrated reduced activation when viewing adult (non-preferred) sexual stimuli in pedophilic sex offenders (PSOs), it is not known if anticipation of preferred versus unpreferred stimuli will elicit differential brain activation.

Methods: Two fMRI studies (1.5 and 7 Tesla) were conducted in separate samples, each with 26 subjects (13/13 PSOs/controls) to assess brain activity during expectancy of subsequent adult (non-preferred) sexual stimuli. In the second study (7 Tesla) additionally child (preferred) cues were presented.

Results: As predicted, expectancy of adult sexual stimuli generated smaller dorsal anterior cingulate cortex (dACC) activation in PSOs in both studies, driven by stronger activation during expectancy of adult erotic stimuli in non-pedophilic controls (HCs). In the second study, PSOs showed significantly increased activations in dACC during expectancy of child stimuli compared with expectancy of adult stimuli. This difference was significantly greater compared to the same contrast in HCs, thus demonstrating preference specificity of dACC activation.

Conclusion: Our findings support the notion of decreased brain activation to adult cues in PSOs and preference specificity in neural response during expectancy of erotic stimuli. The localization of these cue reactivity differences in the salience network supports the interpretation that PSOs show abnormally increased preparatory activation even before relevant sexual stimuli are actually presented.

* Corresponding author at: Head Section for Translational Psychiatry, Dept. of Psychiatry, University of Tuebingen, Osianderstr. 24, 72076 Tübingen, Germany.
E-mail address: martin.walter@uni-tuebingen.de (M. Walter).

1. Introduction

According to DSM-5, people diagnosed with a pedophilic disorder experience recurrent, intense, sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (American Psychiatric Association, 2013). In recent years, increasing research has begun to investigate the physiopathology of this paraphilic disorder (Tenbergen et al., 2015). Nevertheless, its mechanisms are still not completely understood.

Recent improvements in neuroimaging techniques have made it possible to study neural correlates of various brain processes, leading to functional magnetic resonance imaging (fMRI) studies investigating the neural correlates of cognitive control and salience processing. A salience network comprising the anterior insula and the dorsal anterior cingulate cortex (dACC) was proposed to be a crucial factor regarding switching between brain networks as a function of salience detection and attention regulation (Bressler and Menon, 2010). These areas have also been found to be involved with cognitive processes related to sexual arousal (Kühn and Gallinat, 2011; Stoléru et al., 1999; Redouté et al., 2000; Stoléru et al., 2012).

fMRI studies utilizing sexual stimuli, such as pictures with sexually arousing content, have revealed differential brain activation patterns in pedophilic sex offenders (PSOs) compared to healthy control subjects (HCs). For example, Walter et al. (2007) found significantly lower signal intensities in PSOs compared to HCs in the dorsolateral prefrontal cortex in response to sexual pictures of adults. Schiffer et al. (2008a) demonstrated that processing of age-preferred sexual visual stimuli in PSOs was largely similar to that in control subjects. However, significant activation in response to age-preferred visual sexual stimuli was found in the thalamus, globus pallidus and striatum in PSOs but not in HCs. Similar brain activation patterns in PSOs and HCs were also found by Schiffer et al. (2008b), who showed a topographical overlap in limbic structures such as the amygdala and hippocampus, substantia nigra, caudate nucleus, as well as the anterior cingulate cortex, different thalamic nuclei, and associative cortices while viewing preferred sexual stimuli. Supporting the hypothesis of prefrontal disturbances in pedophilia, abnormal activation patterns were observed in the orbitofrontal cortex, which was driven by non-activation in PSOs. Habermeyer et al. (2013) investigated immediate processing of erotic stimuli in male participants who were diagnosed with a pedophilic disorder and HCs. In both groups, stronger activation was found in the right temporal lobe, the right parietal lobe, and both occipital lobes during presentation of adult sexual pictures, whereas pictures of children elicited stronger activation in the right dorsomedial prefrontal cortex in both groups. An interaction of sex (male vs. female), stimulus age (child vs. adult) and participant group (patient vs. control) was reported the right anterolateral orbitofrontal cortex, which was driven by activation in the gender-preferred child condition in pedophilic subjects while controls showed a deactivation in the respective condition.

Further findings in pedophilic samples also indicate the presence of frontal brain abnormalities. For example, Kärgel et al. (2017) investigated inhibitory control abilities in a go/no-go paradigm and reported divergent inhibition-related activation in the left posterior cingulate and the left superior frontal cortex between pedophilic offenders and non-offenders, while no differences were found between pedophiles and HCs. Metabolic alterations in PSOs as indicated by a deficit of the inhibitory neurotransmitter GABA in dACC (Ristow et al., 2018), support the idea that inhibition-related alterations play an important role in this disorder. Further research showed that child sexual offending in pedophilia rather than pedophilia was found to be associated with gray matter anomalies (Schiffer et al., 2017). Moreover, decreased gray matter volume of the dorsomedial prefrontal and anterior cingulate cortex was associated with a higher risk of re-offending in PSOs as indicated by a negative correlation between gray matter volume and SSPI-2 scores (i.e. a measure of the risk of re-offending in pedophilic offenders) (Schiffer et al., 2017).

There is evidence that neural processing of sexual arousal involves both conscious and unconscious aspects (Janssen et al., 2000; van Lankveld et al., 2015; Gillath and Collins, 2016). While unconscious processes are thought to be inevitable and automatic, conscious ones can be described as controlled cognitive processes in the appraisal of sexual events. If a presented sexual cue evokes a sexual meaning, the generated response subsequently leads to increased sexual arousal, including the activation of physiological responses. If not, the stimulus is categorized as nonsexual, leading to decreased sexual arousal. Higher-order cognitive processes, such as inhibitory control of sexual arousal, are also crucially involved in sexual arousal. However, the model by Janssen et al. (2000) provided evidence that even erotic stimuli that are not perceived consciously may still automatically initiate physiological responses. Findings by Wernicke et al. (2017) in healthy subjects support this theory by demonstrating differential neural processing of subliminally presented pictures with sexually preferred versus non-preferred content in brain areas associated with sexual arousal.

From a clinical-therapeutic perspective, attempts to intervene in a habitual response to an acute stimulus may be initiated too late, reducing their efficacy. Active attempts to influence or adjust behavior could be more effective at the preparatory stage, when a cue indicates an imminent stimulus. For example, psychotherapeutic interventions for pedophilic disorder may be most successful when patients learn to avoid any tempting situation involving a child.

Based on these models, we hypothesize that in PSOs, deviant neural activation will already be observable during the presentation of a sexual cue that serves to indicate whether the subsequent stimulus will be more or less sexually arousing. We performed two fMRI studies to investigate whether PSOs process sexual cues differently from HCs. To examine attentional preparatory aspects of sexual information processing, we measured neural activation during an expectancy task that utilized visual cues to indicate the subsequent visual presentation of naked adults or children.

Recently, the reproducibility of neuroimaging studies has been increasingly contested due to low test-retest reliability (Button et al., 2013). A meta-analysis by Bennett and Miller (2010) reported that reliability can change depending on several methodological considerations that cause scanner artifacts, leading to a suboptimal estimation of the signal and its reliability over time. Therefore, questions about reliability might be better answered by repeating a study to investigate if results can be reproduced. With these considerations in mind, we performed two separate fMRI studies at separate times and using separate samples of PSOs and HCs.

2. Methods and materials

2.1. Participants

2.1.1. Study 1

13 male non-medicated PSOs (mean age = 40.0 ± 8.9 SD) were recruited from the State Forensic Hospital Uchtspringe, Germany. At the time of data acquisition, all PSOs met the diagnostic criteria for pedophilia according to DSM-IV (American Psychiatric Association, 2000). Exclusion criteria were previous anti-androgenous medication, other reported psychiatric or neurological disorders, a history of drug abuse or alcoholism, and standard MRI contraindications. All patients had a history of sexual offending against children. The number of victims ranged from 1 to 10 (mean n = 4.3 ± 2.9 SD). Within the patient group, six PSOs reported exclusively heterosexual interests, three exclusively homosexual interests, and four both heterosexual and homosexual interests. All patients were exclusively attracted to children. Gender, group size, age and years of education were defined as matching criteria for the HCs (see demographics in Table 1). HCs exclusively reported heterosexual interests. To ensure the absence of low intelligence scores in patients, IQ scores for verbal (Schmidt and Metzler, 1992) and general (Horn, 1983) intelligence were assessed.

Table 1

Mean values ± SD of all study variables; all sample-matching criteria revealed p > .05. EHI-Index 15 = 15-item index of the German Edinburgh Handedness Inventory; IQ-WAIS = Intelligence quotient assessed using the German Wechsler Adult Intelligence Scale).

		PSOs	HCs
Study 1	Number	13	13
(1.5 T)	Mean age	40.0 ± 8.9	37.3 ± 6.5
	Handedness	12 right, 1 left	13 right
	Years of education	12.4 ± 1.5	14.3 ± 3.5
	Mean n of victims	4.3 ± 2.9	–
Study 2	Number	13	13
(7 T)	Mean age	35.9 ± 10.1	34.7 ± 8.6
	Handedness	11 right, 2 left	11 right, 2 left
	EHI-Index (15)	45.64 ± 60.73	52.82 ± 65.19
	IQ-WAIS	92.62 ± 14.30	103.23 ± 19.03
	Mean n of victims	5.31 ± 4.66	–

The study was approved by the local ethics advisory board of the Medical School, Otto-von-Guericke-University Magdeburg. Prior to inclusion, written informed consent was obtained from all participants.

2.1.2. Study 2

Participants were assessed as part of a larger German multi-site research project called "Neural Mechanisms Underlying Pedophilia and Sexual Offending Against Children" (NeMUP; www.nemup.de), comprising five collaborative research sites from the fields of forensic psychiatry and sexual medicine located in Berlin, Bochum/Essen, Hanover, Kiel, and Magdeburg.

This second sample of PSOs comprised 13 males (mean age = 35.9 ± 10.1 SD) meeting DSM-V diagnostic criteria for a pedophilic disorder (American Psychiatric Association, 2013). Seven PSOs were treated with the GnRH agonist Triptorelin (Salvacyl ®) at the time of participation. The majority of the PSOs group was right-handed (n = 11) as assessed using the updated 15- item index of the Edinburgh Handedness Inventory (Oldfield, 1971; Cohen, 2008). As in Study 1, PSOs were recruited from the State Forensic Hospital Uchtspringe in Germany. The number of victims sexually assaulted by the offenders ranged from 1 to 14 (mean n = 5.3 ± 5.01 SD). Within the patient group, two PSOs reported exclusively heterosexual interests, six exclusively homosexual interests, and five both heterosexual and homosexual interests. Eight PSOs reported exclusive attraction to children, whereas the rest (n = 5) reported sexual interest in both adults and children (pedo-teleiophilic). HCs exclusively reported heterosexual interests.

As depicted in Table 1, gender, group size, age and laterality index were defined as matching criteria for both groups (PSOs and HCs). To assess the participant's individual verbal and general intelligence scores, means of four subtests *Similarities* and *Vocabulary* from the verbal comprehension scale as well as *Block Design* and *Matrix Reasoning* from the perceptual reasoning scale of the German version of the Wechsler Adult Intelligence Scale (4th Edition, WAIS; von Aster et al., 2006) were used.

Exclusion criteria were a history of other psychiatric or neurological disorders and standard MRI exclusion criteria. Acute psychiatric disorders other than pedophilic disorder were ruled out using the German Structured Clinical Interview (SCID) for DSM-4-TR (Wittchen et al., 1997), the German 21-item Hamilton Depression Scale (HAM-D;
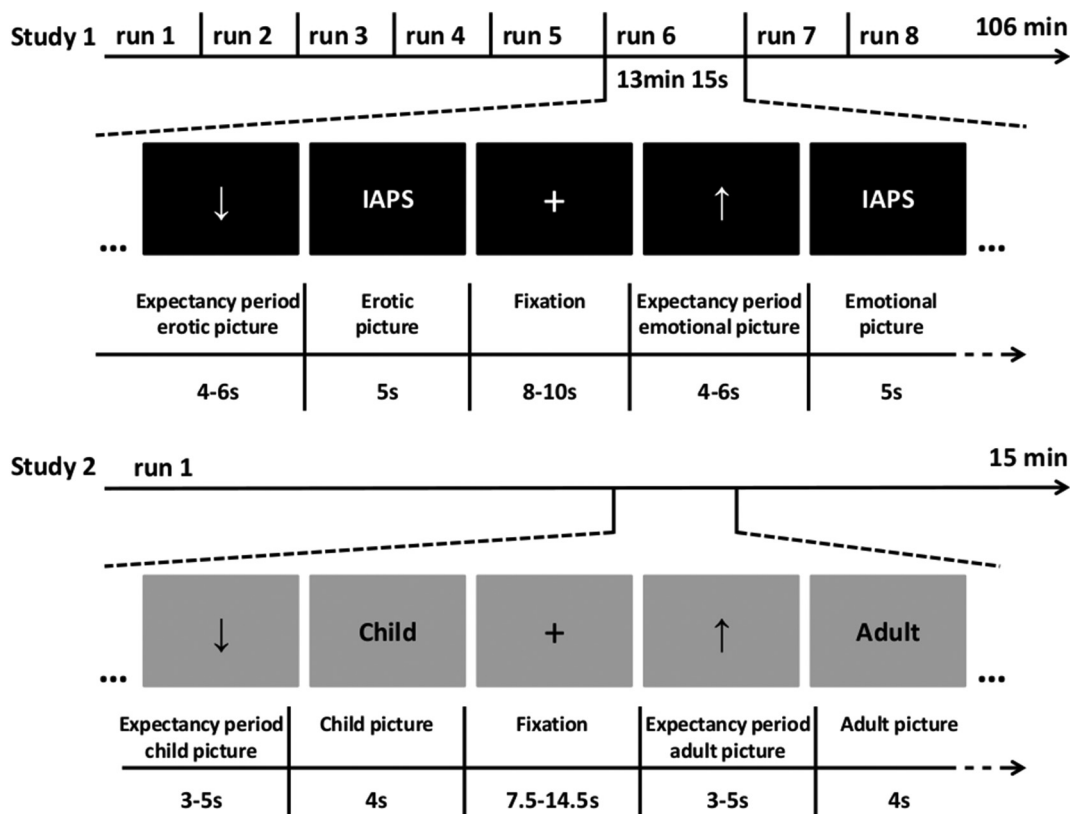
Fig. 1. Procedures of Studies 1 and 2.

A) Across 8 runs, subjects were presented erotic, emotional and neutral pictures of adults (women/men) interspersed with neutral control pictures. Pictures from each category were presented for 5 s. Half of the pictures were preceded by an expectancy cue (arrow). Each run included a total of 32 photographs (n sexual = 10, n emotional = 10, n neutral =12).

B) Subjects were presented erotic pictures of male and female photographs of adults (n = 20) and children (n = 20). Pictures from each category were presented for 4 s. Half of the pictures were preceded by an expectancy cue (arrow).

Hamilton, 1960; excluded if > 9), and the German Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959; CIPS, 1996; excluded if > 17). The study was approved by the local ethics advisory board of the Medical School, Otto-von-Guericke-University Magdeburg. Prior to inclusion, written informed consent was obtained from all participants.

2.2. Imaging

2.2.1. Study 1

2.2.1.1. Expectancy paradigm. During the scanning session, subjects were presented with erotic, positive-emotional, and neutral photographs depicting both males and females from the International Affective Picture System in a randomized order (IAPS; Lang et al., 1997). The experimental setup comprised 8 runs. Each run included 10 sexual, 10 emotional and 12 neutral photographs and added up to 13 min and 15 s. Consequently, the total number of presented pictures added up to $32 \times 8 = 256$ photographs. Erotic and emotional pictures were matched for emotional arousal and valence and presented in a randomized order on a mirror mounted on a standard head coil. Erotic pictures contained single and coupled stimuli of male and female adults. Prior to their use in this paradigm, the erotic pictures were rated for sexual arousal by a separate sample of 21 healthy heterosexual adults (Walter et al., 2008). In the scanner, participants were asked to press a button when each picture appeared, to ensure their active participation throughout the experiment. Patterns of preparatory brain activation (Bermpohl et al., 2006) were measured during an expectancy period of 4–6 s that preceded the presentation of half of the pictures (Fig. 1). During this period, subjects were instructed to actively expect a particular category of picture, depending on the cue. Each cue was a white arrow presented on a dark background. Upward-pointing arrows were used to cue positive-emotional pictures, downward-pointing arrows to cue erotic pictures and rightward-pointing arrows to cue neutral pictures. To control for general anticipation effects, leftward-pointing arrows were also included, but did not provide any information about the type of picture that would subsequently appear ("ambiguous cue"). After each picture (5.0 s), a fixation cross appeared for a variable duration of 8–10s (jitter steps of 0.5 s; Sakai and Passingham, 2003).

2.2.1.2. Data acquisition. Data were acquired on a 1.5 T General Electric Signa scanner (Signa, General Electric Medical System, Milwaukee, Wisconsin). Imaging protocol included 1) acquisition of structural data followed by 2) acquisition of functional data during the expectancy task. Following the imaging protocol previously reported by Schiltz et al. (2006), Düzel et al. (2006), and Szentkuti et al. (2004) inversion recovery T1-weighted echo planar images (voxel size, 0.976 0.976 1.5 mm) were acquired. Images were aligned to the transversal plane through the anterior and posterior commissure and then rotated backward (flip angle = 5°). Functional echo planar functional images (402 volumes, 23 slices with 3.125 mm in-plane resolution, 5 mm thickness, 1 mm gap; T2* weighted gradient echo sequence: TE = 40 ms, TR = 2000 ms) were acquired across eight runs.

2.2.1.3. Data analysis. In each run, 402 functional EPI images were acquired. The first seven images were excluded to ensure a sufficient saturation of the T1 images. Consequently, the total data set included $8 \times 395 = 3160$ volumes for each participant. Image preprocessing and statistical analyses were performed as implemented in SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). To correct for head movement, volumes were realigned to the first image and mean-adjusted by proportional scaling. Next, images were resliced, and normalized into standard MNI space (Montreal Neurological Institute, isotropic 3 mm resolution). Finally, transformed data were smoothed with an 8 mm full-width half-maximum Gaussian kernel. Low-frequency drifts in signals were removed by means of a 128 s high-pass filter.

First-level analysis was modeled using a block design approach with a canonical HRF. Regressors of interest included time blocks for expectancy of erotic adult (XAD), neutral, positive-emotional, and ambiguous cues. Regressors for each picture-viewing condition and fixation-viewing were also included. Effects were calculated with GLM modeling in SPM8. In order to investigate anticipation effects for erotic adult images, XAD > fixation was defined as the primary contrast of interest. For motion correction purposes, rigid motion parameters from the subjects' rp-files were included as regressors in the analysis. Contrasts generated in the first-level analysis were then used for second-level analysis. Group comparisons between HCs and PSOs were tested with a two sample t-test in a random effects model. Age was included as a covariate.

For all whole-brain analyses, the threshold of statistical significance was set at p < .05 and FWE cluster-level corrected with a conservative cluster-defining primary threshold of p < .001, uncorrected, in response to recent criticism regarding inflated false positives when using less-stringent initial height thresholds (Eklund et al., 2016). Analyses investigating exclusively picture perception in the same sample were previously published by Walter et al. (2007).

During review it was suggested by the reviewer to provide information about the contrast expectancy sexual picture adult (XAD) > emotional picture (PEMO), HCs > PSOs. We report the results in Supplementary Fig. 1, however, one should be aware that this contrast is confounded by two factors 1) emotion (sexual vs. emotional) and 2) task (expectancy vs. viewing) thus the interpretation may become very difficult and incomplete without even further contrasts.

2.2.2. Study 2

2.2.2.1. Expectancy paradigm. MR data were obtained between 10 a.m. and 12 p.m. on the same weekday. Prior to the fMRI task, magnetic resonance spectroscopy (MRS) data were acquired in the same scan session (Ristow et al., 2018). Subjects were instructed to view a total of 45 photographs depicting whole-body frontal views of either a naked adult or a naked child in randomized order. Both male and female pictures were included for both age groups. In each picture, only one person was visible without additional context. Photographic material depicting naked adults and children has been utilized in previous fMRI studies (Ponseti et al., 2012; Unterhorst et al., 2018). In order to trigger an erotic neural connotation of the adult sexual stimuli, males displayed signs of genital arousal (e.g., erect penises). Pictures depicting naked adults were open-access photos from the internet. Validation of the pictures was performed by Ponseti et al. (2012) via valence and arousal ratings. In that study, mean ratings of sexual stimuli were in concordance with participants' reported sexual orientations (for further information, see Ponseti et al., 2012).

Expectancy task was presented using Presentation (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA) via New projector JVC DLR-RS49E and a coil-mounted mirror in the scanner. In accordance with Study 1, half of the pictures were preceded by an anticipation period of 3–5 s (jitter steps of 1.0 s). The other half, presented immediately after the fixation cross, were considered "unexpected" (uncued) pictures. Subjects were instructed to actively expect a particular category of picture, depending on the cue. Upward-pointing arrows were used to cue adult pictures and downward-pointing arrows to cue child pictures (Fig. 1). After picture presentation (4.0 s), a fixation cross was shown for a variable duration of 7.5–14.5 s (jitter steps of 0.5 s).

2.2.2.2. Data acquisition. T1 anatomical volume images and functional magnetic resonance images were acquired using a 7 T MR scanner (Magnetom 7 T, Siemens, Erlangen, Germany) with a 32-channel head array coil. Anatomical images were acquired for anatomical reference with a MPRAGE sequence (TE = 2.73 ms, TR = 2300 ms, TI = 1050 ms, flip angle = 5°, bandwidth = 150 Hz/pixel, isotropic voxel size = 0.8 mm³). Individual anatomical images were segmented and used for co-registration. Functional single-shot echoplanar imaging

Table 2

Results table for Study 2 depicting significant main effects and their interaction in a 2 × 2 × 2 ANOVA. The design included two between-subjects factors: condition (anticipation vs. picture-viewing) and stimulus age (child vs. adult), and one within-subjects factor: group (PSOs vs. HCs).

F-contrast		Brain region	Side	MNI coordinates			Cluster extent in voxel	Peak F-value	Cluster-level pFWE
				x	y	z			
1)	Main effect of stimulus age (child vs. adult)	Fusiform gyrus	R	20	−84	−8	417	37.58	< 0.001
		Superior occipital gyrus	L	−14	−94	2	435	30.65	< 0.001
		Superior parietal lobule	L	−38	−48	58	231	27.88	< 0.001
		PCC	R	8	−50	30	204	22.71	< 0.001
		Supramarginal gyrus	R	66	−20	34	85	17.28	0.013
2)	Main effect of condition (expectancy vs. picture-viewing)	Calcarine gyrus	L	−8	−82	8	14,513	147.57	< 0.001
		Precentral gyrus	L	−36	−4	50	1823	96.93	< 0.001
		Anterior insula	L	−32	22	0	403	83.30	< 0.001
		SMA	L	−8	6	58	5701	79.91	< 0.001
		Thalamus	R	4	−20	−2	607	64.58	< 0.001
		MCC	R	6	−16	30	777	57.74	< 0.001
		Middle temporal gyrus	R	42	−62	4	71	5.81	0.032
		Middle temporal gyrus	R	58	−26	−10	2251	37.87	< 0.001
		Inferior parietal lobule	L	−32	−52	38	1722	36.26	< 0.001
		Pallidum	R	20	4	4	101	32.98	0.005
		Angular gyrus	L	−42	−70	30	332	31.58	< 0.001
		Precuneus	R	10	−68	44	360	28.99	< 0.001
		Middle frontal gyrus	L	−32	52	16	519	27.92	< 0.001
		Inferior temporal gyrus	L	−50	−20	−20	693	26.01	< 0.001
		Middle orbital gyrus	R	30	58	−8	223	21.78	< 0.001
		Angular gyrus	R	44	−60	26	78	19.01	0.020
		Inferior frontal gyrus	R	44	44	−18	82	18.58	0.015
3)	Main effect of group (PSOs vs. HCs)	Inferior temporal gyrus	L	−62	−24	−22	72	23.45	0.030
4)	Interaction stimulus age × group	Superior parietal lobule	L	−26	−64	54	807	31.77	< 0.001
		Anterior insula	L	−28	24	4	115	30.20	0.002
		Superior occipital gyrus	R	26	−64	40	343	26.94	< 0.001
		Inferior occipital gyrus	L	−44	−76	−8	164	18.15	< 0.001
5)	Interaction condition × group	Calcarine gyrus	R	2	−84	8	97	20.58	0.006
6)	Interaction stimulus age × condition	Supramarginal gyrus	R	62	−42	28	82	20.41	0.015
		Anterior insula	L	−36	16	−4	73	18.09	0.028
7)	Interaction stimulus age × condition × group	dACC	R	2	24	38	545	25.74	< 0.001
		Rolandic operculum	R	−5	12	35	88	19.65	0.010
		Cuneus	L	−10	−70	25	80	18.36	0.009
		Middle frontal gyrus	R	26	48	30	106	17.75	0.003

(EPI) sequence was obtained using the following parameters: TE = 22 ms, TR = 2.8 s, flip angle = 80°, number of volumes = 300, slices = 62, slice thickness = 2 mm, voxel size = 2 mm^3. Online motion correction was performed (Speck et al., 2008). Functional images were acquired using interleaved slice order with an ascending direction and with the reference slice at the beginning. Whole brain coverage was obtained including cerebellum and brainstem.

Metzger et al. (2010, 2013) demonstrated that the use of ultra-high-field MRI, in principle, results in an increased signal-to-noise ratio. Further, they demonstrated that sufficient contrast-to-noise ratio can be reached with one long run of 13 min by removing negative and neutral stimuli. Following these conclusions, we performed only one run (15 min) in this fMRI study.

2.2.2.3. Data analysis. fMRI data were preprocessed using the SPM8 software package (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) running on MATLAB R2013b (MathWorks, Inc., Natick, Massachusetts, United States). The first three volumes were discarded to obtain stable signal and avoid initial movement of the participant. Preprocessing included slice timing, realignment, segmentation, image calculation, co–registration, deformation and smoothing with a 4 mm full-width-at-half-maximum Gaussian kernel. Functional images were filtered by means of a 128 s high-pass filter to remove slow signal drifts.

First level analysis was modeled using a block design approach with a canonical HRF. Regressors of interest included time blocks for expectancy of an adult (XAD), expectancy of a child (XKI), picture of an adult (PAD), picture of a child (PKI) and fixation (fix). In addition to realignment, the covariates included 6 rigid motion parameters from the non-online corrected data set.

For second-level analysis, an ANOVA was performed with a full factorial 2x2x2 design with two within-subjects factors (condition: expectancy vs. picture-viewing; stimulus age: child vs. adult) and one between-subjects factor (group: PSOs vs. HCs). Age was defined as a covariate. F-contrasts were calculated in order to assess main effects of task, stimulus age, and group, as well as the interaction between these factors. Follow-up two-sample *t*-tests were performed in order to determine the direction of the differential activations during expectancy and picture-viewing between HCs and PSOs. Age was again defined as covariate of nuisance. As in Study 1, we tested for task activation on the whole-brain level at a statistical significance of p < .05, FWE cluster level corrected with a cluster defining primary threshold of *p* < .001, uncorrected.

In post-hoc exploratory analyses, contrast estimates derived from significant clusters were analyzed using SPSS (IBM SPSS Statistics 20, Chicago, IL, USA). Shapiro-Wilk test was performed to test for normality of the sample distribution followed by Levene's test of homogeneity of variances. Task activation clusters for both studies were visualized using BrainNet Viewer (Xia et al., 2013) and MRIcron software (University of South Carolina, Columbia, SC, USA; https://people.cas.sc.edu/rorden/mricron/index.html).

3. Results

3.1. Demographics

In both studies, *t*-tests did not reveal any significant differences (p > .05) between HCs and PSOs with respect to age, handedness, or IQ score (Table 1). PSOs showed normal IQ scores (verbal IQ = 97 ± 14.5; general IQ = 110 ± 12) in Study 1. In Study 2, as described above, no subjects were included with HAM-A scores > 17 (subjects' range = 0–17) or HAM-D scores > 9 (subjects' range = 0–9). Mean HAM-A scores of PSOs (Mean ± SD = 3.85 ± 5.01) did not differ significantly from HCs (Mean ± SD = 1.46 ± 1.45, t(13.99) = 1.65, p = 0.122). Mean HAM-D scores of PSOs (Mean ± SD = 3.38 ± 2.57) were significantly higher than for HCs (Mean ± SD = 1.23 ± 1.92, t (24) = 0.841, p = 0.023).

3.2. Study 2 ANOVA: Main effects and interactions

Besides significant main effects of stimulus age, group, and task (Table 2) analysis revealed a significant interaction effect for group × stimulus age × condition in various brain regions, among them the dACC (Supplementary Fig. 2). In order to provide information about the directionality of the observed effects, color-labelled brain views in Supplementary Fig. 3 depict brain regions for the respective t-contrasts with significant main and/or 2 × 2 interaction effect. Difference between expectancy and picture conditions for child versus adult stimuli between groups was investigated in order to understand the direction of the effects of the 2 × 2 × 2 interaction ANOVA. Results were visualized in Supplementary Fig. 4 utilizing bar charts for significant brain regions, among them the dACC.

3.3. Task-related brain activity during expectancy

3.3.1. Study 1

Neural correlates of preparation for subsequent sexual images were investigated by comparing the contrast expectancy of adult sexual stimuli > fixation cross between groups (XAD > fix, HCs > PSOs) in a two-sample *t*-test. PSOs exhibited significantly reduced BOLD activation in dACC when expecting sexual pictures of adults, compared with HCs (cluster level p_{FWE} = 0.001, k = 296, Fig. 2). The cluster showed an overlap with the supplementary motor area (SMA). Local peaks of the cluster were at MNI 0, 18, 51, *t* = 4.30; MNI 0, 18, 42, t = 4.30; and MNI 12, 3, 72, *t* = 4.84. No significant results of the inverse contrast (fixation cross > expectancy of adult sexual stimuli) were found.

A reproduction of the effects in dACC for the contrast XAD > Xneutral pictures was requested during review which is provided in Supplementary Fig. 5.

3.3.2. Study 2

As here, we are particularly interested in exploring the group related brain activations of stimulus age (adult vs. child cue) within the expectancy condition, a follow up two-sample *t*-test of the contrast expectancy of adult sexual stimuli > expectancy of child sexual stimuli between HCs and PSOs (XAD > XKI, HCs > PSOs) was analyzed. PSOs exhibited significantly reduced BOLD activations, relative to HCs, in dACC, bilateral middle frontal gyrus, bilateral anterior insula, right superior and left inferior parietal lobule and left middle occipital gyrus (Fig. 3, Table 3).

The topographical overlap of dACC clusters during anticipation in Studies 1 and 2 is highlighted in Fig. 4.

3.3.3. Dual preference specificity

In a post-hoc exploratory analysis, beta estimates of the baseline contrasts for both expectancy conditions (XAD > fix; XKI > fix) were calculated separately for PSOs and HCs in dACC (MNI 0, 24, 38). Fig. 5A depicts mean beta estimates of Study 1, whereas Fig. 5B depicts results of Study 2. In contrast to HCs, PSOs did not show significant activations when expecting a picture of an adult (XAD > fix) in either study. DACC effects that were found for adult stimulus in Study 1 have been corroborated in Study 2.

In Study 2, the groups demonstrated an inverse pattern while expecting a picture of a child (expectancy of child sexual stimuli > fixation; Fig. 5B). In sum, PSOs showed significantly greater activation when expecting a child, relative to an adult (expectancy adult picture > fixation vs. expectancy child picture > fixation; t_{12} = −4.32, p = .001), whereas HCs showed significantly greater activation when expecting an adult relative to a child (t_{12} = 5.36, p < .001). A two-sample t-test comparing beta estimates for expectancy of child sexual stimuli > fixation revealed significantly increased dACC activation in PSOs as compared to HCs (t_{12} = 3.17, p = .005). On a trend level, a two-sample t-test for expectancy of adult sexual stimuli > fixation revealed somewhat stronger dACC activation in HCs than in PSOs (t_{24} = −1.92, p = .066).

3.4. Task-related brain activity during picture-viewing

The contrast of erotic adult picture-viewing > erotic child picture-viewing (PAD > PKI, HCs > PSOs) was used to investigate whether presented images of naked adults and children were processed differently across groups. PSOs exhibited significantly reduced BOLD activations, compared with HCs, in bilateral inferior occipital cortex, cerebellum, bilateral middle occipital gyrus, and hippocampus (Table 4,
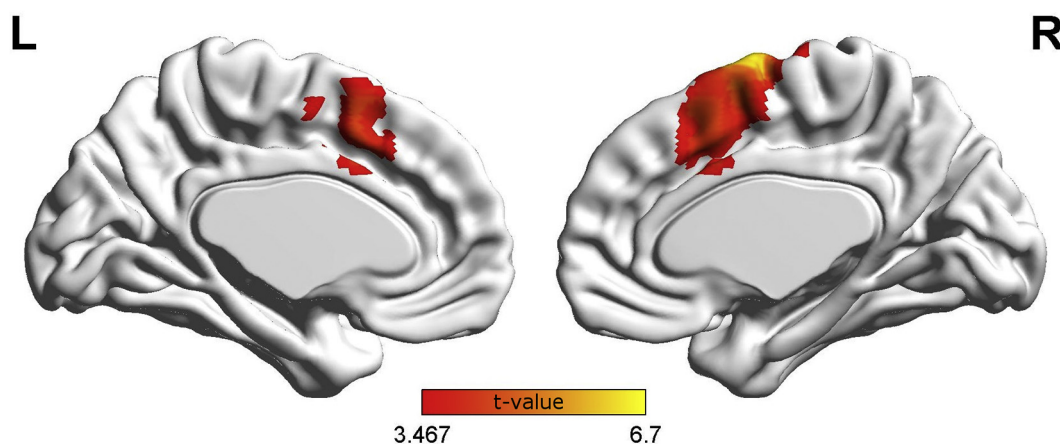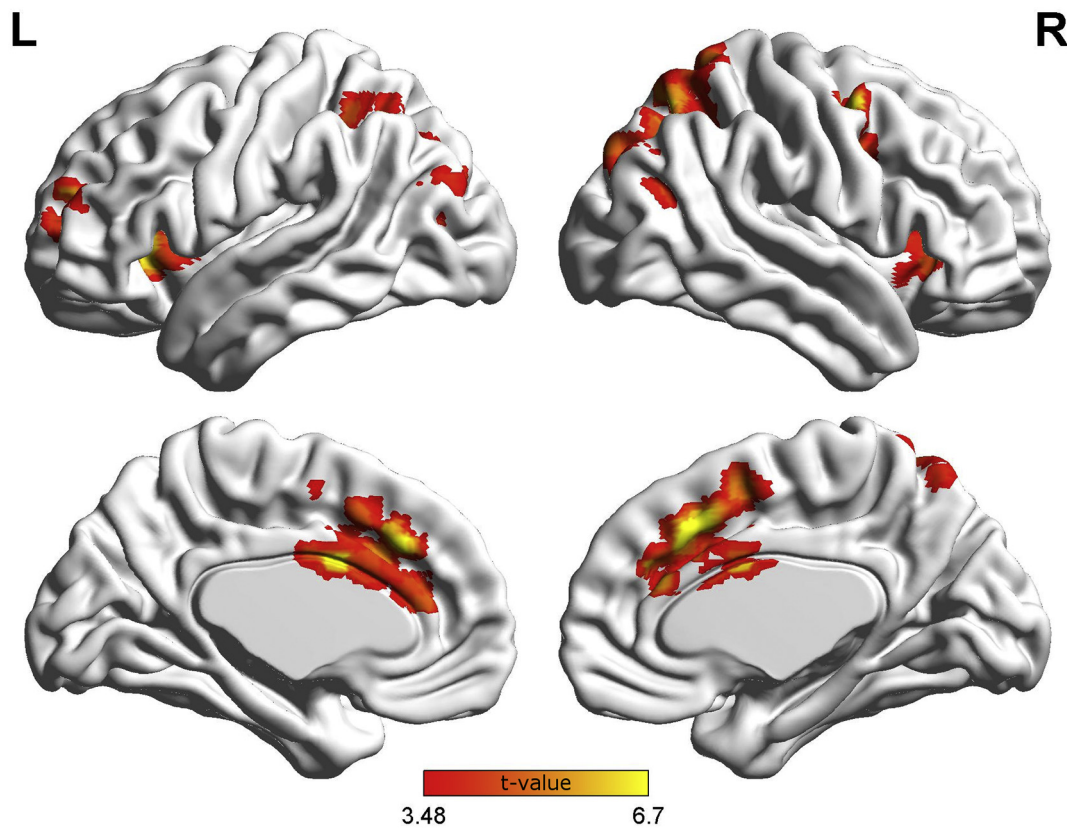

Fig. 2. Brain views show a cluster with significantly greater signal changes (p_{FWE} < 0.05) in healthy control subjects, relative to PSOs, for the contrast of erotic adult expectancy > fixation (XAD > fix, HCs > PSOs) at 1.5 T (Study 1). Illustrated cluster in dACC and SMA, k = 296; cluster threshold was set at k = 90 voxels.

Fig. 3. Brain views show regions with significantly greater signal changes (p_{FWE} < 0.05) in HCs, relative to PSOs, for the contrast of adult expectancy > child expectancy at 7 T (Study 2). Cluster threshold was set at k = 68. Expecting pictures of naked adults leads to decreased dACC signal in PSOs (other clusters are listed in Table 3).

Table 3
Results table for Study 2 depicting significant task effects for expectancy of adult > child picture for HCs > PSOs (XAD > XKI, HCs > PSOs). Age was included as a covariate.

Brain region	Side	MNI coordinates			Cluster extent in voxel	Peak t value	Cluster-level pFWE
		x	y	z			
Dorsal anterior cingulate cortex	L/R	0	24	38	882	7.43	< 0.001*
Middle frontal gyrus	R	40	−2	52	204	6.51	< 0.001
Anterior insula	L	−28	26	4	147	6.44	< 0.001
Superior parietal lobule	R	28	−66	52	456	6.18	< 0.001
Middle frontal gyrus	L	−28	54	20	99	5.68	0.003
Middle occipital gyrus	L	−30	−80	26	134	5.24	< 0.001
Anterior insula	R	34	28	−4	69	4.97	0.025
Inferior parietal lobule	L	−42	−46	50	91	4.72	0.005

Peak voxel coordinates, p < .05 FWE cluster-level corrected *dACC cluster at [0 24 38] was also peak level significant p_{FWE} < 0.05 FWE-corrected (p = .018).

Fig. 6A).

As in the expectancy analyses, we also performed a post-hoc exploratory analysis comparing beta estimates of the global maximum in inferior occipital cortex (MNI -48, −62, −12) during erotic picture-viewing. Analyses did not reveal significant differences between contrasts for adult picture-viewing > fixation vs. child picture-viewing > fixation in PSOs (t_{12} = −1.52, p = .152, Fig. 6B), whereas HCs displayed significantly greater activation when viewing a picture of a naked adult compared to a naked child (t_1 = 10.54, p < .001). PSOs showed greater activation than did controls in the contrast of child picture-viewing > fixation (t_{24} = 2.43, p = .023). There was no significant difference in brain activation for erotic adult picture-viewing > fixation across groups (t_{24} = 0.573, p = .572). There were also no other statistically significant differential activations in the whole brain for the contrast PKI > fix between groups.

Contrast estimates of expectancy and picture-viewing in the two

peak voxel coordinates (dACC and inferior occipital cortex) were plotted in a graph and revealed minimal overlap between groups (Supplementary Fig. 6).

One-way ANOVA and Tukey's Honest Significant Difference test were performed in order to investigate if brain responses in dACC and inferior occipital gyrus during expectancy and picture-viewing showed statistically significant differences between medicated and non-medicated PSOs in study 2. Analyses utilizing all three groups (medicated PSOs, non-medicated PSOs, and HCs) revealed a main effect of group on brain response during the expectancy of a child > fixation contrast (F (2) = 5.456, p = .012). Post-hoc testing was performed using Tukey's Honest Significant Difference test. Brain response was significantly different between non-medicated PSOs and controls for this contrast (p = .015), but medicated and non-medicated PSOs did not differ significantly (p > .05; Supplementary Fig. 7).
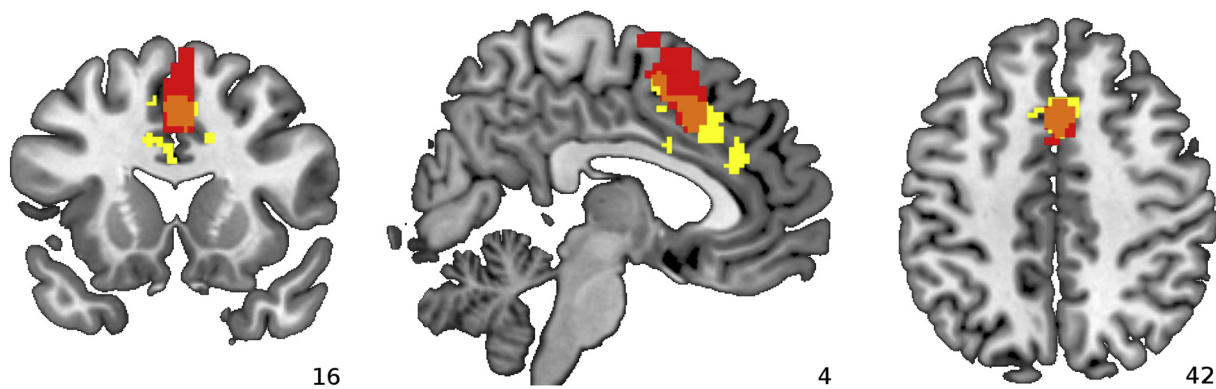
Fig. 4. Brain views show dACC cluster overlap between Studies 1 and 2. Red depicts Study 1 results at 1.5 T for contrasts of expectancy of adult sexual stimuli > fixation in HCs > PSOs (XAD > fix, HCs > PSOs). Yellow depicts Study 2 results at 7 T for contrasts of expectancy of adult sexual stimuli > expectancy of child sexual stimuli in HCs > PSOs (XAD > XKI, HCs > PSOs).
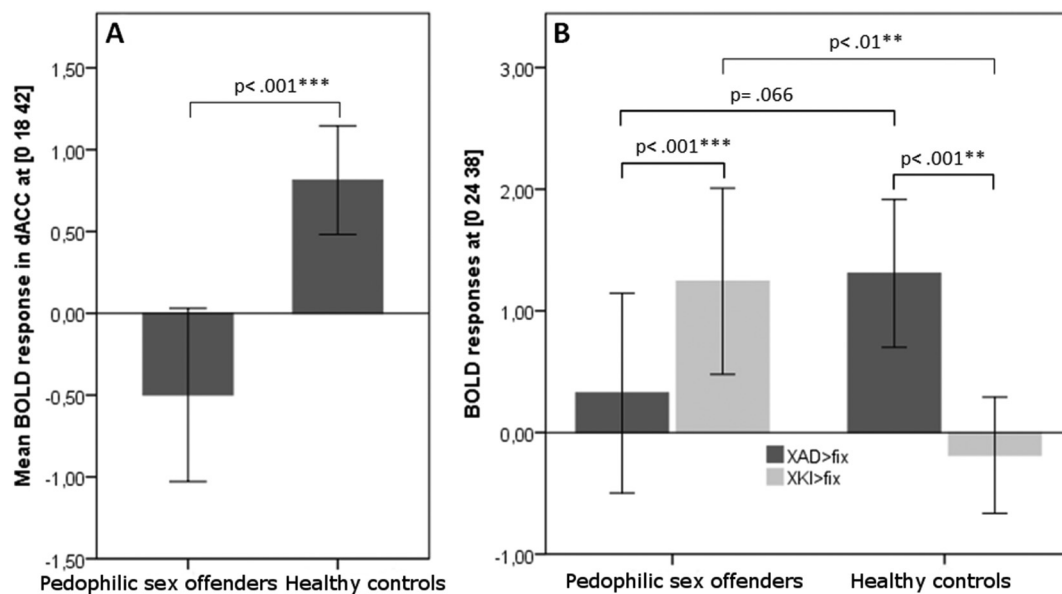
Fig. 5. A) Mean beta estimates for expectancy of adult sexual stimuli > fixation in dACC at MNI [0 18 42] in Study 1 (1.5 T). In this graph, error bars represent standard error.
B) Bar chart depicting preference specificity for erotic adult anticipation and erotic child expectancy conditions in Study 2 (7 T). Beta estimates were derived from baseline contrasts (condition > fixation) in dACC at MNI [0 24 38].

4. Discussion

By including an expectancy period in a sexual information processing fMRI paradigm, we demonstrated differential activation patterns between PSOs and healthy control subjects in dACC, even before explicit sexual stimuli were actually presented. Effects for dACC were found in two separate samples. In addition to reproducing significant group effects during anticipation of erotic adult images (Studies 1 and 2), we were able to detect preference specificity for expectancy of adult versus child stimulus (Study 2). We also found differential activation

Table 4

Results table for Study 2 depicting significant task effects for sexual adult picture-viewing > sexual child picture-viewing for HCs > PSOs (PAD > PKI, HCs > PSOs). Age was included as a covariate.

Brain region	Side	MNI coordinates			Cluster ex-tent in voxel	Peak t value	Cluster-level pFWE
		x	y	z			
Inferior occipital gyrus	L	−48	−62	−12	446	6.70	< 0.001
Cerebellum	R	24	−84	−20	108	5.88	0.001
Middle occipital gyrus	L	−30	−88	22	134	5.56	< 0.001
Middle occipital gyrus	R	32	−82	16	95	5.56	0.003
Middle occipital gyrus	R	40	−74	0	142	5.23	< 0.001
Hippocampus	L	−18	−32	−4	61	4.93	0.041
Inferior temporal gyrus	R	48	−70	−10	101	4.91	0.002

Peak voxel coordinates, p < .05 FWE cluster-level corrected.
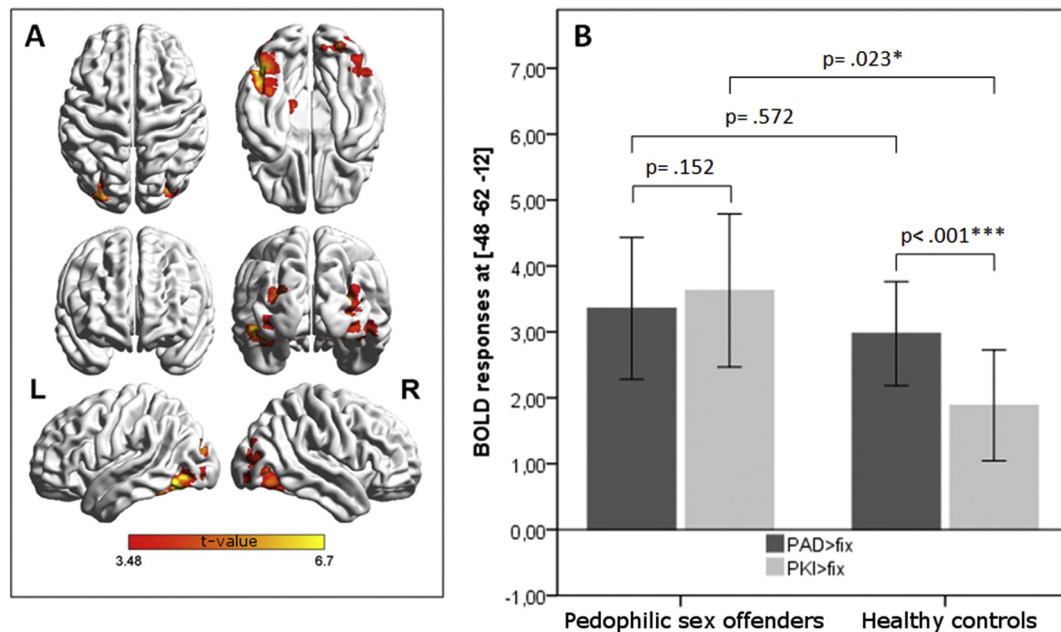
Fig. 6. A) Brain views show regions with significantly larger signal changes (p_{FWE} < 0.05 in HCs, relative to PSOs, for the contrast adult picture-viewing > child picture-viewing (PAD > PKI, HCs > PSOs) at 7 T (Study 2).
B) Bar chart depicting preference specificity for erotic adult picture-viewing > erotic child picture-viewing in Study 2 (7 T). Beta estimates were derived from baseline contrasts (condition > fixation) in inferior occipital gyrus at MNI [−48–62 -12]. In this graph, error bars represent standard error.

while viewing adult versus child picture between the two groups; these differences were evident mainly in visual areas. However, in contrast to anticipation analyses, we did not find a clear disordinal interaction, as indicated by the non-significant post-hoc contrast difference for erotic adult versus child stimuli in PSOs.

PSOs exhibited increased dACC activity while anticipating their preferred sexual stimulus, indicating an abnormal reaction to the expectation of images of children. The present results corroborate previous models of sexual arousal (Stoléru et al., 2012) by demonstrating activation in several regions within the (sexual) salience network during anticipation or viewing of relevant sexual stimuli. However, differences in activation depended on the experimental condition. For example, explicit processing of sexual images was accompanied by activation of a middle and inferior occipital cluster. Moreover, following the model by Stoléru et al. (2012), it is a consideration that during expectancy increased activation of the anterior insula and dACC might reflect an increment of hedonic quality (insula) in combination with potential cognitive and/or behavioral consequences (dACC), induced by the imagination of maximal preferred sexual content. Peaks of the dACC cluster were also located in the SMA, which supports previous evidence for sexual orientation-specific motor preparation processes in human sexual behavior (Schecklmann et al., 2015). Moreover, Poeppl et al. (2016) showed that dACC activation is an important neural correlate of sexual desire in both sexes.

The dACC is involved in two main functions which can be considered opposite: 1) salience detection and desire on the one hand and 2) behavioral inhibition on the other hand. As a brain area involved in anticipation (Bermpohl et al., 2006; Metzger et al., 2010; Li et al., 2017) and one of the core structures of the salience network (Bush et al., 2000; Seeley et al., 2007), the dACC seems essential for sexual arousal, as it builds a bridge between salience signal input (salience detection) and performance output (cognitive control). Li et al. (2017) postulated that the dACC's role in the salience network may be as a causal outflow hub involved in receiving and processing internal and external signal inputs, detecting salient events, and initiating the corresponding cognitive controls, which in turn regulates homeostatic state and physical behavior. As such, the dACC is essential for the control of goal-directed

behavior. Accordingly, and with particular emphasis on the dACC's key role in reward monitoring and salience processing (Heilbronner and Hayden, 2016), expectancy of preferred sexual input may be associated with potential cognitive and behavioral consequences that facilitate activation in this area. Moreover, this region is essential for coupling information about reinforcers with motor centers essential for affect expression and for execution or inhibition of goal-directed behavior (Agam et al., 2010). Given the dACC's role within the salience network, abnormal dACC activity in pedophilic sex offenders might reflect altered network connectivity, which, in turn, could be the consequence of established structural brain abnormalities in pedophilic offenders (Poeppl et al., 2015).

On the other hand, the observed expectancy-related activation patterns in the dACC for preferred sexual stimuli in PSO cohorts confirms a well-known phenomenon seen in physiological condition in normosexuals. Therefore, our results can also be interpreted as a reflection of altered preference. Importantly, our results also suggest that differences during expectancy have much more potential to differentiate between groups than do the effects observed during picture viewing. A reason for this might be that preparatory activation is less susceptible to attentional manipulations and, therefore, is more sensitive to the context of sexual preference detection, as compared to more explicit conditions. Although we found significant group effects during picture-viewing, it is remarkable that effects during expectancy were much stronger and more specific (Tables 3 and 4; Figs. 5B and 6B). Accordingly, preference diagnostics and other potential clinical assessments may benefit from taking into account stimulus anticipation parameters, rather than exclusively focusing on viewing conditions, since the latter revealed non-specific activations in the present study.

With regard to preventive therapeutic approaches, research suggests that cognitive-behavioral techniques, including reorganization of cognitive distortions and empathy training to teach the suppression of sexual arousal to children, may be effective for people with pedophilic disorder (Geer et al., 2000). An fMRI study by Kärgel et al. (2017) on response inhibition showed that non-offending pedophilic participants exhibited superior inhibitory control than did pedophilic offenders or healthy controls, as reflected by a significantly decreased rate of

commission errors. Moreover, Eastvold et al. (2011) showed that pedophilic offenders exhibited impaired performance on behavioral inhibition measures. Massau et al. (2017) supported these observations using the Cambridge Automated Neuropsychological Test Battery (CANTAB) in men grouped according to presence vs. absence of 1) history of sexual offending against children and 2) diagnosed pedophilic disorder. Both groups of child sex offenders exhibited inferior response inhibition capability, relative to both groups of men without any history of child sexual offending, regardless of pedophilic disorder status. These results suggest that neurocognitive dysfunction is related to offense status, rather than pedophilic preference. In line with these observations, research by Schiffer and Vonlaufen (2011) found specific inhibitory deficits in pedophilic sex offenders as compared to nonsexual offenders and non-offender controls. Neurocognitive deficits in PSOs, as indicated by worse performance than controls on measures of behavioral inhibition and information processing, were further established by (Suchy et al., 2014). Clinical measures of risk of re-offending were significantly associated with decreased local gray matter volume in the anterior cingulate cortex, suggesting an impaired functioning of this brain region especially with regard to its critical role in cognitive inhibitory control processes (Schiffer et al., 2017). Recent research has also pointed towards disinhibitory processes in dACC, reflected by decreased levels of the inhibitory neurotransmitter GABA in pedophilic sex offenders, which correlated with lower subjective self-control ratings and higher impulsivity scores (Ristow et al., 2018). In conclusion, these findings emphasize the crucial role of inhibitory control capacity in sexual offending, suggesting that neurocognitive processes play an important role in reducing or controlling sexual urges.

4.1. Limitations

Studies with PSO are often performed with small sample sizes due to difficult study settings and challenging patient recruitment, consequently limiting the studies' statistical power by increasing the margin of error and overestimating effect sizes (Button et al., 2013). This might explain why consistency across studies with PSOs is rather small (Tenbergen et al., 2015; Mohnke et al., 2014). Although multi-site studies are a promising means to overcome these issues, they remain time-consuming given federal restrictions, limited access to patients in suitable institutions, and long-term stays in forensic institutions. Besides multi-side approaches, another option is to perform data acquisition over long period. Considering the fact that stability of scanner situations is limited, we decided to perform two studies in order to reproduce small sample fMRI findings.

One important consideration in the interpretation of these findings is that in Study 2, the experimental paradigm was changed to allow for analysis of differences between erotic child and adult stimuli. The introduction of the child stimuli and the reduction of repeats per category should be considered an effective but consequential adjustment of the original design. For example, dACC activation in the expectancy of an adult picture > fixation contrast, which was significant in Study 1, was only marginally significant ($p = 0.066$) in Study 2 (Fig. 5B). Therefore, in the interest of precision given our lower levels of confidence in these findings, "reproduction" may be a more accurate description of the results than "replication."

Keeping in mind that subjects were instructed to actively expect the stimulus depending on the cue, the performed tasks are not able to investigate pre-attentive or implicit processes of sexual processing. Aim of this design was rather to investigate neural correlates of explicit attentional preparatory processing.

Moreover, we are not able to link our findings to behavioral effects of stimuli. For example, acquisition of ratings for sexual arousal induced by the expectancy of each type of picture and by the presentation of each type of pictures, in both groups, would have been useful to interpret results.

A further limitation is that in Study 2, seven PSOs received an

androgen deprivation therapy. Mitigating this potential concern, PSOs with and without medication did not differ significantly in brain response (Supplementary Fig. 7). Additionally, the dACC effects in Study 2 paralleled findings from Study 1, in which no participants were taking or had ever taken anti-androgenous medication. Nonetheless, medication effects in Study 2 cannot be fully ruled out.

A final limitation is that only PSOs and healthy (non-pedophilic) adults were included in our study samples. Hence, we cannot distinguish whether the observed abnormalities are related to sexual preference, child sexual offending, or both. Future studies should include pedophilic non-offenders to address this question.

Besides the dACC which is of specific interest in this paper, there are also other brain regions that were reported in other contrasts of our results section (Table 2). Further exploration of these regions which have been reported in previous literature (Mohnke et al., 2014) may also contribute to understanding the underlying neurobiological mechanisms of this disorder.

5. Conclusion

The current study demonstrated differential dACC activation in pedophilic sex offenders, compared with healthy controls, for the expectancy of explicit sexual images of both children and adults. During picture-viewing, only the processing of material depicting children differed from that of healthy controls. These results emphasize the importance of the dACC for processes involving salience and sexual arousal, and further suggest that anticipatory activation is more relevant than picture-viewing activation for the distinction of pedophilic sex offenders versus non-pedophilic non-offenders.

Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be perceived as a real or apparent conflict of interest in the context of this publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101863.

References

Agam, Y., Joseph, R.M., Barton, J.J.S., Manoach, D.S., 2010. Reduced cognitive control of response inhibition by the anterior cingulate cortex in autism spectrum disorders. NeuroImage 52 (1), 336–347.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders. American Psychiatric Publishing, Washington, DC.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Washington, DC.

Bennett, C.M., Miller, M.B., 2010. How reliable are the results from functional magnetic resonance imaging? Ann. N. Y. Acad. Sci. 1191, 133–155.

Bermpohl, F., Pascual-Leone, A., Amedi, A., Merabet, L.B., Fregni, F., Gaab, N., et al., 2006. Attentional modulation of emotional stimulus processing: an fMRI study using emotional expectancy. Hum. Brain Mapp. 27 (8), 662–677.

Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn. Sci. 14 (6), 277–290.

Bush, Luu, Posner, 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4 (6), 215–222.

Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., et al., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14 (5), 365–376.

CIPS, 1996. Internationale Skalen für Psychiatrie (4., überarbeitete und erweiterte Auflage). Beltz Test GmbH, Göttingen.

Cohen, M.S., 2008. Handedness Inventory on-Line Form. www.brainmapping.org.

Düzel, E., Schiltz, K., Solbach, T., Peschel, T., Baldeweg, T., Kaufmann, J., et al., 2006. Hippocampal atrophy in temporal lobe epilepsy is correlated with limbic systems atrophy. J. Neurol. 253 (3), 294–300.

Eastvold, A., Suchy, Y., Strassberg, D., 2011. Executive function profiles of pedophilic and nonpedophilic child molesters. J. Int. Neuropsychol. Soc. JINS 17 (2), 295–307.

Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. U. S. A. 113 (28), 7900–7905.

Geer, J.H., Estupinan, L.A., Manguno-Mire, G.M., 2000. Empathy, social skills, and other relevant cognitive processes in rapists and child molesters. Aggress. Violent Behav. 5 (1), 99–126.

Gillath, O., Collins, T., 2016. Unconscious desire: the affective and motivational aspects of subliminal sexual priming. Arch. Sex. Behav. 45 (1), 5–20.

Habermeyer, B., Esposito, F., Händel, N., Lemoine, P., Klarhöfer, M., Mager, R., et al., 2013. Immediate processing of erotic stimuli in paedophilia and controls: a case control study. BMC Psychiatry 13, 88.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Heilbronner, S.R., Hayden, B.Y., 2016. Dorsal anterior cingulate cortex: a bottom-up view. Annu. Rev. Neurosci. 39, 149–170.

Horn, W., 1983. Leistungsprüfungssystem (LPS): Handanweisung. Hogrefe, Göttingen.

Janssen, E., Everaerd, W., Spiering, M., Janssen, J., 2000. Automatic processes and the appraisal of sexual stimuli: toward an information processing model of sexual arousal. J. Sex Res. 37 (1), 8–23.

Kärgel, C., Massau, C., Weiß, S., Walter, M., Borchardt, V., Krueger, T.H.C., et al., 2017. Evidence for superior neurobiological and behavioral inhibitory control abilities in non-offending as compared to offending pedophiles. Hum. Brain Mapp. 38 (2), 1092–1104.

Kühn, S., Gallinat, J., 2011. A quantitative meta-analysis on cue-induced male sexual arousal. J. Sex. Med. 8 (8), 2269–2275.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. International Affective Picture System (IAPS). NIMH Center for the Study of Emotion, Gainesville, Florida.

Li, S., Demenescu, L.R., Sweeney-Reed, C.M., Krause, A.L., Metzger, C.D., Walter, M., 2017. Novelty seeking and reward dependence-related large-scale brain networks functional connectivity variation during salience expectancy. Hum. Brain Mapp. 38 (8), 4064–4077.

Executive Functioning in Pedophilia and Child Sexual Offending. J Int Neuropsychol Soc. 23 (6), 460–470. https://doi.org/10.1017/S1355617717000315. Epub 2017 May 17. https://www.ncbi.nlm.nih.gov/pubmed/28511726.

Metzger, C.D., Eckert, U., Steiner, J., Sartorius, A., Buchmann, J.E., Stadler, J., et al., 2010. High field FMRI reveals thalamocortical integration of segregated cognitive and emotional processing in mediodorsal and intralaminar thalamic nuclei. Front. Neuroanat. 4, 138.

Metzger, C.D., van der Werf, Y.D., Walter, M., 2013. Functional mapping of thalamic nuclei and their integration into cortico-striatal-thalamo-cortical loops via ultra-high resolution imaging-from animal anatomy to in vivo imaging in humans. Front. Neurosci. 7, 24.

Mohnke, S., Müller, S., Amelung, T., Krüger, T.H.C., Ponseti, J., Schiffer, B., et al., 2014. Brain alterations in paedophilia: a critical review. Prog. Neurobiol. 122, 1–23.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.

Poeppl, T.B., Eickhoff, S.B., Fox, P.T., Laird, A.R., Rupprecht, R., Langguth, B., et al., 2015. Connectivity and functional profiling of abnormal brain structures in pedophilia. Hum. Brain Mapp. 36 (6), 2374–2386.

Poeppl, T.B., Langguth, B., Rupprecht, R., Safron, A., Bzdok, D., Laird, A.R., et al., 2016. The neural basis of sex differences in sexual behavior: a quantitative meta-analysis. Front. Neuroendocrinol. 43, 28–43.

Ponseti, J., Granert, O., Jansen, O., Wolff, S., Beier, K., Neutze, J., et al., 2012. Assessment

of pedophilia using hemodynamic brain response to sexual stimuli. Arch. Gen. Psychiatry 69 (2), 187–194.

Redouté, J., Stoléru, S., Grégoire, M.C., Costes, N., Cinotti, L., Lavenne, F., et al., 2000. Brain processing of visual sexual stimuli in human males. Hum. Brain Mapp. 11 (3), 162–177.

Ristow, I., Li, M., Colic, L., Marr, V., Födisch, C., Düring, F. von, et al., 2018. Pedophilic sex offenders are characterised by reduced GABA concentration in dorsal anterior cingulate cortex. NeuroImage Clin. 18, 335–341.

Sakai, K., Passingham, R.E., 2003. Prefrontal interactions reflect future task operations. Nat. Neurosci. 6 (1), 75–81.

Schecklmann, M., Engelhardt, K., Konzok, J., Rupprecht, R., Greenlee, M.W., Mokros, A., et al., 2015. Sexual motivation is reflected by stimulus-dependent motor cortex excitability. Soc. Cogn. Affect. Neurosci. 10 (8), 1061–1065.

Schiffer, B., Vonlaufen, C., 2011. Executive dysfunctions in pedophilic and nonpedophilic child molesters. J. Sex. Med. 8 (7), 1975–1984.

Schiffer, B., Krueger, T., Paul, T., de, Greiff A., Forsting, M., Leygraf, N., et al., 2008a. Brain response to visual sexual stimuli in homosexual pedophiles. J. Psychiatry. Neurosci. JPN 33 (1), 23–33.

Schiffer, B., Paul, T., Gizewski, E., Forsting, M., Leygraf, N., Schedlowski, M., et al., 2008b. Functional brain correlates of heterosexual paedophilia. NeuroImage 41 (1), 80–91.

Schiffer, B., Amelung, T., Pohl, A., Kaergel, C., Tenbergen, G., Gerwinn, H., et al., 2017. Gray matter anomalies in pedophiles with and without a history of child sexual offending. Transl. Psychiatry 7 (5), e1129.

Schiltz, K., Szentkuti, A., Guderian, S., Kaufmann, J., Münte, T.F., Heinze, H.J., et al., 2006. Relationship between hippocampal structure and memory function in elderly humans. J. Cogn. Neurosci. 18 (6), 990–1003.

Schmidt, K., Metzler, P., 1992. Wortschatztest (WST). Beltz Test, Weinheim.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., et al., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27 (9), 2349–2356.

Speck, O., Stadler, J., Zaitsev, M., 2008. High resolution single-shot EPI at 7T. Magma (New York, N.Y.) 21 (1–2), 73–86.

Stoléru, S., Grégoire, M.C., Gérard, D., Decety, J., Lafarge, E., Cinotti, L., et al., 1999. Neuroanatomical correlates of visually evoked sexual arousal in human males. Arch. Sex. Behav. 28 (1), 1–21.

Stoléru, S., Fonteille, V., Cornélis, C., Joyal, C., Moulier, V., 2012. Functional neuroimaging studies of sexual arousal and orgasm in healthy men and women: a review and meta-analysis. Neurosci. Biobehav. Rev. 36 (6), 1481–1509.

Suchy, Y., Eastvold, A.D., Strassberg, D.S., Franchow, E.I., 2014. Understanding processing speed weaknesses among pedophilic child molesters: response style vs. neuropathology. J. Abnorm. Psychol. 123 (1), 273–285.

Szentkuti, A., Guderian, S., Schiltz, K., Kaufmann, J., Münte, T.F., Heinze, H.-J., et al., 2004. Quantitative MR analyses of the hippocampus: unspecific metabolic changes in aging. J. Neurol. 251 (11), 1345–1353.

Tenbergen, G., Wittfoth, M., Frieling, H., Ponseti, J., Walter, M., Walter, H., et al., 2015. The neurobiology and psychology of pedophilia: recent advances and challenges. Front. Hum. Neurosci. 9, 344.

Unterhorst, K., Gerwinn, H., Pohl, A., Kärgel, C., Massau, C., Ristow, I., et al., 2018. An exploratory study on the central nervous correlates of sexual excitation and sexual inhibition. J. Sex Res. 1–12.

van Lankveld, J., Odekerken, I., Kok-Verhoeven, L., van Hooren, S., de, Vries P., van den Hout, A., et al., 2015. Implicit and explicit associations with erotic stimuli in sexually functional and dysfunctional men. J. Sex. Med. 12 (8), 1791–1804.

von Aster, M., Neubauer, A.C., Horn, R., 2006. Wechsler Intelligenztest für Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler. Harcourt Test Services, Frankfurt/Main.

Walter, M., Witzel, J., Wiebking, C., Gubka, U., Rotte, M., Schiltz, K., et al., 2007. Pedophilia is linked to reduced activation in hypothalamus and lateral prefrontal cortex during visual erotic stimulation. Biol. Psychiatry 62 (6), 698–701.

Walter, M., Bermpohl, F., Mouras, H., Schiltz, K., Tempelmann, C., Rotte, M., et al., 2008. Distinguishing specific sexual and general emotional effects in fMRI-subcortical and cortical arousal during erotic picture viewing. NeuroImage 40 (4), 1482–1494.

Wernicke, M., Hofter, C., Jordan, K., Fromberger, P., Dechent, P., Müller, J.L., 2017. Neural correlates of subliminally presented visual sexual stimuli. Conscious. Cogn. 49, 35–52.

Wittchen HU, Zaudig M, Fydrich T (1997): Strukturiertes Klinisches Interview für DSM-IV. Achse I und II. Hogrefe: Göttingen.

Xia, M., Wang, J., He, Y., 2013. BrainNet viewer: a network visualization tool for human brain connectomics. PLoS ONE 8 (7), e68910.