The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: www.tandfonline.com/journals/iwbp20

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To cite this article: Carolina Fiederer, Tara Chand, Louise Martens, Inka Ristow, Verena Durner, Birgit Abler, Martin Walter & Heiko Graf (2025) Resting-state functional connectivity within the reward system mediates subcortical integration during erotic stimulus processing, The World Journal of Biological Psychiatry, 26:6, 244-253, DOI: 10.1080/15622975.2025.2509988

To link to this article: https://doi.org/10.1080/15622975.2025.2509988

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
2025, VOL. 26, NO. 6, 244–253
https://doi.org/10.1080/15622975.2025.2509988

ORIGINAL INVESTIGATION

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Resting-state functional connectivity within the reward system mediates subcortical integration during erotic stimulus processing

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ABSTRACT

Objectives: Erotic stimuli lead to activations in various brain regions, including the reward system. Several neuroimaging studies have investigated neurofunctional activations during visual erotic stimulation. Little research has investigated whether these functional activations are characterised by an intrinsic network architecture in the resting-state.

Methods: We therefore examined 37 healthy male heterosexual subjects by combining resting-state and task-related fMRI. In task-related fMRI, we used an established video clip task (erotic and non-erotic video clips). Vectors comprising different neuronal activations during the processing of visual erotic stimuli were then correlated with the strength of resting-state functional connectivity between two core regions of the human reward system (NAcc and midbrain).

Results: We observed an increase in neurofunctional activations in cortical and subcortical regions previously described in task-based fMRI studies during visual erotic stimulation. Increased rs-FC between midbrain and NAcc was associated with higher differential neuronal responsiveness in subcortical regions, particularly in the hypothalamus, thalamus and periaqueductal grey.

Conclusion: Our results support the role of the mesolimbic reward pathway in the processing of erotic stimuli. In particular they show that a higher rs-FC between midbrain and NAcc facilitates the simultaneous activation of subcortical brain regions that are relevant for the integration of processes in sexual behaviour.

ARTICLE HISTORY
Received 5 March 2025
Revised 17 May 2025
Accepted 18 May 2025

KEYWORDS
Erotic stimulus processing; fMRI; resting-state; reward; salience

Introduction

Sexual arousal is crucial for survival of the human species (Hamilton 1964) and is mediated by a complex integration of endocrine, vascular, peripheral and central nervous mechanisms. Functional magnetic resonance imaging (fMRI) studies highlighted the neural processing of sexual stimulation and behaviour (Redouté et al. 2000a; Georgiadis et al. 2012; Stoléru et al. 2012) and the pivotal role of the brain as 'master organ' of sexual function (McKenna 1999).

Various neuroimaging studies demonstrated enhanced neurofunctional activation within a wide set of brain regions involved in the processing of sexual stimuli. An increase of neural responses in cortical (e.g. the anterior cingulate cortex (ACC), the insula, the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC) as well as subcortical regions (e.g. the nucleus accumbens (NAcc), the putamen and the hypo-/thalamus) have been described at different stages of male sexual arousal (Stoléru et al. 1999; Redouté et al. 2000b). A meta-analytic approach linked psychological with physiological and neurofunctional processes and conceptualised a so-called neurophenomenological model of sexual arousal comprising an emotional, cognitive, autonomic and motivational component (Stoléru et al. 2012).

Considering sexual stimuli as primary reinforcers (Georgiadis and Kringelbach 2012), sexual response can also be characterised according to other reward related concepts in terms of motivation-consummation-satiety or wanting-liking-inhibition. Thus, numerous studies demonstrated enhanced neurofunctional activity within the human reward system during visual sexual stimulation (Hamann et al. 2004; Stark et al. 2005; Walter, Bermpohl, et al. 2008; Georgiadis et al. 2012). The mesolimbic reward system origins from

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15622975.2025.2509988.

dopaminergic neurons located in the ventral tegmental area (VTA) that project to the NAcc (Haber and Knutson 2010). The relevance of these regions for reinforced learning and signalling motivational salience of (sexual) stimuli have been widely described (Schultz et al. 1997; Watabe-Uchida et al. 2012; Eshel et al. 2015).

In the context of sexual behaviour, most of the evidence regarding neural responses within the reward system stems from investigations conducted with task-based fMRI under visual sexual or genital stimulation. Though, there is evidence that the brain`s functional network during task performance is shaped primarily by an intrinsic network architecture that is also present during rest and evoked by task-general and task-specific network changes (Cole et al. 2014). However, only a few studies investigated functional connectivity (FC) under rest in the context of sexual arousal and focused primarily on sexual preference (Hu et al. 2013), patients with psychogenic erectile dysfunction (Wang et al. 2017), premature ejaculation (Chen et al. 2020) or compulsive sexual behaviour (Schmidt et al. 2017).

By combining resting-state (rs) and task-based fMRI within one study design, we investigated neural FC under rest and its relationship to neural responsiveness during visual erotic stimulation in healthy subjects. Considering the pivotal role of VTA dopaminergic neurons projecting to the NAcc in sexual motivation and arousal (Pfaus and Phillips 1991; Fiorino et al. 1997; Kippin et al. 2004; Brom et al. 2014), we focused on rs-FC between these regions as potential predictor for differential task-based neural activities. According to the positive relationship between reward sensitivity and rs-FC between the VTA and regions of the human reward system (Adrián-Ventura et al. 2019), we hypothesised that higher VTA-NAcc rs-FC is associated with enhanced neural responsiveness in brain regions relevant for sexual arousal.

Methods

Participants

We investigated 42 healthy, Caucasian heterosexual male subjects within a broader research project with different experiments of which findings are reported elsewhere (Abler et al. 2011; Graf et al. 2013; Metzger et al. 2013; Viviani 2013; Graf et al. 2014, 2016, 2017, 2018; Metzger et al. 2015). This research projects comprised a randomised, double-blind pharmacological intervention with different antidepressant agents. To exclude pharmacological alterations on task- and resting-state-fMRI activations, it is of note that we used only data acquired in the placebo condition in this study. Five subjects had to be excluded due to technical MRI-artefacts during resting-state data acquisition ($n=4$), and due to glial lesions ($n=1$), resulting in a total number of 37 subjects in the mean age of 24.7 years (*SD* 3.07, range 20–34) in the final analyses. Prior to the inclusion of the study, participants received a full medical examination including the assessment of medical history, a physical examination, laboratory blood tests and an electrocardiogram to exclude renal, hepatic, and cardiac pathologies. Further exclusion criteria were any current or past psychiatric or neurological disorders. All participants were screened by a Structured Clinical Interview for DSM-IV (Hörz et al. 2012; Doering et al. 2013). In addition, we excluded participants with excessive consumption of caffeine, alcohol (> 14 standard units per week), and consumption of psychotropic drugs. To exclude participants with sexual dysfunction, the Massachusetts General Hospital Sexual Functioning Questionnaire (Labbate and Lare 2001) was administered prior to recruitment. The study was approved by the local ethical committee of Ulm University and all participants gave written informed consent confirming to the Declaration of Helsinki.

fMRI procedures and stimuli

Resting-state fMRI data were acquired within an eight-minute eyes-closed resting-state scan. During task-based fMRI, we used an established erotic video paradigm during task-based fMRI as reported in detail elsewhere (Abler et al. 2011; Graf et al. 2014). Briefly, erotic and neutral video clips were used for visual stimulation within a standard block design. Erotic video clips depicted sexual interaction (petting, oral sex, vaginal intercourse) between one man and one or two women. Non-erotic clips showed men and women in emotionally neutral interactions. Both, erotic and non-erotic video clips were matched for colour, the number and gender of subjects interacting, length of interaction, and whether the depicted subjects were clothed or naked. We presented 9 video clips of each of the two conditions for 20 s each, separated by a 20 s fixation period, resulting in a total length of the paradigm of 12 min. Video clips were presented in a pseudo-randomised order and counterbalanced across subjects.

MRI data acquisition and analysis

fMRI acquisition

MRI data were acquired using a 3 T Siemens MAGNETOM Allegra (Siemens, Erlangen, Germany) scanner, equipped with a standard head coil. Resting-state fMRI and

task-based fMRI were acquired using the same gradient echo EPI protocol with repetition time (TR) of 1.5 s, an echo time of 35 ms, and a flip angle of 90°. A total of 23 transversal slices were acquired with a matrix size of 64 × 64 and a field view (FOV) of 192 mm. Slice thickness was 3 mm with 0.75 mm gap, resulting in a voxel size of 3 × 3 × 3.75 mm. Slices were planned with an angle of −15° relative to the anterior commissure-posterior commissure line to reduce susceptibility artefacts in subcortical regions of interest (amygdala, midbrain and striatum). For the erotic video task, a total of 487 volumes were obtained. The first seven volumes were discarded to account for equilibration effects. During resting-state-fMRI, 320 volumes were acquired resulting in a total duration of the scan of 8 min. Participants were instructed to keep their eyes closed. The first 10 volumes were discarded to account for equilibration effects.

Structural scan

After resting-state and fMRI measurements, high resolution T1-weighted structural images were obtained by administering a magnetisation prepared rapid acquisition gradient echo sequence (MPRAGE, TR = 2300 ms, TE = 3.93 ms, TI = 1100 ms, flip angle = 12°, FOV = 256 mm, matrix size = 256 × 256). To allow for selective denoising of rs-fMRI voxels with a high probability of containing grey matter and the removal of white matter signal, structural scans were segmented using the voxel-based morphometry (VBM) implemented in the CAT12 toolbox (Ashburner and Friston 2005).

Resting-state fMRI ROI definition

According to our hypothesis, we defined the NAcc and midbrain as region of interests (ROIs). The bilateral NAcc was derived from the Harvard-Oxford probabilistic anatomical brain atlas (Desikan et al. 2006). The midbrain ROI comprising the bilateral substantia nigra (SN) pars compacta, the bilateral SN pars reticularis and the bilateral VTA, was obtained from the Reinforcement Learning Atlas (Pauli et al. 2018; Teckentrup et al. 2019). These ROIs were resliced to the space of the preprocessed video task BOLD images using Statistical Parametric Mapping (SPM12, Wellcome Department, London, UK), resulting in ROIs with a voxel size of 3 mm isotropic.

rs-fMRI preprocessing

Preprocessing of the rs-fMRI data was carried out using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). Images were realigned and unwarped (motion correction) and slice-time corrected. Both functional and structural images were then segmented using default tissue probability maps and normalised to MNI space. Images were smoothed using an 8x8x8 mm isotropic FWHM Gaussian smoothing kernel. Images were subsequently resampled to 3x3x3 mm MNI (Montreal Neurological Institute, MNI) space using SPM12. Further denoising was performed using custom MATLAB code. Time series from voxels with a grey matter probability of 0.35 or higher were z-scored, despiked, and subjected to quadratic detrending, after which six motion parameters (estimated during the realignment step) and mean white matter signal were regressed out. Bandpass-filtering was not performed, as most high-frequency fluctuations related to physiological noise were likely removed during residualizing for the mean white matter signal (Kahnt et al. 2012) and low-frequency drifts were removed in the detrending step (Tanabe et al. 2002).

FC calculation

Denoised images were loaded in MATLAB. For each participant, we calculated rs-FC between two ROIs as the Pearson correlation between the mean time series of the seed and target ROIs. The resulting correlation vectors were each *z*-transformed. The two ROIs depicted in Figure 1 were considered.

Task-based fMRI analysis

Image pre-processing and statistical analyses were carried out using SPM12. Preprocessing steps included slice-time correction, realignment with estimation and reslicing, segmentation, and normalisation into a 3 × 3 × 3 mm standard MNI template. Subsequent smoothing was performed with an 8 mm FWHM isotropic Gaussian smoothing kernel.

First-level analyses were performed for each subject. We defined regressors for each of the conditions (erotic and non-erotic). To this end, we modelled video clips as 20 s blocks and convolved these with the SPM default hemodynamic response function. We included the six residual motion regressors estimated during the realignment step as covariates of no interest in the individual models. The resulting contrast images (erotic > non-erotic) were then included in second-level group analyses. For this, the map was corrected with a threshold of $p < 0.05$ (family-wise error rate, FWE) based on cluster extent ($k = 313$) with a conservative initial threshold for cluster definition of $p < 0.001$ (uncorrected).

We performed separate analyses for the FC vectors in the resting condition. In this model, the condition (erotic/non-erotic) was used as the first factor. The respective resting-state FC vectors were included as

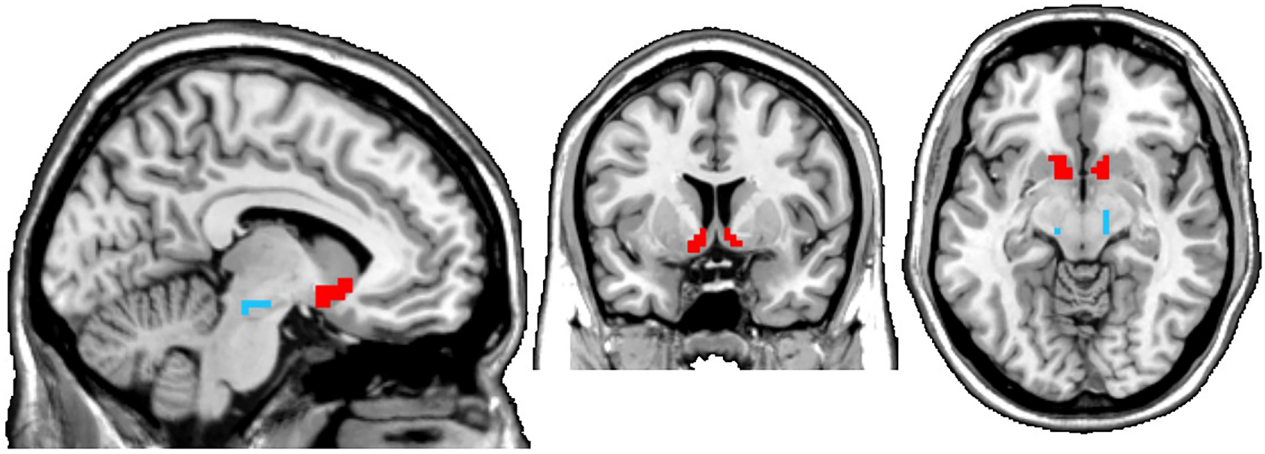

Figure 1. Regions of interests (ROIs): The bilateral nucleuc accumbens ROI is depicted in red. The midbrain ROI (blue) comprises the bilateral substantia nigra (SN) pars compacta, the bilateral SN pars reticularis and the bilateral VTA.

covariates in the t-test to test for significant interaction effects of resting-state FC fingerprints and the contrast of erotic vs. non-erotic stimuli.

To specify the exact clusters, we performed a small volume correction. For this, we created a mask from task activation with FWE cluster-corrected thresholds.

Results

Neural activation during visual erotic versus non-erotic stimulation

Contrasting erotic minus non-erotic video stimulation during fMRI, we observed significant main effects in several brain regions that have been previously described in the context of sexual arousal. In detail, we observed significantly increased neurofunctional activation in the occipitotemporal cortex (48, −58, −10), in the lateral occipital cortex (36, −76, 5 and −45, −67, −1), in the middle occipital cortex (−36, −85, 11 and −36, −85, 11), in the prefrontal cortex (−66, −25, 32), in the inferior frontal lobe (48, 8, 20), in the midbrain (−3, −25, −13), in the periaqueductal grey (0, −31, −19), in the inferior parietal lobe (51, −22, 32 and −51, −28, 26) and in the cerebellum (24, −67, −46 and −24, −61, −28) (see Supplementary Material Figure S1 and Table S1).

Correlation analyses of rs-FC between midbrain and NAcc and neurofunctional activations during task-based fMRI

To analyse the temporal correlation of rs-FC between the midbrain and NAcc with differential (erotic minus non-erotic) neurofunctional activations during task-based fMRI, a one-sample t-test was performed with the response vector from the erotic/non-erotic analysis and rs-FC of the midbrain and NAcc ($p < 0.001$, FWE corrected by cluster level). We observed a significant positive correlation between the strengths of rs-FC between the midbrain and the NAcc with differential neurofunctional activations within the hypothalamus, the midbrain, the periaqueductal grey and the thalamus (see Figures 2, 3 and Table 1). No significant negative associations were observed.

Discussion

We examined a sample of healthy male heterosexual subjects using combined resting-state and task-related fMRI to determine whether functional connectivity (FC) between core regions of the human reward system, namely the VTA and NAcc, under rest is associated with neural responsiveness of brain regions relevant to the processing of sexual stimulation. We observed that increased rs-FC between the midbrain/VTA and NAcc was associated with higher differential neuronal responsiveness in subcortical regions such as the hypothalamus, thalamus, midbrain, and periaqueductal grey during erotic versus non-erotic visual stimulation.

For task-based fMRI, we applied an established video paradigm that has previously been shown to reliably elicit neural responses in brain regions relevant to sexual and emotional arousal (Walter, Bermpohl, et al. 2008; Walter, Stadler, et al. 2008; Graf et al. 2013; Metzger et al. 2013). We observed significantly increased differential neurofunctional activations in subcortical and cortical regions (e.g. midbrain, inferior frontal gyrus, inferior frontal temporal gyrus, inferior parietal lobe, and postcentral gyrus) that have been

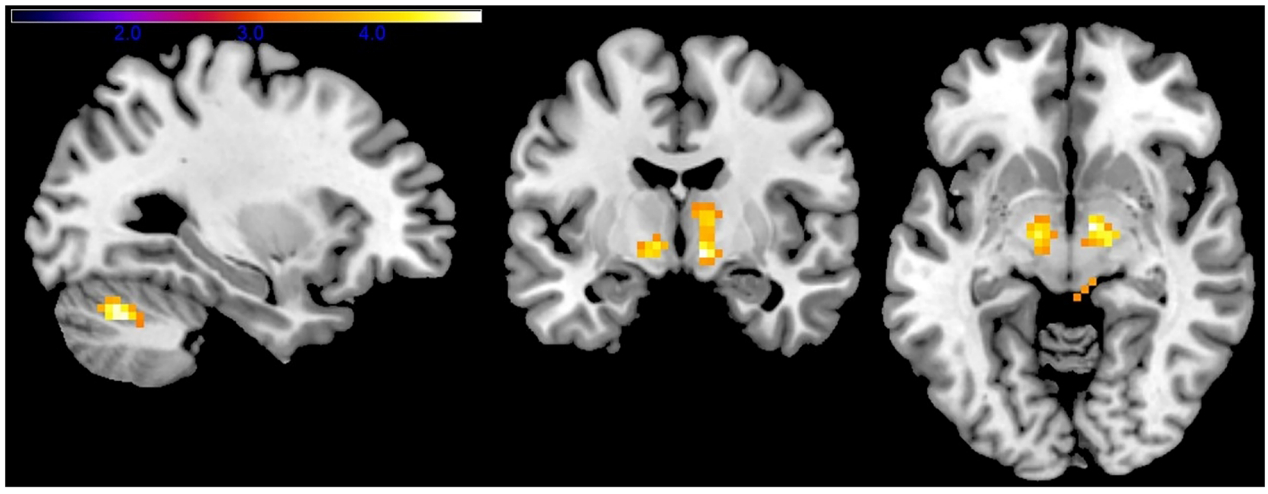

Figure 2. Significant association of resting state functional connectivity of the two ROIS midbrain/VTA and nucleus accumbens with differential (erotic minus non-erotic) neurofunctional activations during visual erotic stimulation within the hypothalamus, the midbrain, the periaqueductal gray and the thalamus.

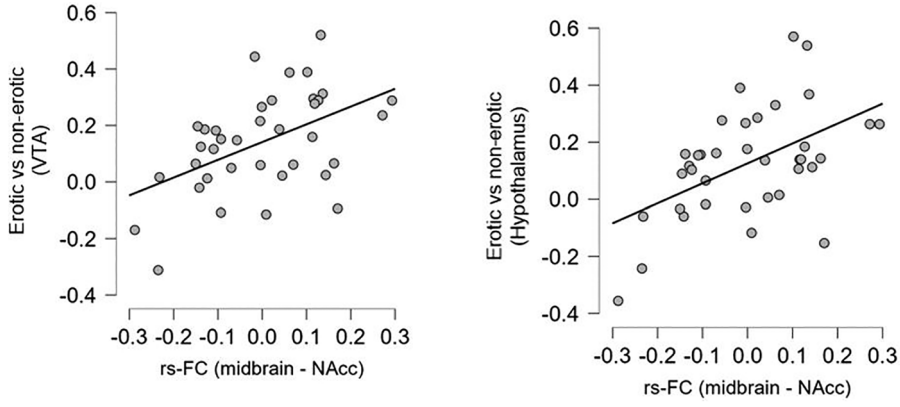

Figure 3. Results of correlation analyses between rs-FC between the two ROIs midbrain/VTA and nucleus accumbens (NAcc) with differential (erotic minus non-erotic) neurofunctional activations during visual erotic stimulation related to the significant cluster.

Table 1. Brain regions with significant association between differential (erotic minus non-erotic) neural responsiveness during visual erotic stimulation and functional connectivity between the nucleus accumbens and the midbrain/VTA ROI under rest.

Anatomic label	Side L/R	Cluster size (NV)	Peak voxel(MNI,mm) x	y	z	T (peak)	pFWE (Cluster-level)	*p* (uncorrected) (Cluster level)
hypothalamus	R	117	9	−7	−7	4.87	0.003	0.002
midbrain	R		3	−25	−13	4.60	0.003	0.002
periaqueductal grey	R		6	−31	−4	3.97	0.003	0.002
thalamus (ventral lateral nucleus)	R		12	−10	5	4.46	0.003	0.002
cerebellum	L	55	−30	−61	−31	4.72	0.040	0.023
ventral tegmental area	L	40	−12	−10	−7	4.44	0.080	0.048
hypothalamus	L		−9	−7	−4	4.32	0.080	0.048

reported in previous studies (Redouté et al. 2000a; Arnow et al. 2002; Stoléru et al. 2003; Walter, Bermpohl, et al. 2008; Metzger et al. 2010; Abler et al. 2011; Graf et al. 2014; Poeppl et al. 2014; Graf et al. 2015), supporting the reliability of our functional challenge.

Given the central role of the dopaminergic mesolimbic reward system in sexual arousal and processing (Hamann et al. 2004; Stark et al. 2005; Georgiadis and Kringelbach 2012), we focused on the putative association of rs-FC between the NAcc and the midbrain/VTA as core regions of the dopaminergic pathway and differential neural responsiveness to erotic and non-erotic visual stimulation. The NAcc has been previously related to sexual processing (Mannella et al. 2013) and corresponding goal-directed behaviour (Liu et al. 2011; Botvinick et al. 2009; Mannella et al. 2013)

and neural activations within this region are correlated with increases in dopaminergic transmission to the extent of sexual motivation (Childress et al. 2008; Gillath and Canterberry 2012; Oei et al. 2012). Neural activations within the midbrain/VTA have been consistently related to the prediction of rewards and sexual motivation (Georgiadis and Kringelbach 2012). Both regions, midbrain/VTA and NAcc, are directly connected *via* neurons and this direct projection is crucial for sexual motivation and arousal (Pfaus and Phillips 1991; Fiorino et al. 1997; Kippin et al. 2004; Brom et al. 2014).

Correlating the strengths of rs-FC between the NAcc and the midbrain/VTA with differential neurofunctional activations during visual erotic versus non-erotic stimulation, we observed a significant positive association between the rs-FC of the two core regions of the human reward system and the neurofunctional responsiveness in the hypothalamus. Neurofunctional activations of the hypothalamus in the context of sexual processing have been linked to autonomic components of sexual arousal to lead subjects to a state of physiological readiness for sexual behaviour (Ferretti et al. 2005). In addition, the hypothalamus is critically implicated in diverse motivated behaviours (e.g. seeking food, sex and drugs) *via* its connections with the VTA and the NAcc (Stellar 1954; Castro et al. 2015; MacNiven et al. 2020). Accordingly, neurofunctional activations of the hypothalamus correlate with subjectively experienced sexual arousal and, together with the striatum, they specifically reflect the intensity of sexual stimuli (Walter, Bermpohl, et al. 2008).

We also observed a significant association between rs-FC between the NAcc and the midbrain/VTA with differential neurofunctional activations within the thalamus under visual erotic stimulation. Beyond its unequivocal role in complex sensomotoric information processing, mounting evidence underpins the crucial role of the thalamus in multiple circuits supporting cognition, emotion and perception (Halassa and Kastner 2017; Halassa and Sherman 2019; Wolff and Vann 2019). Accordingly, previous research commonly observed neurofunctional activations of the thalamus related to the emotional dimension of sexual arousal (Redouté et al. 2000a; Park, Kang, et al. 2001; Park, Seo, et al. 2001; Ferretti et al. 2005; Moulier et al. 2006). As part of the reward circuit, the thalamus is further thought to form a final link (Haber et al. 2006) mediating erotic stimulus experience (Holstege 2010; Metzger et al. 2010; Metzger et al. 2013). Owing to its reciprocal connections with cortical and subcortical structures, the thalamus orientates neural resources towards behavioural relevant stimuli and is thus critically involved in salience processing (Zhou et al. 2021). Of note, particularly the anterior nuclei and proportion of the thalamus as found in our study, contribute to this attention control primarily *via* projections to limbic structures such as the NAcc (Parnaudeau et al. 2013; Wright et al. 2015; Wolff and Vann 2019; Zhou et al. 2021) to orientate motivation.

Increased rs-FC between the midbrain/VTA and the Nacc was also associated with higher neural responsiveness of the periaqueductal grey (PAG) under erotic stimulation. The PAG is known for its pivotal role in autonomic control, the modulation of pain and defensive behaviour (Bandler and Depaulis 1991; Behbehani 1995). In addition, there is substantial evidence for its crucial involvement in mediating complex emotional and motivated behaviour through its vast connections in the brain (Motta et al. 2017), including the VTA, the NAcc and the hypothalamus (Omelchenko and Sesack 2010; Koob and Volkow 2016; Ntamati et al. 2019). Accordingly, neurofunctional activation of the PAG promotes reward (Lüthi and Lüscher 2014) and salience processing of socioemotional cues (Rijpma et al. 2022). In the context of sexual behaviour, it has been previously implicated in gating corresponding motor outputs and as well as mediating male erection and ejaculation (Calabrò et al. 2019; Bayless et al. 2023).

Despite demonstrating significant associations between rs-FC of the midbrain/VTA and the NAcc with neural responsiveness of brain regions mediating autonomic functions, reward and salience processing under erotic stimulation, the following shortcomings have to be considered. It is of note that our investigation was restricted to healthy young male subjects to avoid biasing variations related to menstrual cycle and different hormonal states in women. This limits generalisability and our results cannot be transferred to a female sample. Moreover, we did not assess and control for further demographic aspects such as employment or in particular relationship status in our sample that may potentially alter neural responses to erotic stimuli or functional connectivity.

In addition, we expected a significant association between rs-FC of our two ROIs and further subcortical and cortical regions such as the amygdala and the anterior cingulate cortex (ACC), given their pivotal role in neurofunctional modulation of sexual behaviour and salience processing (Menon 2015). However, we found increased neurofunctional activations of the ACC under erotic stimulus processing that correspond to higher rs-FC between the NAcc and the midbrain/VTA under a more lenient statistical threshold. This lack of significance may owe to our investigation of a relatively small sample and we encourage future

studies, encompassing not only higher sample sizes but also a broader range of participants including sex. Moreover, we have to mention that our study does not consider behavioural state or trait measures comprising sexual arousal, that may correspond to different rs-FC strengths or neurofunctional responsiveness.

Conclusion

In our fMRI study, we investigated the neural signature of erotic visual stimulation in healthy male subjects and their association with rs-FC between two core regions of the reward circuit, namely the NAcc and the midbrain/VTA. We observed a compelling association between higher midbrain/VTA- and NAcc-rsFC and increased differential neuronal responsiveness of the hypothalamus, the thalamus, and the periaqueductal grey. This finding underpins the pivotal role of the mesolimbic reward pathway in the processing of erotic stimuli. In particular, our data support that higher rs-FC between the midbrain/VTA and the NAcc mediates the concurrent activation of subcortical brain regions, relevant for the integration of motivational, sensory, autonomic, emotional and salience processes in sexual behaviour. Our results shed light on the intricate interplay between rs-FC and differential neuronal activity in the context of erotic stimulus processing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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