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Neural correlates of antidepressant-related sexual dysfunction - a placebo-controlled fMRI study on healthy males under subchronic paroxetine and bupropion

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ABSTRACT

Sexual dysfunction is a common side effect of serotonin reuptake inhibitors like paroxetine in the treatment of depression imposing a considerable risk on medication adherence and hence therapeutic success. Bupropion, a norepinephrine and dopamine reuptake inhibitor is recommended as an alternative treatment without adverse effects concerning sexual arousal and libido. We investigated the neural bases of paroxetine-related subjective sexual dysfunction as compared to bupropion and placebo. We scanned 18 healthy, heterosexual males in a randomized double-blind within-subjects design while watching video clips of erotic and non-erotic content under steady state conditions after taking 20 mg of paroxetine, 150 mg of bupropion and placebo for 7 days each. Under paroxetine, ratings of subjective sexual dysfunction increased compared to placebo or bupropion. Activation along the anterior cingulate cortex including subgenual, pregenual and midcingulate cortices, in the ventral striatum and midbrain was decreased as compared to placebo. By contrast, bupropion let subjective ratings and ACC activations unchanged and increased activity of brain regions including posterior midcingulate cortex, mediodorsal thalamus and extended amygdala relative to placebo and paroxetine. Brain regions that have been related to the processing of motivational (ventral striatum), emotional, and autonomic components of erotic stimulation (anterior cingulate) in previous studies showed reduced responsiveness under paroxetine in our study. Drug effects on these regions may be part of the mechanism underlying SSRI-related sexual dysfunction. Increased activation under bupropion may point to an opposite effect that may relate to the lack of impaired sexual functioning.

Keywords: Bupropion, Paroxetine, erotic stimulation, sexual dysfunction, fMRI

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressant drugs (Bauer, *et al* 2008). For the majority of relevant diagnoses, regular intake is recommended for months or even longer (Gaebel and Falkai 2001). However, despite the positive profile of SSRIs, premature discontinuation is common and frequently discussed to account for non-response and relapse (Bull, *et al* 2002). Sexual dysfunction is a typical side effect of SSRI treatment (Serretti and Chiesa 2009) that conditions discontinuation and may represent the most clinically relevant side effect among patients in their twenties or thirties (Bishop, *et al* 2006). Decreased sexual desire and interest in sexual activity along with erectile dysfunction is reported in up to 60% of treatments with SSRIs (Gregorian, *et al* 2002) with the highest rates of up to 64% observed under paroxetine (Clayton, *et al* 2002). Since sexual dysfunction is similarly reported under treatment with dual antidepressants inhibiting serotonin and norepinephrine reuptake (Montejo, *et al* 2001), but not under selective norepinephrine reuptake inhibitors (Clayton, *et al* 2003), the serotonergic component seems to represent the crucial part in mediating sexual dysfunction.

Bupropion is a selective dopamine and norepinephrine reuptake inhibitor and is named as an alternative which is reportedly not associated with side effects on sexual functioning (Coleman, *et al* 2001). Bupropion has even been suggested as a potential treatment for SSRI-induced sexual dysfunction or hypoactive sexual desire disorder in women (Modell, *et al* 2000). This is in line with clinical observations relating dopamine agonists to hypersexuality (Voon, *et al* 2009) and dopamine antagonists to sexual dysfunction (Baldwin and Mayer 2003). Animal experiments clearly support the notion that modulation of central, but not peripheral serotonergic pathways is involved in SSRI-related alteration of sexual functioning (Waldinger, *et al* 1998). Enhancement of central serotonergic neurotransmission with stronger

activation of inhibitory postsynaptic autoreceptors (Blier, *et al* 1988) has been postulated as a likely SSRI effect modulating the inhibitory control of ejaculation (Giuliano and Clement 2006). However, the actual pathophysiology of SSRI related sexual dysfunction is poorly understood. Using functional magnetic resonance imaging (fMRI), we investigated the neural correlates of erotic stimulation under paroxetine. Because sexual dysfunction including decreased libido and anorgasmia is a common symptom of depression irrespective of antidepressant treatment, we investigated healthy subjects under subchronic treatment. To control for the effects of serotonergic versus dopaminergic/noradrenergic antidepressant treatment, we set up a randomized cross-over design with each subject receiving either paroxetine, or bupropion or placebo over the course of one week separated by sufficient washout phases. Stimulation with erotic video clips has already been demonstrated as a reliable tool to investigate brain regions related to sexual functioning (Redoute, *et al* 2000) and to contrast medication effects on these brain regions in patients suffering from depression (Kim, *et al* 2009). Under placebo, we expected to find activation in those brain regions reported to be active during erotic stimulation according to previous fMRI studies, i.e. the anterior cingulate cortex, lateral occipital cortex, insula, amygdala, hypothalamus, thalamus and the ventral striatum (Arnow, *et al* 2002; Ferretti, *et al* 2005; Moulier, *et al* 2006; Mouras 2004; Redoute, *et al* 2000; Walter, *et al* 2008a; Walter, *et al* 2008b). In line with previous studies of blunted ventral striatal activation under SSRIs (McCabe, *et al* 2010), paroxetine was expected to exert inhibitory effects on reward system activation, the latter being identified as specifically elicited by erotic stimulation as a primary reward (Walter, *et al* 2008a). By contrast, bupropion, as a dopamine reuptake inhibitor, was expected to enhance activation of the dopaminergic reward system as reported for the administration of L-dopa or dopamine agonists in healthy subjects (Pessiglione, *et al* 2006). SSRI-

related attenuation of ventral anterior cingulate cortex (ACC) and insula was expected from recent findings of similar effects of subchronic administration of citalopram on emotional anticipation in healthy subjects (Simmons, *et al* 2009).

MATERIALS AND METHODS

Subjects: 23 healthy male, heterosexual subjects (3 left-handed) were randomized to take placebo, bupropion and paroxetine at routine clinical doses for seven days each in a counterbalanced order. After each medication period these subjects were scheduled to take part in the fMRI experiment. From this sample, 18 subjects aged 23-34 years (mean 25.4, SD 2.9, 3 left-handed) completed all three fMRI sessions (see figure 1) and were therefore included in the final analyses. Two of the five subjects who did not enter the final analyses were excluded because data from one of the three fMRI session could not be considered due to technical problems (spiking, coil malfunction). Two further subjects were excluded from the analyses because blood levels of paroxetine were too low to be quantified rendering intake of the drug doubtful. One subject had to be excluded because the blood sample for the bupropion levels was lost. The mean plasma bupropion-level of included subjects was 59.9 ng/ml (SD 27.7), the mean plasma paroxetine-level was 28.1 ng/ml (SD 17.9). Blood samples were taken after each fMRI session, that is about three hours after drug intake. Plasma levels were assessed as an estimate of drug exposure and drug adherence. More precise pharmacological profiles would have meant taking more blood samples which, however, was not compatible with the present study design. Blood levels were not analyzed before completion of the whole study.

The study was approved by the local ethical review board of the University of Ulm. All volunteers gave written informed consent prior to the study in accordance with the Declaration of Helsinki. Each participant received a full medical evaluation including a

medical history, a physical examination, and a Structured Clinical Interview for DSM-IV Axis I Psychiatric Disorders (SCID) as well as laboratory blood tests and an electrocardiogram to exclude cardiac, renal or hepatic preconditions. Exclusion criteria were any current or past psychiatric or neurological illnesses, any serious general medical condition, use of illegal drugs and excessive consumption of caffeine or alcohol (>14 units/week). Subjects were also excluded for any significant baseline sexual dysfunction or sexual disorders (see supplementary materials for details). One subject took a single dose of acetaminophen, one a single dose of metamizole and one used a steroid inhaler for mild allergic asthma parallel to the study medication. Other than that, none of the subjects took any medication and none had taken any other medication within the week before the study. Subjects were asked to refrain from alcohol parallel to the study medication and from coffee on the day of the scans. Upon recruitment, subjects completed two self-report scales, the Center for Epidemiologic Studies Depression Scale, CES-D (Radloff 1977), German version: Allgemeine Depressions Skala/ADS, (Hautzinger and Bailer 1993) and a German version (Reinecke, *et al* 2006) of the Massachusetts General Hospital Sexual Function Questionnaire, MGH-SFQ (Labbate and Lare 2001). The MGH-SFQ is based on self-report and assesses sexual interest, sexual arousal, ability to achieve orgasm, ability to achieve and maintain an erection, and overall sexual satisfaction over the past month. The questionnaire was modified to reflect subjective sexual dysfunction only over the past week of medication.

Study design and procedures: The entire study was performed as a randomized double-blind placebo-controlled within-subject cross-over design (figure 1). Each subject was investigated on three different occasions, once under placebo (PLAC: gelatine capsule filled with mannitol powder), once under paroxetine (PAR: 20 mg,

identical capsule with pulverized paroxetine) and once under bupropion (BUP: 150 mg, identical capsule with bupropion) at intervals of at least fourteen days washout-time. For each treatment subjects were instructed to take one capsule each morning for seven days to reach steady state blood levels. SSRI related changes of sexual functioning have been reported after single doses concerning premature ejaculation (Patel and Hellstrom 2009) as well as after 8 days of intake concerning a broader spectrum of sexual functions including libido and sexual arousal (Dunn *et al* 2007). On the seventh day, subjects were scheduled for an fMRI scan two hours after intake of the last capsule.

Task and stimuli: In the scanner, a standard block design with prolonged visual stimulation using erotic and neutral video clips was used. Erotic video clips showed sexual interactions between one man and one or two women (petting, oral sex and vaginal intercourse) extracted from commercial adult films. The neutral video clips depicted men and women in emotionally neutral, non-erotic interactions (at a shop, at the airport). Nine video clips of each type were presented at a length of 20 sec each, separated by a 20 sec interstimulus interval with a white fixation cross shown on a black screen. Video clips were presented in a pseudo-randomized order with a maximum of two consecutive clips of the same type.

fMRI acquisition: A 3.0 Tesla Magnetom ALLEGRA Scanner (Siemens, Erlangen, Germany) equipped with a head coil was used to acquire T1 anatomical volume images (1x1x1 mm voxels) and functional magnetic resonance images. 23 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 0.75 mm gap resulting in a voxel size of 3x3x3.75 mm. Images were centered on basal structures of the brain

including subcortical regions of interest (basal ganglia and prefrontal regions). Functional images were recorded using T2*-sensitive gradient echo echo-planar imaging measuring changes in BOLD-contrast. 487 volumes were obtained during viewing of video clips at a TR of 1500 ms (TE 35 ms, flip angle 90°).

fMRI analysis: Image preprocessing and statistical analyses were carried out using Statistical Parametric Mapping (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK) with a random effects model for group analyses. Preprocessing of the individual functional scans included realignment to correct for motion artifacts, slice timing, spatial normalization to a standard template (Montreal Neurological Institute, MNI) and smoothing with an 8 mm full width at half maximum (FWHM) Gaussian kernel. Intrinsic autocorrelations were accounted for by AR(1) and low frequency drifts were removed via high pass filtering.

After preprocessing, first level analyses were performed for each subject. According to the general linear model we defined regressors to analyze each of the two types of video stimuli (erotic, non-erotic). Video blocks were modeled as timely extended events of 20 sec and convolved with the hemodynamic response function. The 6 realignment parameters modeling residual motion were also included in the individual models. The individual contrast images for the erotic and non-erotic condition were then included in a second level group analysis using an ANOVA model with condition (EROTIC/NON-EROTIC) as the first factor. Treatment (PLAC/BUP/PAR) was added as a second factor with three levels to test on significant interaction effects of medication on the contrast of erotic vs. non-erotic stimuli. Inference of significant treatment effects was computed using directed condition-by-treatment t-contrasts for pairwise differences between treatment levels. To account for the post-hoc character of these tests, their computation was inclusively masked by an omnibus F-test on

condition-by-treatment interactions within the 2x3 ANOVA. The statistical threshold for this mask was set to a value of $p < 0.005$ uncorrected to avoid false negative results due to overly strict thresholding. However, significant treatment effects were inferred only if results of the post-hoc t-contrasts survived a statistical threshold of $p < 0.05$ false discovery rate (FDR) corrected to account for multiple comparisons, and if clusters of significant voxels comprised at least 10 contiguously significant voxels. In a second step, a conservative omnibus F-test was applied thresholded at $p < 0.05$ with false discovery rate (FDR) corrections for multiple comparisons.

Neuropsychological testing and additional questionnaires: After scanning and blood sampling, subjects performed three simple reaction time tasks (subtests from the Testbattery for Attentional Performance, Zimmermann & Fimm, Psychologische Testsysteme, Herzogenrath, Germany): simple reaction to a visual stimulus (RT1), reaction to a visual stimulus after a warning tone (RT2), and divided attention (RT3), involving reaction to distinct visual and auditory stimuli at the same time. Reaction time tasks were applied to assess for general medication effects on attention and concentration as potential moderators of treatment effects. Subjects also completed the self-report questionnaires on side effects and sexual functioning (MGH-SFQ, for detailed description see supplements) during the past week on each occasion. Cumulative ratings on the MGH-SFQ ranged from 5 (minimal value: improvement of sexual functioning) over 10 (sexual functioning unchanged compared to normal) to 30 (maximal value: sexual functioning markedly impaired compared to normal). Ratings above 10 indicate subjectively impaired sexual functioning as compared to normal in the sense of subjective sexual dysfunction. Subjective side effects were additionally assessed in a medical interview with open questions and a structured part (UKU side effects scale, (Lingjaerde, *et al* 1987)) by one of the study physicians (BA or AS) on

each visit. Repeated-measures ANOVAs and post-hoc paired t-tests were applied to analyse reaction time and questionnaire results.

RESULTS

Questionnaires and neuropsychological tasks

Results from the ADS scale (mean: 6.9, SD 5.0) confirmed that none of the subjects suffered from depression at the time of the study.

56% of the subjects complained about side effects of any kind under placebo according to the UKU side effects scale. There were complaints over a wide range of different symptoms at a rate of 67% under bupropion and of 83% under paroxetine, without reaching significance when compared to placebo (ANOVA: $F(2,34)=2.58$, $p=0.09$). Particularly, subjective ratings of sedation did not differ (one-way ANOVA: $F(2,34)=2.06$, $p=0.14$) between treatments.

Upon enrolment subjectively rated sexual function as assessed by the mean cumulative score of the MGH-SFQ was 11.06 (SD 1.7). Above normal values (one-sample t-test, $p < 0.05$) of more than 2 points per subscale were observed only for question (5) concerning sexual satisfaction (mean = 2.67, SD = 1.0), indicating minimal sexual dissatisfaction. However, subjective MGH-SFQ ratings differed significantly between medications (repeated measurements ANOVA: $F(2,34)=5.05$, $p=0.01$) with average overall scores of 12.0 (SD 2.4) under placebo, 11.8 (SD 2.9) under bupropion and 14.6 (SD 4.3) under paroxetine (figure 2A). Post-hoc paired t-tests confirmed significantly higher overall scores under paroxetine as compared to placebo ($t(17)=2.58$, $p=0.02$) or bupropion ($t(17)=2.30$, $p=0.03$). No significant differences were observed when bupropion was compared against placebo. Analyzing rating scores of each of the 5 MGH-SFQ subscales revealed a significant interaction effect of factors treatment and scale (repeated measurements ANOVA:

$F(8,136)=2.41, p=0.02$) with increases of subjective ratings (paired t-tests, $p < 0.05$) concerning diminished sexual arousal and diminished ability to achieve orgasm under paroxetine as compared to both, enrolment and placebo ratings (figure 2B). It is of note, that the ability to get an erection was not affected by any of the treatments. Furthermore, none of the symptoms caused marked distress or interpersonal difficulty or otherwise justified a clinical diagnosis of sexual dysfunction.

Mean reaction times in the neuropsychological tests after scanning did not differ between treatments for the tests RT1 and RT2 (simple reaction without/with warning tone, one-way ANOVAs: RT1: $F(2,34)=0.11, p=0.89$; RT2: $F(2,34)=0.65, p=0.53$). For RT3, divided attention, we found a significant effect of medication ($F(2,34)=4.40, p=0.02$). Mean reaction times under placebo (mean 601.7 ms, SD 56.7) were significantly faster than under both drugs, bupropion (mean 629.3 ms, SD 52.0; $t(17)=2.46, p=0.02$) and paroxetine (mean 642.7ms, SD 69.8, $t(17)=3.11, p=0.006$). No significant difference was found for bupropion vs. paroxetine ($t(17)=0.78, p=0.45$).

fMRI results

Main effect of erotic stimulation under placebo: Contrasting erotic minus non-erotic visual stimulation under placebo revealed significantly ($p < 0.05$ FDR corrected) increased activations along the anterior cingulate cortex (ACC), in the amygdala, hypothalamus, ventral striatum, midbrain, lateral occipital cortex, precuneus and the fusiform gyrus.

Treatment effects: Significant results ($p < 0.05$, FDR corrected) of the directed post-hoc tests on pairwise differences between treatment levels are summarized in table 1. Compared to placebo, decreased activation under paroxetine was significant in

midbrain structures, the ventral striatum as well as in three different sections along the cingulate gyrus (sgACC, pgACC and aMCC). Comparing bupropion against placebo, only aMCC activation was decreased while the pMCC showed increased activity. Contrasting bupropion against paroxetine, increased activation was evident in the sub- and pregenual ACC as well as in the pMCC. Differential signals along the cingulate gyrus under the three different treatments are depicted in figure 3. Furthermore, bupropion was associated with increased activation compared to both, paroxetine and placebo, in various brain regions including the SLEA, ventrolateral and dorsomedian thalamus, parahippocampus, lateral orbitofrontal cortex and fusiform gyrus (table 1).

To test on the reliability of the inclusive mask ($p < 0.005$, uncorrected) used for the post-hoc testing above, the same omnibus F-test on treatment effects used to create the mask was replicated at a statistical threshold of $p < 0.05$, FDR corrected. This test revealed again significant effects in the midbrain, the sub- and pregenual ACC (sgACC and pgACC), the anterior and posterior mid-cingulate cortex (aMCC and pMCC), the left sublenticular extended amygdala (SLEA), the left ventral striatum, and the left parahippocampal area (see also table 1).

To further investigate drug effects on the fMRI signal, signal time courses were extracted from three prototypical regions (figure 4): 1) the midbrain which, like rostral ACC regions, showed decreased activations under paroxetine as compared to placebo and bupropion, 2) the extended amygdala as a representative brain region for the network with increased activation under bupropion 3) the aMCC as the only brain region with decreased activation under both drugs compared to placebo. Paired t-tests of differences in signal time courses at single time points indicated prolonged differential effects in midbrain and particularly the extended amygdala under

bupropion as compared to placebo. Differential effects in all three brain regions were most pronounced in the first part of the video stimulation.

Correlation analyses: Whole brain analyses did not reveal any significant correlations between functional activations and subjective ratings, reaction time data or medication blood levels (even when tested at different, rather liberal thresholds). However, a significant correlation (figure 3) was observed between total MGH-SFQ score and averaged parameter estimates obtained from the pMCC region (voxels significant in the omnibus F-test at $p < 0.05$ corrected). This region had been selected for further investigation based on previous literature showing correlations between brain activation in the mid-cingulate cortex with behavioural measures of sexual functioning (Redoute, *et al* 2000, Moulier, *et al* 2006, Georgiadis, *et al* 2010). The more the brain activation decreased under paroxetine compared to placebo, the more overall ratings of sexual dysfunction (paroxetine minus placebo) increased ($r = 0.42$; $p = 0.041$). Furthermore, individual blood levels of paroxetine were also significantly ($r = 0.40$, $p = 0.050$) correlated with the differential neural activation (figure 5). No further significant correlations with rating scores, blood levels, or reaction times were observed in other cingulate areas significant in the above interaction analysis (particularly, not the aMCC). Computation of meaningful correlations between brain activations and behavioural ratings under bupropion was not possible due to the small variance of the rating scores with zero differences of ratings (placebo minus bupropion) in half of the subjects.

DISCUSSION

We investigated the effects of one week administration of the SSRI paroxetine and the dopamine and norepinephrine reuptake inhibitor bupropion in a double-blind placebo-controlled cross-over design in healthy male volunteers. We observed increased subjective ratings of sexual dysfunction under paroxetine compared to placebo and bupropion. Specifically, subjective sexual arousal and the ability to achieve orgasm were significantly impaired under paroxetine while the ability to get an erection, ratings of sexual interest and sexual satisfaction were not significantly altered under this drug.

Behavioural effects were accompanied by specific functional alterations in brain regions previously associated with sexual function in humans. Brain activation related to dynamic visual erotic stimulation under medication revealed antipodal results in two different networks. Compared against placebo and bupropion, paroxetine attenuated brain activation in neural structures comprising the midbrain, the nucleus accumbens, and sub- and pregenual anterior cingulate cortex. By contrast, bupropion led to an enhanced and prolonged activation in the parahippocampus, the amygdala (SLEA), thalamus and fusiform gyrus when compared against placebo or paroxetine. Bupropion and paroxetine were associated with reduced activation within the anterior mid-cingulate cortex (MCC) and activation of the posterior MCC upon erotic stimulation was increased under bupropion. Individual parameters of decreased neural activation in the pMCC under paroxetine correlated with individually increased overall ratings of sexual dysfunction and with individual drug concentrations obtained from plasma samples.

Blunted anterior cingulate activation under Paroxetine

According to the four-region neurobiological model of human cingulate cortex architecture (Palomero-Gallagher, *et al* 2009; Vogt, *et al* 2003), the four cingulate foci with differential medication effects are related to areas along the cingulate gyrus with distinct cytoarchitectonic and functional properties. This model postulates that subgenual ACC (sgACC) and pregenual ACC (pgACC) are reciprocally connected with the amygdala and are involved in emotional and autonomic processing. The aMCC is associated with reward processing and is active during fear. The pMCC has been related to error detection and is not primarily activated by simple emotions (Phan, *et al* 2002; Vogt *et al* 2003). Paroxetine led to decreased fMRI activations in all of these regions along the cingulate gyrus. Particularly sgACC with its high density of 5-HT_{1A} receptors in Brodman area 25 being the primary target of SSRI treatment (Haddjeri, *et al* 1998), has been postulated to be critical for understanding effects of antidepressant therapy (Ressler and Mayberg 2007). Decreased sgACC activation under paroxetine is in line with findings of treatment effects in depression (Mayberg, *et al* 2005), and with findings of another fMRI study investigating the effects of subchronic SSRI administration in healthy subjects using emotional faces (Arce, *et al* 2008). This may point to a receptor specific but functionally more general SSRI effect independent of the type of stimulus material.

Like the sgACC, also the more rostral pgACC has been found to be modulated by subchronic escitalopram administration upon aversive stimuli (Simmons, *et al* 2009). Activity of the pgACC has also been postulated to correlate with subjective sexual intensity and its hedonic value (Walter, *et al* 2008a) and was identified as a brain region specifically coding the interaction of sexual intensity and emotional value of a stimulus. In Redoute's model of sexual arousal, activation of rostral ACC, comprising subgenual and pregenual parts, has been ascribed to the autonomic component of

sexual behaviour mediating physiological readiness (Redoute, *et al* 2000). It is of note though, that sgACC and pgACC have also been characterized as brain regions coding emotional contents in a wider context (Beckmann, *et al* 2009), of which autonomic reactions and self-referential processes may represent certain subsets. This suggests that paroxetine may lead to an impaired responsiveness of brain regions previously ascribed to the processing of emotional and autonomic functions that are associated with but also reach beyond the pure autonomic triggering of sexual arousal. Our observation that activation of the hypothalamus as a key autonomic component of sexual arousal (Arnou, *et al* 2002; Ferretti, *et al* 2005) did not show an effect of medication at the predefined statistical thresholds might be in line with this claim, although interpretation of this null result should be treated with caution.

A rather more specific role in the mediation of sexual dysfunction can be attributed to the mid-cingulate cortex. In a PET study using erotic stimulation, activation of this brain region was found to correlate with penile tumescence (Redoute, *et al* 2000), and a recent study using fMRI could replicate this finding by demonstrating that the activation of the MCC correlated with penile tumescence in the early phase of sexual arousal and preceded physiological reactions (Moulier, *et al* 2006). Georgiadis, *et al* (2010) reported blood flow changes in MCC and lateral hypothalamus that correlated with penis stimulation and perceived sexual arousal. In a recent study comparing effects of mirtazapine versus SSRIs (paroxetine and fluoxetine) during fMRI of dynamic erotic stimulation, patients with major depression showed decreased activation under SSRIs (Kim, *et al* 2009) in cingulate areas in close proximity to the junction of the pMCC and posterior cingulate cortex. This pattern of results together with the present observation of decreased pMCC activation under paroxetine

correlating with increased subjective sexual dysfunction supports a rather specific role of the MCC in mediating sexual functioning which is affected by SSRIs.

SSRI-related alteration of midbrain and ventral striatum activation

SSRI-dependent modulations of activity in midbrain and ventral striatum align with recent evidence indicating that the functioning of these brain regions is tuned by serotonin (Kranz, *et al* 2010). The positive activation of these regions upon erotic stimulation in the sense of a primary reward under placebo adds to the accepted interpretation of these brain regions as part of the dopaminergic reward system (Kranz, *et al* 2010). Despite of the inconsistencies concerning the general role of serotonin in reward processing with reports on reward increasing and on reward decreasing effects of serotonin, the latter results seem more prevalent. Particularly, diminished sexual desire and pleasure under SSRIs have been associated with the inhibition of dopaminergic reward circuits (Kranz, *et al* 2010). This inhibition of dopamine transmission by SSRIs has been shown to be mediated by 5-HT₂ receptors (Alex and Pehek 2007), and research in animals demonstrated inhibitory effects of serotonin in the lateral hypothalamus upon sexual behaviour (Lorrain, *et al* 1997) and on dopamine release in the ventral striatum (Lorrain, *et al* 1999). A 5-HT_{2A} receptor polymorphism in humans has been reported to modulate sexual arousal under SSRIs in patients with depression (Bishop, *et al* 2006). SSRIs have also been reported to be less effective in reducing reward-related symptoms of depression like loss of interest and motivation (Price, *et al* 2009). By contrast, greater positive effects in this respect have been ascribed to antidepressants with enhancing effects on catecholamine levels (Nutt, *et al* 2007) like bupropion. Accordingly, paroxetine attenuated activation in brain regions that are associated with the rewarding, motivational aspects of sexual behaviour.

Activity increases of subcortical regions under bupropion

Consistent with the proposed opponency of dopamine and serotonin (Daw, *et al* 2002), effects under bupropion as a dopamine and norepinephrine reuptake inhibitor were almost contrary to the SSRI paroxetine in midbrain and ventral striatal areas. Furthermore, differential effects under bupropion were found over a prolonged time course during video stimulation even when compared to placebo. Modulation of ventral striatal activation by the subjectively perceived sexual intensity of a stimulus has been described before (Walter, *et al* 2008a), and changes in activity of the ventral striatum have been reported in various contexts of a rewarding sexual stimulation (Hamann, *et al* 2004; Stark, *et al* 2005). Dopamine agonists have been shown to induce penile erection in animals and humans (Carson 2007) and have been suggested as promising agents for the treatment of sexual dysfunction (Albersen, *et al*). Dopamine agonists have further been related to hypersexuality in the treatment of parkinson's disease (for review see (Voon, *et al* 2009)). Impaired recruitment of the midbrain was suggested as a correlate of decreased sexual interest in an fMRI study on pedophilia (Walter, *et al* 2007). These findings support the interpretation that increased activation of the ventral striatum and the midbrain as dopaminergic brain regions may represent a neural correlate of increased responsiveness to sexual stimuli triggered by the dopamine agonistic properties of bupropion. This effect may also explain the concomitantly increased activation of the thalamus, parahippocampus and SLEA, since these structures are heavily interconnected. According to animal studies, the mediodorsal thalamus has subcortical connections to the ventral tegmental area and the midbrain's periaqueductal grey, to the amygdala, the SLEA and the hypothalamus (Erickson, *et al* 2004; Ongur and Price 2000). The thalamus and amygdala have already been related to the emotional dimension of sexual arousal (Ferretti, *et al* 2005; Redoute, *et*

al 2000), and particularly the mediodorsal proportion of the thalamus was found active for both, erotic and emotional stimulation (Walter, *et al* 2008b). Recently, a region around the SLEA with similar stereotactic coordinates as in the present study was reported to show the strongest blood flow changes when penile erection and perceived sexual arousal peaked and was suggested to potentially relate to orgasmic pleasure (Georgiadis, *et al* 2010). Together with cortical regions like the MCC, posterior cingulate and anterior insula, the network of these subcortical regions has been referred to as the 'salience network', integrating functions of conflict monitoring, autonomic functions and reward-processing (Seeley, *et al* 2007). Activation in pMCC was increased under bupropion as the cortical part of the network which has been suggested to represent the approach component of sexual arousal (Redoute, *et al* 2000).

Unidirectional effects of both antidepressants

Despite opposite effects in extended networks, both drugs led to a decrease of activation compared to placebo in one subregion of the cingulate cortex, the aMCC. Since both drugs otherwise led to differential effects upon processing erotic stimulation this unidirectional effect does not integrate in a stimulation-bound interpretation. Alternatively one might assume that the activation decrease in the aMCC may reflect an alteration of neural functioning not necessarily interfering with sexual functioning. This might be supported by the observation that both drugs also led to unidirectional behavioural effects with impaired performance on the divided attention task. This task puts the subject in a dual-task situation where task-set processes have been suggested to constitute a core resource of limited capacity shared across different tasks (Dosenbach, *et al* 2006). Midcingulate activation in the vicinity of the aMCC focus was suggested to be part of a frontoparietal network

exerting active and adaptive online control helping to direct selective attention (Dosenbach, *et al* 2007). Although we could not observe substantial across subjects correlations between reaction time and decreased activity of the aMCC, one might speculate that impaired divided attention and decreased aMCC activation may both result from an impaired task set processing under both drugs presumably via different receptor pathways. Interactions of dopamine receptors with NMDA receptors (Chen and Yang 2002) with their particularly high density in aMCC (but not other ACC subregions; Palomero-Gallagher, *et al* 2009) could help to explain the differential effects of bupropion on aMCC and pMCC.

Conclusion

Enhancement of serotonergic and noradrenergic/dopaminergic neurotransmission led to differential effects in the subjective experiences of sexual functioning accompanied by opposite drug effects on local neural activities upon erotic stimulation. Overall, most brain activations elicited by erotic movies were reduced under paroxetine but not under bupropion. Particularly, under paroxetine neural activities decreased in the ventral striatum, midbrain and distinct areas along the cingulate gyrus. These regions have already been described by others to mediate aspects of motivational and emotional processes related to sexual behaviour although their specific role awaits further research. The combined noradrenalin/dopamine reuptake inhibitor bupropion showed opposite fMRI effects and was associated with a prolonged and increased activation of brain regions previously related to the processing of rewarding and salient stimuli. If clinically possible, this suggests enhancement of dopaminergic transmission as a plausible add-on treatment to counteract the side effects of anti-depressant SSRI medication on sexual functioning which impose a high risk on medication adherence and hence therapeutic success.

DISCLOSURE/CONFLICT OF INTEREST

All authors declare that they have received no financial support or compensation from any individual or corporate entity over the past 3 years for research or professional service, except for income received from their primary employers, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

ACKNOWLEDGMENTS

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TITLES AND LEGENDS TO FIGURES

Figure 1: Study design. 6 subjects were assigned to each of the three randomization arms.

Figure 2: (A) Group averaged cumulative rating scores obtained from the 5-item Massachusetts General Hospital Sexual Function Questionnaire MGH SFQ. Overall subjective sexual dysfunction was significantly (*: $p < 0.05$) increased under paroxetine during the past week. A. minimal cumulative score of 5 indicates increased sexual interest as compared to normal; 'average' cumulative score of 10 indicates no change in sexual functioning compared to before (dashed black line); scores above 10 indicate decreased sexual functioning; the maximal cumulative score of 30 has the meaning of no sexual interest. **(B).** Group averaged ratings for each subscale. MGH-SFQ subscales ratings indicate diminished (*: $p < 0.05$) ability to get sexually aroused and to achieve orgasm under paroxetine as compared to enrolment, placebo (arousal and orgasm) and bupropion (orgasm only).

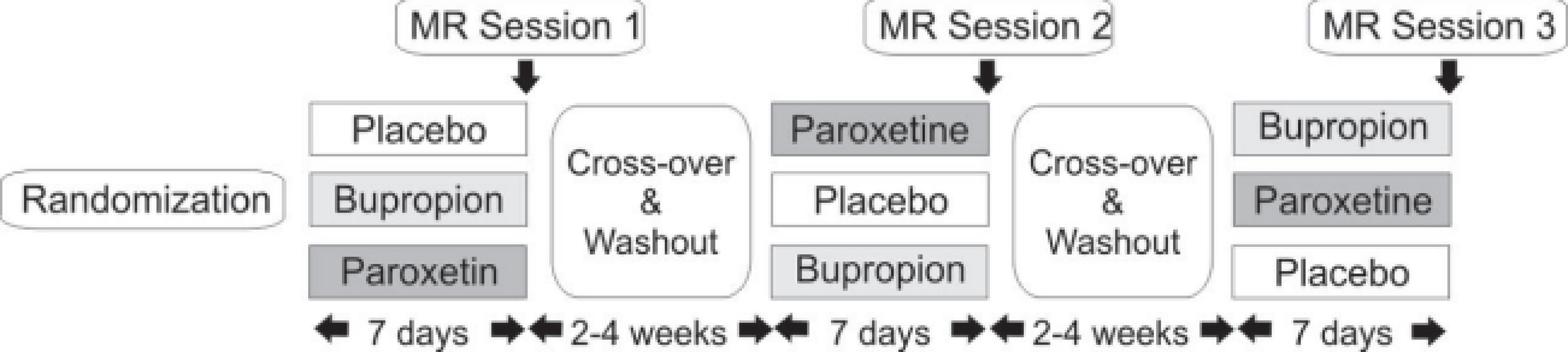
Figure 3: Significant treatment effects ($p < 0.05$ FDR corrected) along the anterior cingulate gyrus as revealed by an appropriate omnibus F-test on treatment effects for placebo, bupropion and paroxetine (for demonstration purposes the threshold was lowered to $p < 0.005$ uncorrected). Parameter estimates of modelled effects were extracted from the peak voxel of each cluster i.e. the subgenual anterior cingulate cortex, sgACC, the pregenual anterior cingulate cortex, pgACC, the anterior mid-cingulate cortex, aMCC and the posterior mid-cingulate cortex, pMCC. Activation decreased under paroxetine as compared

to placebo and bupropion in sgACC, pgACC and pMCC. In aMCC activation decreased under both drugs compared to placebo.

Figure 4: Statistical parametric maps (SPMs) and fMRI signal time courses extracted from three prototypical regions significantly associated with erotic visual stimulation with differential drug effects in an omnibus F-test ($p < 0.05$ FDR corrected): midbrain with decreased activation under paroxetine, sublenticular extended amygdala (SLEA) with increased and prolonged activation under bupropion and decreased activation under paroxetine; anterior midcingulate cortex (aMCC) with decreased activation under both drugs compared to placebo. The depicted SPMs are thresholded at $p < 0.005$ uncorrected for demonstration purposes. Mean 1st eigenvariate values were extracted from the clusters for each subject and then averaged.

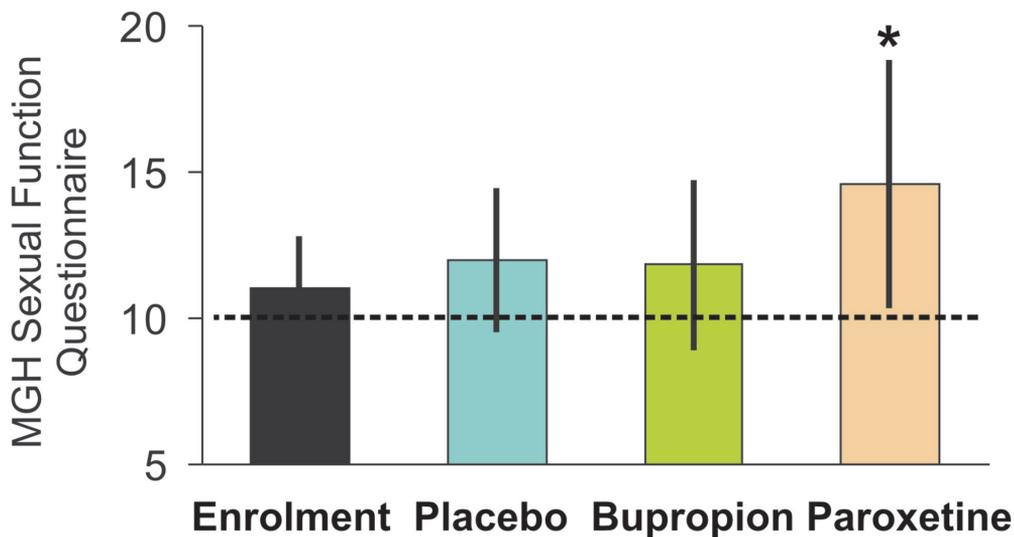
*: significant difference at $p < 0.05$ in a paired t-test of the fMRI signal at each time point.

Figure 5: Significant ($p < 0.05$) correlations of fMRI activation in the pMCC region of interest (parameter estimates: placebo > paroxetine) with **(A)** increases in ratings of subjective sexual dysfunction under paroxetine relative to placebo and **(B)** with paroxetine blood levels.

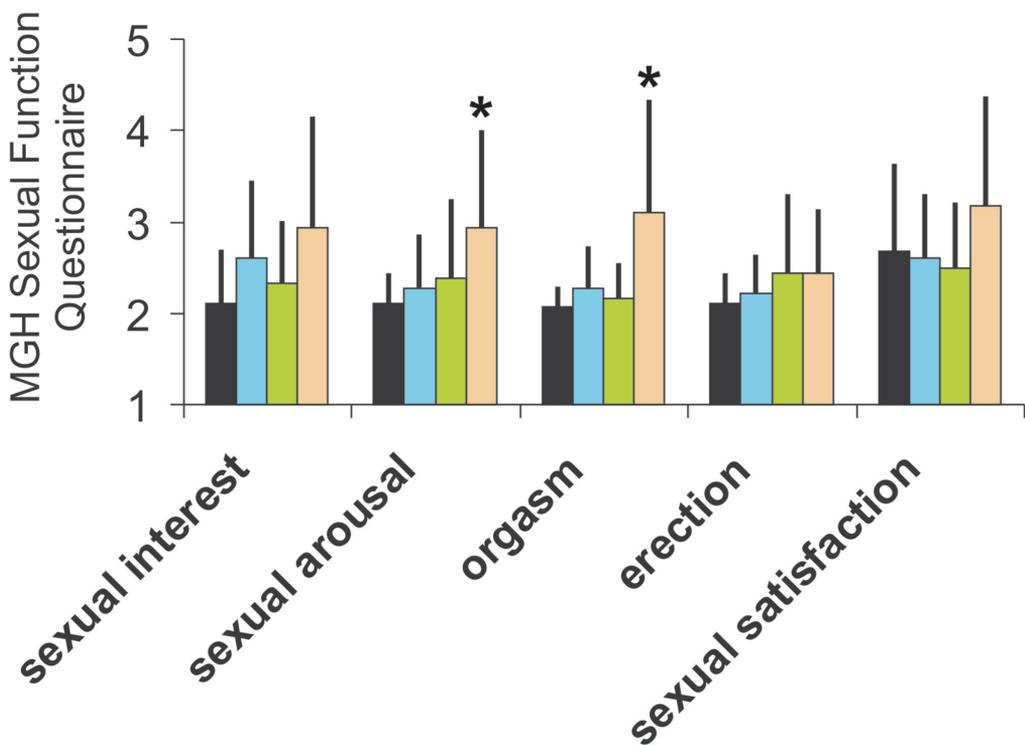


A

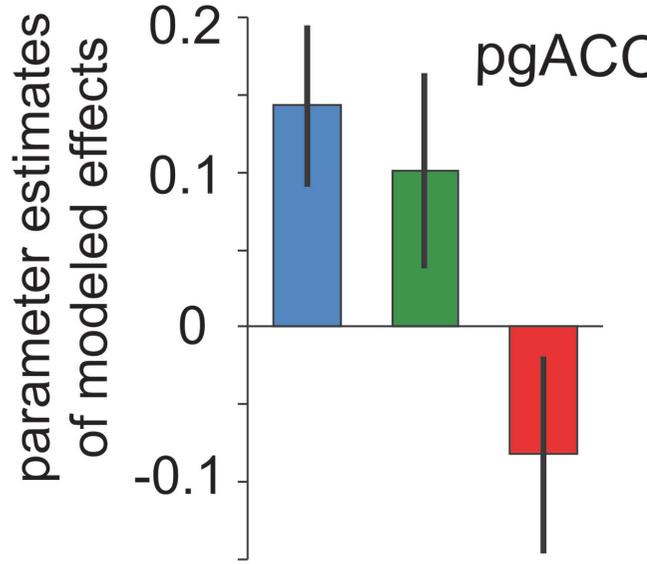
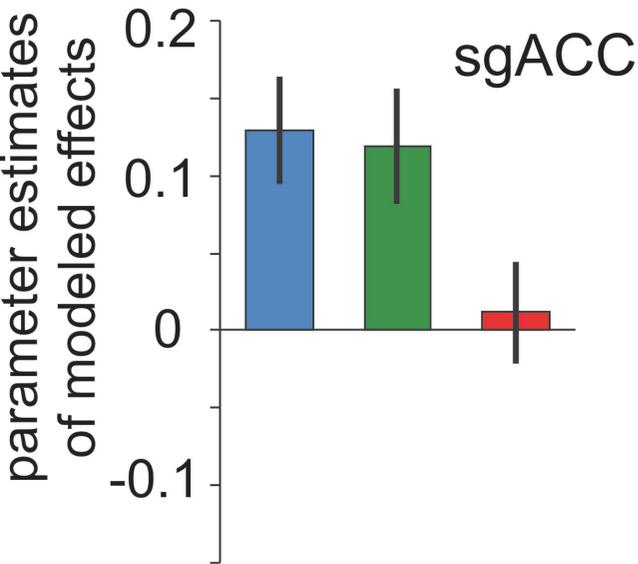
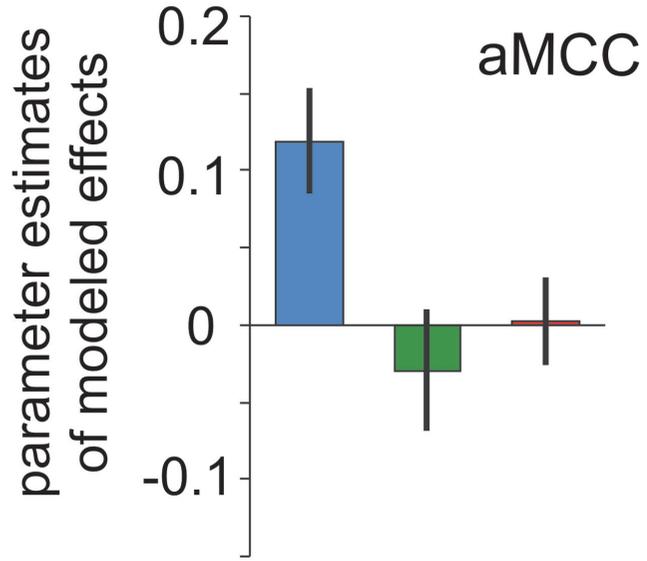
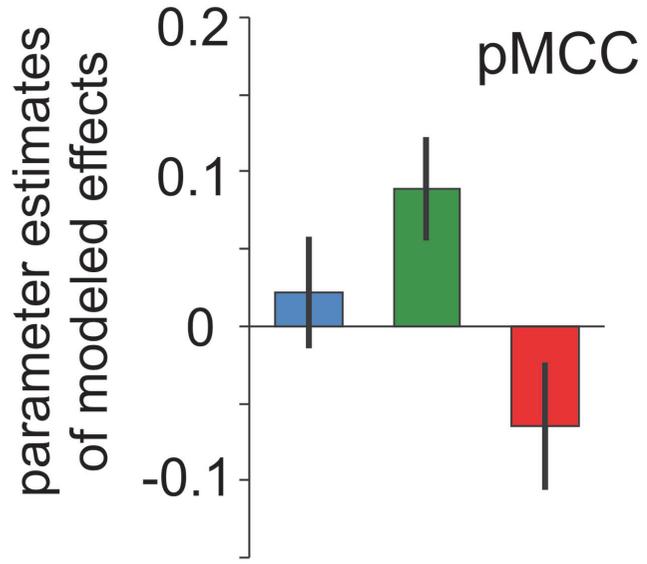
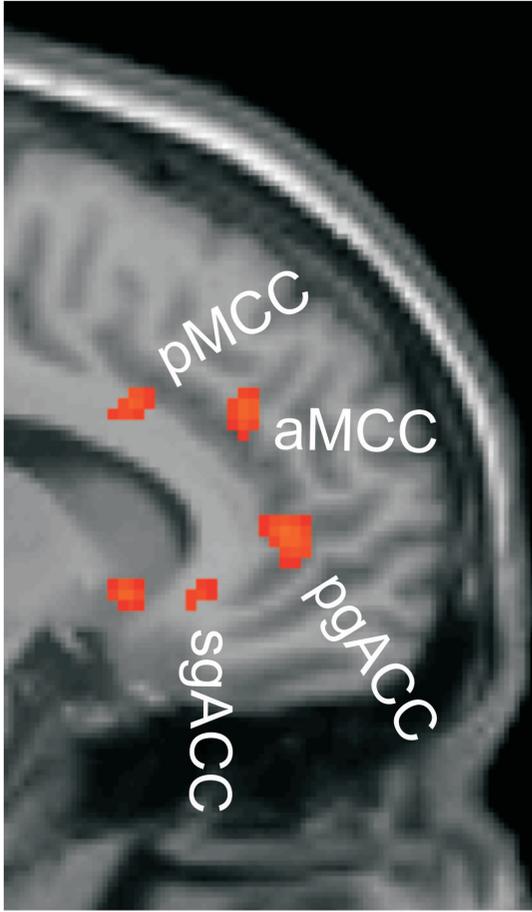
Cumulative ratings of subjective sexual dysfunction

**B**

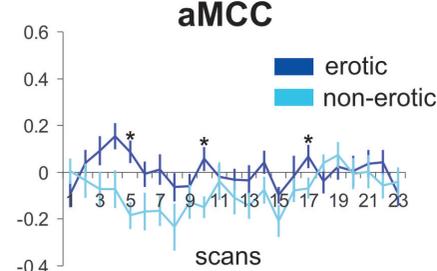
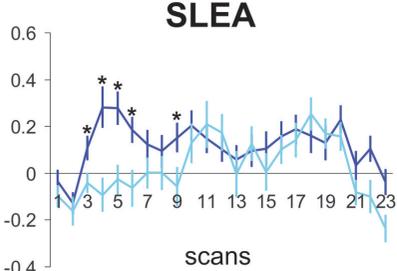
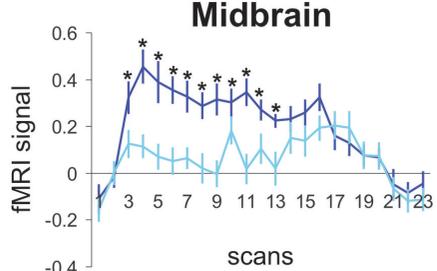
Subscales ratings of subjective sexual dysfunction



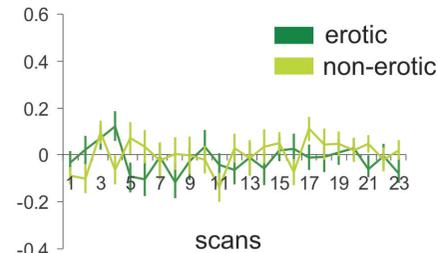
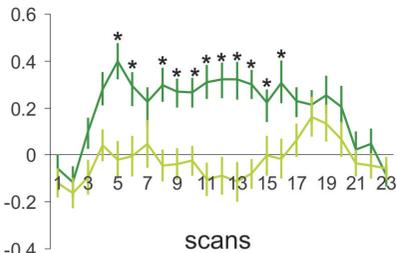
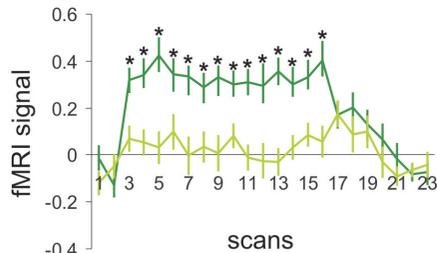
- Placebo
- Bupropion
- Paroxetine



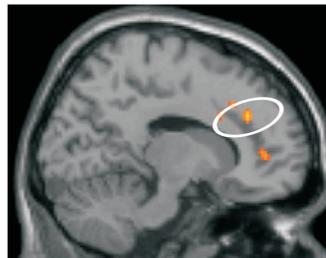
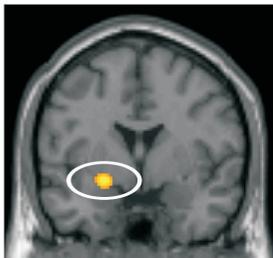
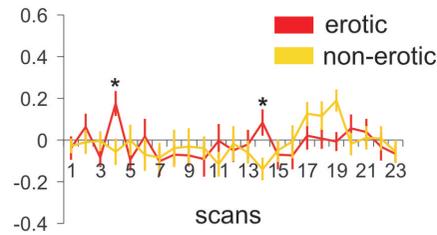
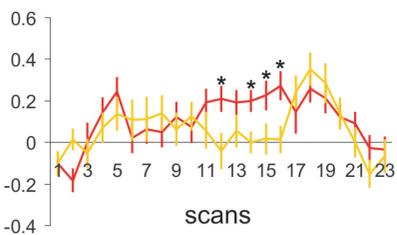
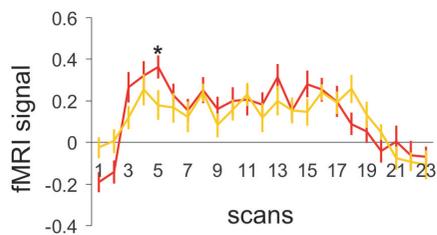
Placebo



Bupropion



Paroxetine



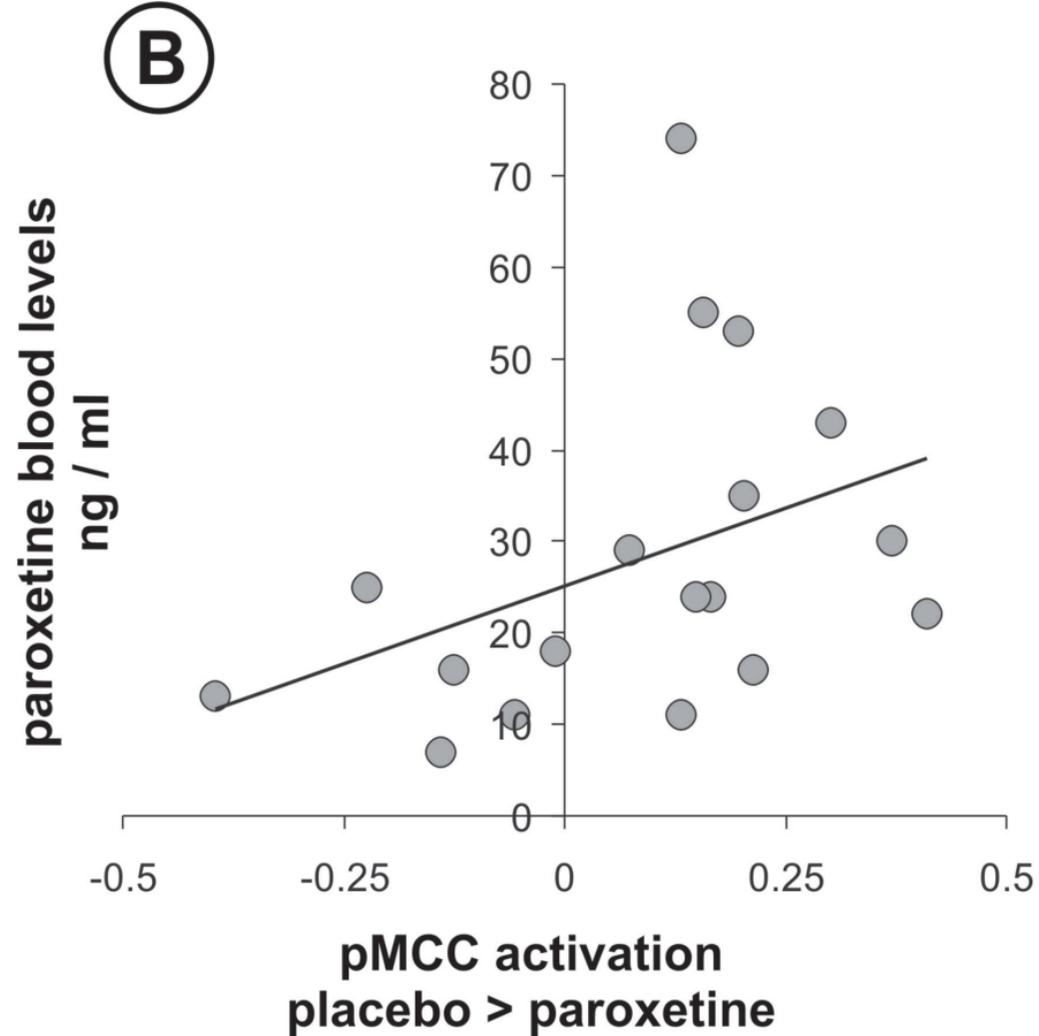
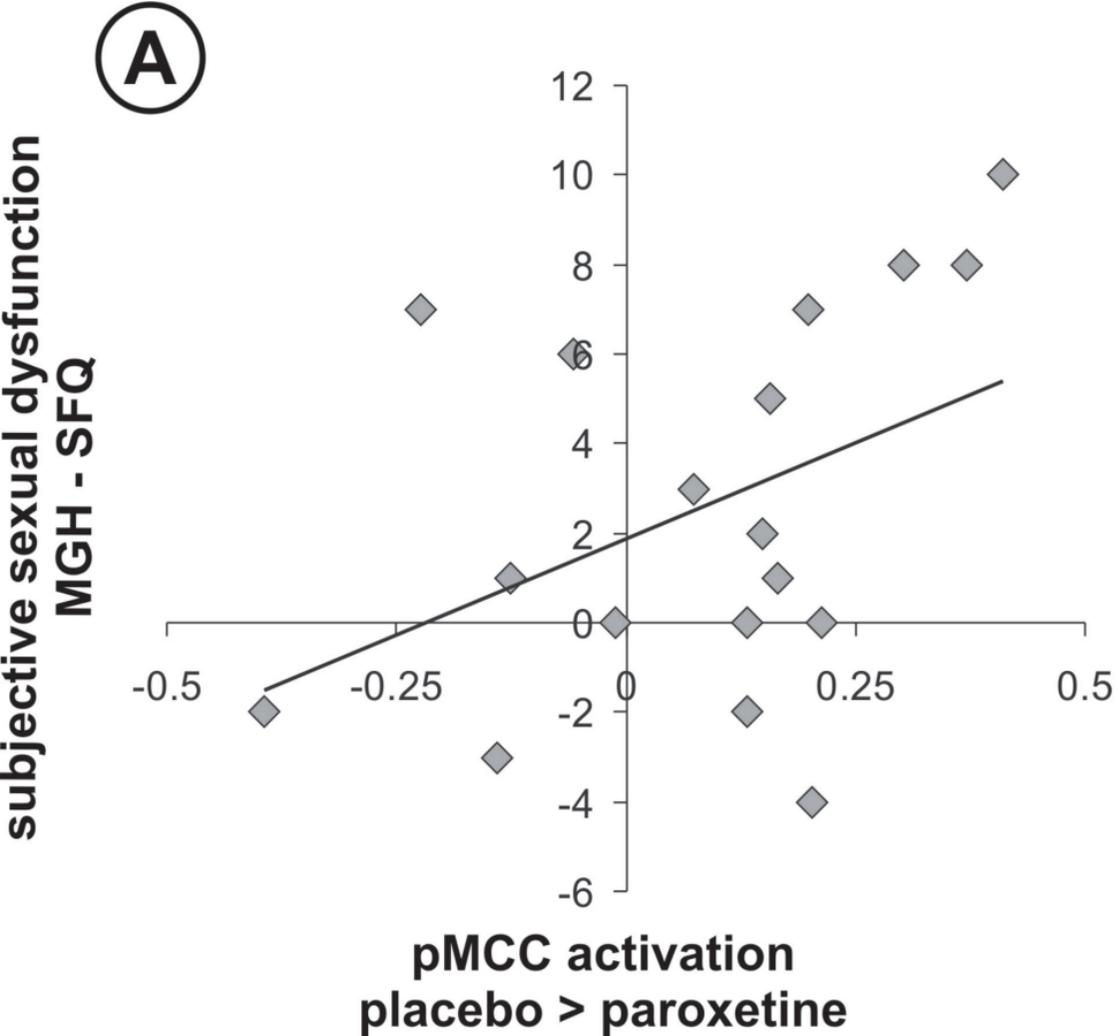


Table 1: Significant condition-by-treatment interaction effects

	Placebo > Paroxetine			Placebo > Bupropion			Bupropion > Placebo			Bupropion > Paroxetine		
	Z	NV	Peak Coord.	Z	NV	Peak Coord.	Z	NV	Peak Coord.	Z	NV	Peak Coord.
Video: erotic vs. non-erotic stimuli	x/y/z			x/y/z			x/y/z			x/y/z		
Cingulate Cortex												
Subgenual ACC*	4.21	46	-12/32/-6							3.61	37	-14/32/-6
Pregenual ACC*	4.08	104	14/46/4							2.95	94	12/44/6
Anterior MCC*	3.37	30	14/32/32	4.67	90	16/34/30						
Posterior MCC*							3.30	102	16/20/34	4.43	119	16/24/36
Subcortical structures												
Midbrain*	4.72	150	-4/-24/-14							5.29	485	-4/-24/-14
Ventral striatum, right	3.04	16	6/14/-6							3.66	30	10/12/-6
Ventral striatum, left										4.24	650	-18/12/-6
Extended amygdala, left*							4.82	650	-22/0/-10	4.20	#	-22/0/-10
Extended amygdala, right							3.29	125	26/-8/-12	4.16	137	26/-6/-10
Ventrolateral Thalamus, right							3.64	44	18/-14/6	3.22	44	12/-14/2
Ventrolateral Thalamus, left*							3.80	285	-22/-14/14	4.33	299	-22/-14/14
Dorsomedian Thalamus							2.43	#	-6/-12/8	3.74	#	-4/-10/6
Cortical activations												
Lateral orbital FC* (BA11/47)							3.64	58	-36/40/-8	4.04	61	-34/36/-6
Medial FC, BA 6							3.70	140	52/0/30	3.60	129	56/6/34
Medial/superior temporal Gyrus* (BA 39/40)							3.79	268	38/-56/30	4.55	271	36/-58/28
Fusiform gyrus, left (BA 19/37)							3.50	44	-34/-62/-4	3.79	44	-36/-62/-6
Fusiform gyrus, right* (BA 19/37)										3.76	56	38/-40/-12
Parahippocampus, left*							3.58	450	-22/-34/-6	4.38	450	-20/-34/-6
Parahippocampus, right							4.00	142	42/-20/-14	2.85	61	40/-22/-10
Parahippocampus, right							3.99	56	36/-38/-12			
Cerebellum, left*							3.85	524	-42/-56/-24	4.05	521	-42/-56/-24
Cerebellum*							3.77	#	2/-74/-28	4.05	#	-8/-70/-18
Cerebellum, right							3.35	22	22/-48/-18	3.00	22	18/-50/-18

The table shows results of post-hoc testing of pairwise differences between treatments at $p < 0.05$ FDR corrected. Post-hoc testing was locally constrained to voxels surviving a threshold of $p < 0.005$ in the 2x3 ANOVA with factors condition (erotic, non-erotic) and treatment. Brain areas with significant interaction effects in the 2x3 ANOVA even at the more conservative threshold of $p < 0.05$, FDR corrected are marked with (*). No significant interactions were observed for Paroxetine > Placebo or Paroxetine > Bupropion.

#: activation is part of cluster above; Z: z-score; NV: number of contiguously significant voxels; peak coordinates of clusters are are MNI (Montreal Neurological Institute) normalized stereotactic coordinates: -x: left from the anterior commissure (AC); -y: posterior from AC; -z: inferior from AC. ACC: anterior cingulate cortex; MCC: midcingulate cortex; FC: frontal cortex; BA: Brodman area