

## RESEARCH ARTICLE

# Erotic Stimulus Processing under Amisulpride and Reboxetine: A Placebo-Controlled fMRI Study in Healthy Subjects

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## Abstract

**Background:** Impaired sexual function is increasingly recognized as a side effect of psychopharmacological treatment. However, underlying mechanisms of action of the different drugs on sexual processing are still to be explored. Using functional magnetic resonance imaging, we previously investigated effects of serotonergic (paroxetine) and dopaminergic (bupropion) antidepressants on sexual functioning (Abler et al., 2011). Here, we studied the impact of noradrenergic and antidopaminergic medication on neural correlates of visual sexual stimulation in a new sample of subjects.

**Methods:** Nineteen healthy heterosexual males (mean age 24 years, SD 3.1) under subchronic intake (7 days) of the noradrenergic agent reboxetine (4 mg/d), the antidopaminergic agent amisulpride (200 mg/d), and placebo were included and studied with functional magnetic resonance imaging within a randomized, double-blind, placebo-controlled, within-subjects design during an established erotic video-clip task. Subjective sexual functioning was assessed using the Massachusetts General Hospital-Sexual Functioning Questionnaire.

**Results:** Relative to placebo, subjective sexual functioning was attenuated under reboxetine along with diminished neural activations within the caudate nucleus. Altered neural activations correlated with decreased sexual interest. Under amisulpride, neural activations and subjective sexual functioning remained unchanged.

**Conclusions:** In line with previous interpretations of the role of the caudate nucleus in the context of primary reward processing, attenuated caudate activation may reflect detrimental effects on motivational aspects of erotic stimulus processing under noradrenergic agents.

**Keywords:** impaired sexual function, erotic stimulus processing, amisulpride, reboxetine, fMRI

## Introduction

Impaired sexual functioning is increasingly recognized as a side effect of psychopharmacological treatments affecting quality of life and adherence with treatment regimens (Taylor et al., 2005;

Park et al., 2012; Baldwin et al., 2013; La Torre et al., 2013) with a growing interest in the underlying mechanisms. Since sexual dysfunction is also a common symptom of psychiatric disorders,

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like major depression, in and of itself, purely treatment-related effects are hard to investigate in patients affected (Baldwin and Mayers, 2003), requiring the investigation of treatment effects in healthy controls (Graf et al., 2014).

Intact sexual functioning is based on a complex interplay of cerebral and spinal centers as well as hormonal, peripheral, and autonomic functions. The influence of different neurotransmitters and pharmacological principles on these interactions is still largely unclear. We have already investigated the neural correlates of sexual stimulation in healthy subjects using functional magnetic resonance imaging (fMRI) under subchronic treatment (7 days) with the selective serotonin reuptake inhibitor (SSRI), paroxetine, and with bupropion, a selective dopamine and noradrenaline (NA) reuptake-inhibitor. We demonstrated that subjectively impaired sexual functioning under the SSRI was accompanied by diminished neural activations within limbic and reward-related brain areas (Abler et al., 2011), potentially related to increased reciprocal interactions between orbito-frontal cortex and the ventral striatum (Abler et al., 2012). As expected from clinical observations (Coleman et al., 2001; Taylor et al., 2013), impaired sexual functioning was not evident under bupropion, which led to even increased neural activations within brain regions related to salient and emotional stimulus processing (ie, sublenticular extended amygdala). Whereas these opposite effects of SSRI and dopamine and NA reuptake-inhibitor treatments were shown for direct erotic stimulation, decreased activation within fronto-parietal and cingulo-opercular attention networks was evident for both bupropion and paroxetine during expectation periods preceding erotic picture stimuli (Graf et al., 2013). Thus, serotonergic and noradrenergic/dopaminergic medications showed divergent and concordant effects depending on the aspects of erotic stimulus processing investigated. In line with previous hypotheses (Pessiglione et al., 2006), the dopaminergic component of bupropion was held responsible for the increased activation upon direct visual erotic stimulation (Abler et al., 2011), and the noradrenergic component was interpreted to mediate the effects on the expectation of erotic stimulation (Graf et al., 2013). Supplementing our previous investigation with a new sample of subjects, we intended to further disentangle the neural effects of monoaminergic drugs, now applying a selective noradrenergic and an antidopaminergic treatment.

The selective noradrenalin reuptake inhibitor (SNRI), reboxetine, is an antidepressant with high selectivity towards the noradrenalin transporter and relatively low affinity for the serotonin transporter, monoamine, histamine, and acetylcholine receptors (Hajos et al., 2004). Therefore, it presents a well-suited vehicle to investigate the impact of NA on neural correlates of sexual stimulation. Effects of reboxetine on some aspects of sexual functioning have already been reported in patients (Clayton et al., 2003b), with less detrimental effects compared with SSRIs (Whiskey and Taylor, 2013), particularly regarding sexual satisfaction, the ability to become sexually excited (Baldwin et al., 2006), and achieving orgasm (Langworth et al., 2006). However, in line with case reports (O'Flynn and Michael, 2000; Habermann, 2002; Sivrioglu et al., 2007), the product's professional information reports a commonly increased risk to develop sexual side effects in terms of erectile dysfunction and prolonged/delayed and painful ejaculation for up to 10% of treated cases, with an increased rate of such side effects under higher dosages in depressed patients (Tanum, 2000).

The atypical antipsychotic drug amisulpride has high and selective affinity to postsynaptic D<sub>2</sub> and D<sub>3</sub> receptors (Perrault et al., 1997; Castelli et al., 2001; Hartter et al., 2003). The most

common hypothesis to explain sexual dysfunction under antipsychotics (see La Torre et al., 2013 for review) is blockade of dopamine D<sub>2</sub> receptors (Haddad and Sharma, 2007) in the tuberoinfundibular pathway, with secondary increases of prolactin levels (Park et al., 2012). Accordingly, we expected decreased activation of dopaminergic neural correlates of sexual stimulation in particular under this specific drug.

Investigating the neural correlates of sexual stimulus processing under noradrenergic (reboxetine) and antidopaminergic (amisulpride) medication in healthy subjects, we intended to complement results from our previous investigations regarding the neural impact of serotonergic and dopaminergic principles in sexual functioning (Abler et al., 2011) and to further characterize the monoaminergic mechanisms regarding sexual functioning and stimulus processing within a new sample of healthy males.

## Materials and Methods

### Participants

We investigated 20 healthy, heterosexual, male, right-handed subjects under subchronic medication with amisulpride (AMS), reboxetine (REB), and placebo (PLA) in a randomized counterbalanced order. Exclusion of 1 subject from further analysis due to cerebral pathology (gliotic lesions) led to a final sample of 19 participants (mean age 24.0 years, SD 3.1; range 20–32). Participants were recruited by personal communication or written advertisements at the campus of Ulm University. Prior to the study, each participant received a full medical evaluation, including medical history, physical examination, and a Structured Clinical Interview for DSM-IV Axis I Psychiatric Disorders. Participants with any current or past psychiatric disorder observed in the psychiatric exploration with open questions by one of the study physicians (H.G. or B.A.) or with symptoms coded as “present” or “subthreshold” in any of DSM-IV Axis I Psychiatric Disorders modules would have been excluded from the study. Laboratory blood tests and electrocardiograms were performed to exclude renal, hepatic, or cardiac pathology. Further exclusion criteria were any serious general medical condition, current or past neurological illness, relevant baseline sexual dysfunction or sexual disorders, use of illegal drugs, and excessive consumption of caffeine or alcohol. Upon recruitment, baseline depressive symptoms were assessed by the German version (Hautzinger and Bailer, 1993) of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977). The Massachusetts General Hospital Sexual Functioning Questionnaire (MGH-SFQ; Labbate and Lare, 2001) was administered to evaluate baseline sexual interest, sexual arousal, ability to achieve orgasm, ability to achieve and maintain an erection, and overall sexual satisfaction prior to the study. According to the study protocol, the questionnaire was modified to assess changes in subjective sexual functioning only over the past week of medication (Abler et al., 2011). Upon inclusion, subjects presented with sum scores of this specific questionnaire around 10 (mean 10.7; SD 1.7), indicating unimpaired subjective sexual functioning.

The study was approved by the local ethical committee of Ulm University, and all participants gave written informed consent conforming to the Declaration of Helsinki.

### Study Design and Procedures

Within a randomized, double-blind, placebo-controlled, within-subject crossover design, subjects received 200 mg AMS (100 mg

twice per day), 4 mg REB (2 mg twice per day), and PLA (twice per day) for 7 days each, separated by a wash-out phase of at least 2 weeks. As with our previous study protocol (Abler et al., 2011), this new sample of subjects was investigated on 3 different occasions, and the fMRI scans took place on the seventh day of medication, 2 hours after intake of the last capsule. Subjects were asked to refrain from alcohol parallel to the study medication and especially for 3 days prior to fMRI. They were also asked to refrain from coffee on the day of the scans. To warrant drug exposure and adherence, blood samples were obtained after each scan (about 3 hours after drug intake) and analyzed after completion of the whole study. The average plasma amisulpride level was 137.7 ng/mL (SD 54.8), and the mean plasma reboxetine level was 75.7 ng/mL (SD 28.9). Blood levels within the expected range were detected in each of the 19 subjects for both drugs, indicating that adherence to drug intake was consistent across subjects.

### Additional Questionnaires

Sexual functioning during the past week with drug or placebo intake was assessed using the MGH-SFQ after each scan. The MGH-SFQ consists of 5 questions with ratings from 1 to 6. Cumulative ratings range from 5 (minimal value: improvement of sexual functioning) over 10 (sexual functioning unchanged compared with normal) to 30 (maximal value: sexual functioning markedly impaired compared with normal). Ratings of <2 for single questions or a cumulative score >10 indicate subjectively impaired sexual functioning (for details, see Labbate et al., 2001; Abler et al., 2011). Side effects of medication were assessed by one of the study physicians (H.G. or B.A.) within a medical interview with open questions and a structured part (UKU side-effects scale, Lingjaerde et al., 1987) on each session. Sedative effects of the medication were assessed with the Stanford Sleepiness Scale (SSS; Hodes et al., 1973). Repeated-measures analysis of variance (ANOVA) and post-hoc Newman Keuls tests were computed to analyze questionnaire results.

### fMRI Stimuli

Erotic and neutral video clips were used for prolonged visual stimulation within a standard block design as in our previous experiment (Abler et al., 2011). Erotic video clips were extracted from commercial adult films and depicted sexual interaction (petting, oral sex, vaginal intercourse) between 1 man and 1 or 2 women. Neutral video clips showed men and women in emotionally neutral, nonerotic interactions. Erotic and neutral stimuli were matched for color, the number and gender of subjects interacting, length of interaction, and whether the depicted subjects were clothed or naked. Nine video clips of each of the 2 conditions were presented for 20 seconds each, separated by a 20-second fixation period, resulting in a total paradigm length of 720 seconds. Video clips were presented by magnetic resonance-compatible video goggles in a pseudo-randomized order with a maximum of 2 consecutive clips of the same condition. The order of the same video segments was counterbalanced across subjects and medications.

### fMRI Acquisition

T1 anatomical volume images (1x1x1-mm voxels) and functional magnetic resonance images were acquired using a 3T head-only magnetic resonance imaging system (Siemens Magnetom Allegra, Erlangen, Germany). Twenty-three transversal slices

were acquired with an image size of 64x64 pixels and a field of view of 192 mm. Slice thickness was 3 mm with a 0.75-mm gap, resulting in a voxel size of 3x3x3.75 mm.

Slices were oriented steeper than the bicommissural line at an angle of  $-15^\circ$  between transversal and coronal planes to minimize the risk of susceptibility in basal structures of the brain including subcortical regions of interest (amygdala, basal ganglia, and inferior prefrontal regions). Because of the reduced number of slices as a consequence of the rather short repetition time (TR) of 1.5 seconds, there was no full brain coverage. Functional images were recorded using T2\*-sensitive gradient echo echo-planar imaging measuring changes in BOLD contrast. A total of 487 volumes was obtained during viewing of video clips at a TR of 1500 milliseconds (TE 35 milliseconds, flip angle  $90^\circ$ ). The first 7 images were acquired to allow for T1 saturation effects and later discarded. Two additional image acquisitions at the very beginning of each sequence and not saved to disk added to the T1 equilibration time (3 seconds). At the end of scanning, a high resolution T1-weighted structural image was obtained by administering a magnetization prepared rapid acquisition gradient echo sequence (TR = 2300 milliseconds, TE = 3.93 milliseconds, inversion time = 1100 milliseconds, flip angle =  $12^\circ$ , FoV = 256 mm, matrix size: 256 x 256, voxel volume = 1 mm<sup>3</sup>, slice orientation: sagittal; scan time = 517 seconds).

### fMRI Analysis

Image preprocessing and statistical analyses were carried out using Statistical Parametric Mapping (Wellcome Department, London, UK) with a random effects model for group analyses. Data from each session were preprocessed including slice-timing, realignment, and normalization into a standard template (Montreal Neurological Institute) with a spatial resolution of 2x2x2 mm<sup>3</sup>. Smoothing was applied with an 8-mm FWHM isotropic Gaussian kernel. Intrinsic autocorrelations were accounted for by AR(1), and low frequency drifts were removed via high-pass filtering.

Analogous to Abler et al. (2011), first-level analyses were performed for each subject. According to the general linear model, we defined 2 regressors to analyze each of the 2 types of video stimuli (erotic, nonerotic). Video blocks were modeled as timely extended events of 20 seconds and convolved with the hemodynamic response function. The 6 realignment parameters modeling residual motion were also included in the individual models. None of the time series contained movements of 1 mm or more in any direction or rotations of  $>1$  degree between consecutive volumes. The individual contrast images for erotic and nonerotic conditions were then included in a second-level group analysis using an ANOVA model with condition (erotic/nonerotic) as the first factor. Treatment (PLA/AMS/REB) was added as a second factor with 3 levels to test on significant interaction effects of treatment on the contrast of erotic vs nonerotic stimuli. A third factor modeled the subject-related variance.

Treatment effects were analyzed by computing 1-tailed condition-by-treatment interactions to account for 1 active compound and 1 active condition vs 1 placebo and 1 control condition (erotic, nonerotic; placebo, verum). Taking the one-sidedness of the t-contrasts into account, effects were considered significant at a statistical threshold of  $P < 0.0025$ , uncorrected at the voxel level and a cluster extent of at least 419 contiguously significant voxels corresponding to a level of  $P < 0.05$ , familywise error (FWE) corrected on the cluster level.

To investigate significant correlations between fMRI treatment effects and individual subjective sexual functioning, we

further computed a multiple regression analysis incorporating each of the 5 MGH-SFQ subscales within the mask of the significant condition-by-treatment interaction. The dependent variables were the individual parameter estimates of condition-by-treatment interaction from contrasting placebo against reboxetine. Regressors were each individual's difference score between placebo and reboxetine for each of the 5 subscales. One-tailed t-contrasts were used to test for significant regression effects. Effects were considered significant at a level of  $P < 0.0025$  at the voxel level and a cluster extent of at least 16 contiguously significant in-mask voxels, corresponding to a level of  $P < 0.05$ , FWE corrected on the cluster level.

## Results

### Questionnaires

An average Center for Epidemiologic Studies Depression Scale sum-score of 8.0 (SD 6.04) indicated no relevant depressive symptoms in the participants.

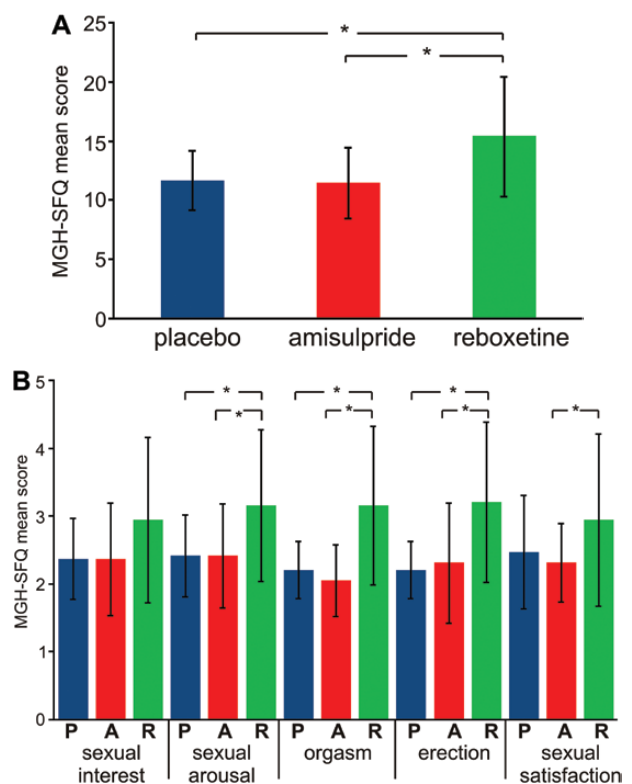
Side effects as assessed by the UKU side effect scale did not appear for the following variables: increased duration of sleep, increased dream activity, dystonia, rigidity, hypokinesia/akinesia, hyperkinesia logic, tremor, akathisia, epileptic seizures, paraesthesias, increased salivation, diarrhea, micturition disturbances, polyuria/polydipsia, orthostatic dizziness, palpitations/tachycardia, increased tendency to sweating, rash, pruritus, photosensitivity, increased pigmentation, weight gain, weight loss, galactorrhoea, and gynaecomastia. At least one indication of a side effect under either drug was given for the following items, whereas between-treatment differences were not significant: concentration difficulties ( $F(2,36)=0.55$ ;  $P=0.582$ ), asthenia/lasitudinal/fatigability ( $F(2,36)=2.15$ ;  $P=0.131$ ), sleepiness/sedation ( $F(2,36)=1.61$ ;  $P=0.214$ ), failing memory ( $F(2,36)=1.00$ ;  $P=0.378$ ), depression ( $F(2,36)=1.31$ ;  $P=0.283$ ), emotional indifference ( $F(2,36)=1.18$ ;  $P=0.320$ ), accommodation disturbances ( $F(2,36)=0.19$ ;  $P=0.827$ ), nausea/vomiting ( $F(2,36)=0.24$ ;  $P=0.788$ ), constipation ( $F(2,36)=0.08$ ;  $P=0.924$ ), and (tension) headache ( $F(2,36)=0.12$ ;  $P=0.888$ ). Significant between-treatment differences were observed for the 3 side effects: reduced salivation ( $F(2,36)=4.58$ ;  $P=0.017$ ), inner unrest ( $F(2,36)=3.71$ ;  $P=0.034$ ), and reduced duration of sleep ( $F(2,36)=6.87$ ;  $P=0.003$ ). Post-hoc testing showed decreased salivation under reboxetine (REB) compared with placebo ( $P=0.033$ ) and amisulpride ( $P=0.013$ ), whereas amisulpride (AMS) did not differ from placebo ( $P > 0.05$ ). Inner unrest was also more evident under REB when compared with AMS ( $P=0.032$ ) but not relative to placebo ( $P=0.067$ ); again, AMS and placebo did not differ ( $P > 0.05$ ). Reduced duration of sleep was reported under REB compared with placebo ( $P=0.006$ ) and AMS ( $P=0.004$ ), whereas duration of sleep was not significantly different under AMS relative to placebo ( $P > 0.05$ ). It is of note in this context that an ANOVA for repeated measurements showed no significant treatment effect on sedation or sleepiness immediately after fMRI scanning (SSS;  $F(2,36)=1.47$ ;  $P=0.244$ ; for details see Table S1).

The mean overall score in the MGH-SFQ upon enrollment was 10.7 (SD 1.70) and 11.7 (SD 2.50) under placebo. Paired t-testing revealed no significant difference between placebo and enrollment scores ( $t(18)=-1.55$ ;  $P=0.138$ ), and MGH-SFQ-data upon enrollment were not considered further. Treatment effects on sum-scores in the MGH-SFQ were significant ( $F(2,36)=8.10$ ;  $P=0.001$ ). Post-hoc tests (Newman-Keuls) confirmed more impaired sexual functioning under the SNRI reboxetine compared with both placebo ( $P=0.002$ )

and amisulpride ( $P=0.003$ ). Sexual functioning under the antidopaminergic drug amisulpride did not differ from placebo ( $P=0.850$ ). Considering the different subscales (Table 1), reboxetine had detrimental effects relative to either placebo or amisulpride for sexual arousal, orgasm, and the ability to achieve/maintain an erection. Reduced sexual satisfaction was also observed under reboxetine relative to amisulpride, but not when compared with placebo. Comparisons between amisulpride and placebo did not reveal significant differences in any of the subscales (Figure 1A-B).

**Table 1.** Results from the ANOVA with the Factor "Treatment" (Reboxetine/Amisulpride/Placebo) on Group-Averaged Ratings for Each Subscale of the MGH-SFQ.

MGH-SFQ	treatment	
Subscale	F(2,36)	p
Sexual interest	2.69	0.082
Arousal	5.51	0.008*
Orgasm	11.24	0.000*
Erection	8.20	0.001*
Satisfaction	3.59	0.038*



**Figure 1.** A, Mean total scores (SD) in the Massachusetts General Hospital Sexual Functioning Questionnaire (MGH-SFQ). Overall, subjective sexual functioning was significantly ( $P < 0.05$ ) impaired under reboxetine compared with placebo and amisulpride. Sexual functioning did not differ between amisulpride and placebo. \* = indicates statistical significance (post-hoc;  $P < 0.05$ ); higher values describe greater subjectively perceived impairment of sexual functioning. B, Mean total scores (SD) of each subscale in the MGH-SFQ. Sexual arousal, the ability to achieve orgasm, and the ability to achieve and maintain erection were significantly ( $P < 0.05$ ) impaired under reboxetine (R) compared with placebo (P) and amisulpride (A). Sexual satisfaction was lower under reboxetine compared with amisulpride, whereas amisulpride and placebo did not differ regarding sexual functioning. \* = indicates statistical significance ( $P < 0.05$  from post-hoc Newman-Keuls tests).



## fMRI Results

### Main Effects

Replicating previous results (Abler et al., 2011), main effects of erotic visual stimulation under placebo (erotic minus nonerotic video clips) in the present sample showed significantly ( $P < 0.05$  FWE cluster level corrected) increased neural activations in the superior and inferior temporal gyrus, middle occipital gyrus, inferior parietal lobule, inferior frontal gyrus, precentral gyrus, insula, hippocampus, midbrain (comprising parts of the substantia nigra), putamen, and caudate nucleus.

### Treatment Effects

Significant condition-by-treatment interactions were found for a cluster comprising the right caudate nucleus and parts of the right anterior putamen and the lentiforme nucleus. Post-hoc tests confirmed that these effects were related to attenuated neural activations under reboxetine compared with placebo (see Table 2; Figure 2A-B). The inverted t-contrast testing on increased neural activation under reboxetine against placebo did not reveal any significant effects. Furthermore, no significant results were obtained when contrasting placebo against amisulpride or amisulpride against reboxetine, even at a more lenient statistical threshold of  $P < 0.025$  and without cluster corrections.

### Correlation Analyses

A multiple regression analysis was computed to test for relations of subjectively experienced changes in sexual functioning and differential fMRI activations under the SNRI reboxetine against placebo. We revealed a significant partial correlation within the ventral part of the right caudate nucleus (mean partial correlation coefficient  $r = 0.709$ ,  $P = 0.05$  FWE corrected at cluster level; number of voxels: 22; peak Z-value: 3.10;  $x, y, z = 10, 22, 4$ ) with the MGH-SFQ subscale “sexual interest” indicating that decreased neural activation was accompanied by decreased sexual interest (Figure 3). None of the other MGH-SFQ subscales correlated significantly with fMRI activation differences.

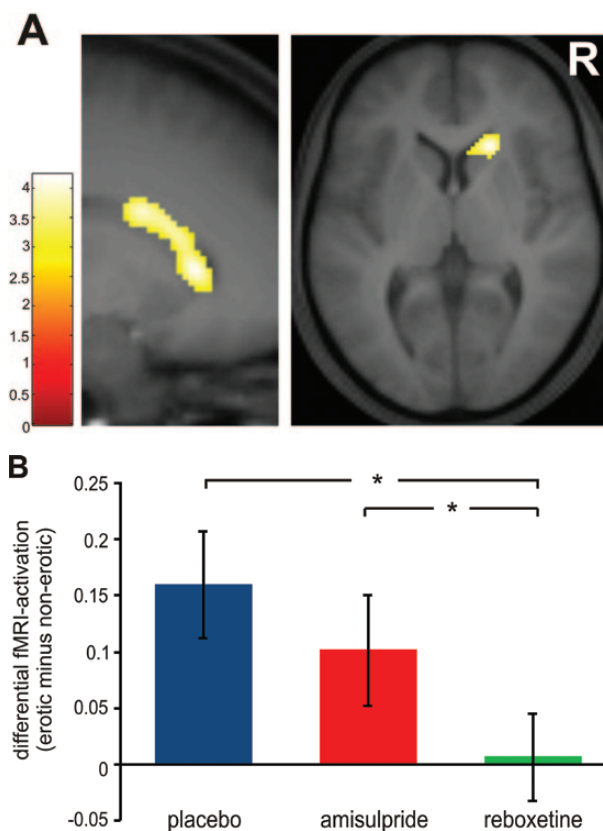
## Discussion

Expanding our previous investigation (Abler et al., 2011) on neural correlates of sexual stimulation under serotonergic and dopaminergic medication, in the present study we focused on the effects of noradrenergic and antidopaminergic medication within a new sample of subjects. Within a double-blind, placebo-controlled, crossover design, we investigated 19 healthy male volunteers using an established erotic video clip task under administration of the noradrenergic drug reboxetine, the antidopaminergic agent amisulpride, and placebo. Reboxetine

**Table 2.** Significant Treatment-by-Condition Interaction When Contrasting Placebo Minus Reboxetine for the Contrast of Erotic Minus Non-erotic Stimulation (ANOVA;  $P < 0.0025$ , Uncorrected at the Voxel Level and a Cluster Extent of at Least 419 Contiguously Significant Voxels Corresponding to  $P < 0.05$ , FWE Corrected on Cluster Level).

	cluster	MNI-coordinates				
		$P$ (FWE corrected)	NV	Z	x	y
caudate nucleus	0.018	565	3.90	18	24	4
			4.02	22	6	22
			3.14	26	-6	30

NV = number of voxels; MNI-coordinates ( $x, y, z$ ) in [mm]; FWE = familywise error.

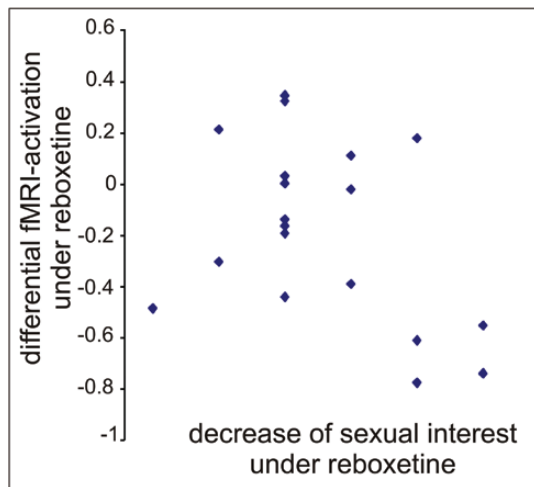


**Figure 2.** A, Significant placebo-by-reboxetine interaction within the right caudate nucleus depicted in sagittal and transversal slices at the peak voxel ( $P < 0.0025$ , uncorrected at the voxel level and cluster extent of at least 419 contiguously significant voxels corresponding to  $P < 0.05$ , FWE corrected on the cluster level). B, Bar graphs depict differential (erotic minus nonerotic) fMRI activations (parameter estimates calculated as a mean over all voxels in the cluster) under placebo and reboxetine with standard error of the mean. \* = indicates statistical significance ( $P < 0.05$ ) from post-hoc t-testing of differential parameter estimates (placebo vs amisulpride:  $t(1,18) = 1.11$ ,  $P = 0.141$ ; placebo vs reboxetine:  $t(1,18) = 3.39$ ,  $P = 0.002$ ; amisulpride vs reboxetine:  $t(1,18) = 2.17$ ,  $P = 0.022$ ). Montreal Neurological Institute-coordinates of peak voxel (mm):  $x, y, z = 18, 24, 4$ ; R = right.

reduced subjective ratings of sexual functioning compared with both placebo and amisulpride, whereas ratings of sexual functioning did not change under amisulpride. Specifically, sexual arousal and the ability to achieve orgasm and achieve and maintain an erection were affected under reboxetine relative to placebo and amisulpride.

fMRI during erotic stimulation replicated significant activations of brain regions that have already been reported in previous studies (Redoute et al., 2000; Park et al., 2001; Arnow et al., 2002; Walter et al., 2008; Metzger et al., 2010; Abler et al., 2011; Georgiadis and Kringelbach, 2012), thus supporting the reliability of the functional challenge. Significant treatment-by-condition interactions were exclusively related to reboxetine (SNRI) in terms of decreased activation of the right caudate nucleus compared with placebo and amisulpride. Moreover, activation changes in the ventral part of the caudate nucleus were correlated with changes in subjective ratings of sexual interest. Along with unchanged behavioral data, no significant treatment effects on neural activation upon erotic stimulation were observed for AMS relative to PLA.

Given the role of dopamine in processing sexual stimuli (Abler et al., 2011; Oei et al., 2012) and the antidopaminergic properties



**Figure 3.** Results of the multiple regression analysis of fMRI data and MGH-SFQ subscales as regressors within a mask comprising the voxels with a significant placebo-by-reboxetine interaction (actual cluster size: 565). A significant correlation (mean partial correlation coefficient  $r=0.709$ ) was observed within the ventral part (head) of the right caudate nucleus for the subscale “sexual interest” under reboxetine relative to placebo. Statistical threshold was chosen at  $P<0.0025$  with a critical cluster extent of 22 voxels to control for multiple testing within the reduced search volume. It is of note that the multiple regression was computed for exploratory purposes only to exploit the different information given by the 5 different subscales. Inference of the affected brain region had exclusively been based on the statistical comparisons on the categorical between-treatment differences.

(Castelli et al., 2001; Assem-Hilger and Kasper, 2005) of amisulpride, more pronounced effects were expected than observed (Figure 2B). This absence of greater effects may most likely associate with dose-dependent pharmacological properties of the drug (Andrade, 2013). Antipsychotic effects of amisulpride were reported for high dosages from about 400 to 600 mg/d, resulting in reliable  $D_2$  receptor occupancy (Perrault et al., 1997). However, reports have suggested antidepressant efficacy at lower dosages of 50 to 200 mg/d (as used in our study) by blocking presynaptic dopamine autoreceptors (Perrault et al., 1997; Smeraldi, 1998; Montgomery, 2002). These mild prodopaminergic effects may account for the lack of impaired sexual functioning in our sample. As another possible explanation, present dosage of amisulpride may not have sufficiently increased plasma prolactin levels that are commonly linked to amisulpride-related sexual dysfunction (Hartter et al., 2003) and may exert their effects via peripheral rather than central dopaminergic pathways.

Because the noradrenergic agent reboxetine has been reported favorably regarding sexual dysfunction associated with antidepressant medication (Clayton and Zajecka, 2003a; Baldwin et al., 2006), we rather expected less detrimental effects of this drug than observed. However, previous reports of prolonged orgasm (Haberfellner, 2002), erectile dysfunction, and spontaneous ejaculation (O’Flynn et al., 2000; Sivrioglu et al., 2007) as well as anorgasmia (Langworth et al., 2006) under reboxetine are in line with present results. Assuming an inverted u-curve relationship, an increase of noradrenergic neurotransmission beyond the optimum of an already balanced, healthy NA system may relate to the decrease in sexual functioning, similar to previous results where NA overstimulation negatively affected cognitive functioning in healthy subjects (Graf et al., 2011).

Functionally, significant treatment effects on neural activations were limited to the right caudate nucleus with attenuated neural activations under the SNRI reboxetine compared with

placebo or amisulpride. Activation of the caudate nucleus has been consistently involved in aspects of social behavior, romantic love, and erotic stimulus processing (Redoute et al., 2000; Bartels and Zeki, 2004; Aron et al., 2005; Walter et al., 2008) with a lateralization to the right as in our study (Aron et al., 2005; Walter et al., 2008). Furthermore, in previous studies, measures of increasing penile turgidity and erection have been associated with elevated neural activations of the caudate nucleus (Park et al., 2001; Arnow et al., 2002). During erotic stimulation, caudate nucleus activation has been linked to goal-directed behavior and reward (Arnow et al., 2002). Although activity within the most ventral parts of the striatum, particularly those comprising the nucleus accumbens, are commonly associated with the expectation and receipt of incentives, a recent investigation in healthy subjects (Miller et al., 2014) could associate the different aspects of reward vs motivational processing with differential activation along the caudate. Dorsal striatal activation increased with motivation while increasing activation of more ventral parts of the nucleus increased with reward. Therefore, our finding of decreased caudate activation under reboxetine and the correlation of decreased activation with diminished sexual interest may express predominantly motivational aspects of erotic stimulation. In line with this interpretation, a recent study on the effects of reboxetine at similar dosages and also in healthy subjects revealed unaffected ventral striatal activity upon processing of rewarding food stimuli (McCabe et al., 2010).

Since the striatum in humans is not significantly innervated by noradrenergic neurons (Wallman et al., 2011), attenuated neural activations within the caudate under the SNRI most likely reflect an indirect effect of increased NA levels. Reciprocal interactions between the dopamine and NA system (Guiard et al., 2008) and the inhibitory action of NA on dopaminergic neurons (El Mansari et al., 2010) may offer an explanation here.

### Limitations

In the present study, only male subjects were investigated to avoid biasing results due to hormonal variations related to the menstrual cycle in women (eg, Abler, et al., 2013). Therefore, the present results cannot easily be transferred to a female sample, which would require an additional study explicitly controlling for hormonal state. The reduced duration of sleep under reboxetine as an expected side effect of a noradrenergic agent might constitute a possible factor to interfere with data acquisition under a functional challenge. However, results from the SSS immediately obtained after fMRI scanning did not indicate that sleepiness or sedation would have played a significant role. Compared with subjective assessments upon enrollment, we observed a slight although insignificant increase in MGH-SFQ sum scores already under placebo, which may indicate that information about putative side effects could have triggered some form of expectation effects even under placebo. Such expectation effects, however, would have opportunistically influenced differences between verum and placebo, only if these effects would have reduced MGH-SFQ scoring under placebo leading to a biased increase between verum and placebo. The slight increase in MGH-SFQ scoring speaks against this possibility.

Although questionnaire data may well inform about subjective experiences with sexual functioning, objective measurements of aspects of sexual response, eg, penile turgidity, should be considered additionally in future studies on the same topic. In a similar vein, an objective measurement of alcohol intake could be useful to complement verbal reports on adherence to the study protocol particularly in an investigation in young and

healthy university students. Finally, further investigations might consider different dosages of the same drug in one experiment to investigate dose-dependent effects that might explain the absence of an interaction effect under the relatively low dose of amisulpride.

## Conclusion

Within a double-blind, placebo-controlled, crossover design, we investigated the neural correlates of erotic stimulus processing in healthy subjects under the noradrenergic antidepressant reboxetine and the dopamine antagonist amisulpride to examine drug effects independent from otherwise illness-related alterations in sexual functioning under these medications. Low-dose amisulpride did not alter subjective ratings of sexual functioning, and accordingly, neural activations remained unaffected, which may relate to possible prodopaminergic effects under low dosages of this drug. For the noradrenergic agent reboxetine, we observed subjectively impaired sexual functioning in healthy subjects accompanied by attenuated neural activations within the caudate nucleus that may reflect diminished motivational aspects of erotic stimulus processing under noradrenergic agents.

## Supplementary Material

For supplementary material accompanying this paper, visit <http://www.ijnp.oxfordjournals.org/>

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## Statement of Interest

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