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Escitalopram attenuates posterior cingulate activity during self evaluation in healthy volunteers

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Abstract

Medial cortex is critically involved in self-referential processing. Little is known about how SSRIs affect medial cortical activity during self-assessment. We hypothesized that 3 week oral administration of escitalopram 10mg per day would alter activity related to self-referential processing in medial cortex. Fifteen healthy females performed a self-assessment task during fMRI on two occasions – once after 3 weeks of placebo and once at the end of 3 weeks of escitalopram. Task conditions involved responding “yes” or “no” to whether various positive and negative adjectives described the subject (i.e., “self” evaluation trials) or the subject’s best friend (i.e., “other” evaluation trials), whereas the comparison condition involved responding whether the valence of various adjectives was positive or negative (i.e., “word” evaluation trials). Behaviorally after escitalopram, subjects less frequently endorsed that negative adjectives described themselves. Three main neuroimaging results were observed: (1) increased activation in medial prefrontal cortex and posterior cingulate related to self minus word evaluation trials, (2) increased activation in posterior cingulate related to escitalopram minus placebo for self and word evaluation trials, (3) drug by task interactions in the insula, cerebellum and prefrontal cortex. These results show that SSRIs change medial cortical activity and may alter self-evaluation.

Keywords

SSRI; medial cortex; fMRI; self; cingulate; emotion processing

1. Introduction

Reflection on one’s internal feeling state is important for adaptive emotional experiences. A network of medial cortical structures is activated during self-referential processing (Fossati et al., 2003; Northoff et al., 2006). Self-referential processing of emotional words activates medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and precuneus (Yoshimura et al., 2009a)-regions that are critically involved in self generated emotional feelings and autobiographical memory (D’Argembeau et al., 2008; Gusnard et al., 2001; Northoff et al.,

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2006). Medial cortical structures are also activated when individuals are “at rest” during neuroimaging experiments (Raichle et al., 2001). Some have speculated that this activation occurs because subjects are in fact not “at rest”, but rather are highly focused on autobiographical thoughts and memories (Mazoyer et al., 2001; Gusnard et al., 2001).

Hyperactivity of medial cortical circuitry has been observed in psychiatric disorders such as major depressive disorder (MDD) (Kennedy et al., 2001; Mayberg et al., 1999). Recent evidence shows that MDD individuals show hyperactivity in the mPFC during self-referential processing of negative words (Yoshimura et al., 2009b). Altered medial cortical activity in MDD may reflect an impaired ability to disengage from negative self referential emotion processing in this disorder (Ellenbogen et al., 2002; Lyubomirsky et al., 1998; Matthews et al., 2009; Siegle et al., 2002; Wenzlaff, 1998) and could be related to dysregulated serotonin function. The anterior medial cortex (i.e., mPFC and anterior cingulate cortex (ACC)) may be differentially activated when individuals engage specifically in self-referential processing related to their hopes and aspirations, whereas the posterior medial cortex (i.e., PCC and precuneus) may be differentially activated when individuals engage specifically in self-referential processing related to their duties and obligations (Grimm et al., 2009; Johnson et al., 2009). MDD individuals also show dysregulated activity of cortical regions including dorsolateral prefrontal cortex (DLPFC), insula, ventral striatum and thalamus during self-referential processing (Grimm et al., 2009; Lemogne et al., 2009a).

The effects of serotonergic drugs on resting brain activity in medial cortex have been previously investigated using PET. Acute administration of the SSRI citalopram (40mg of IV citalopram administered over 60 min on two consecutive days) was associated with decreased metabolism in the precuneus and PCC in healthy volunteers during resting PET (Smith et al., 2009). A related study showed that chronic (i.e., 12 week) administration of the SSRI escitalopram led to a significant reduction in the 5-HT_{1A} receptor binding potential in the subgenual cingulate and PCC in individuals with anxiety disorders during resting PET (Spindelegger and Holik, 2008). Taken together, this evidence suggests that self referential processing engages the anterior and posterior medial cortex and administration of SSRIs leads to decreased resting activity of this circuitry. However, little is known about the effects of SSRI administration on functional brain activity during performance of a task which specifically engages neural circuitry involved in self referential processing.

The purpose of this study was to use blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to investigate the degree to which administration of an SSRI would affect activity within the anterior and posterior medial cortex when individuals engaged in self referential processing. Escitalopram was chosen because it is a widely used, well tolerated, pharmacologically selective SSRI. We hypothesized that 3 weeks of escitalopram administration would decrease functional activity in the medial cortex during self referential processing. Such a finding would advance understanding of normal self referential processing, and potentially have important implications for both the treatment of psychiatric illnesses such as MDD, and for the use of self-referential paradigms to examine the effects of novel antidepressant therapies.

2. Materials and Methods

2.1. Subjects

Fifteen healthy, nonsmoking females [age range 19 to 27 years (mean $\pm$ SD= 22.3 $\pm$ 2.3 years) with 11 to 17 years of education (mean $\pm$ SD= 15.5 $\pm$ 1.8 years)] provided written informed consent and were paid for their participation in this study, which was approved by the University of California San Diego Human Research Protection Program. Participants had no current or lifetime history of major depression or other Axis I psychiatric disorders, and no

major medical problems as determined by medical history and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (First, 1997). Subjects had no lifetime history of drug or alcohol dependence, no history of drug or alcohol abuse within 30 days of the study, and no lifetime history of previously taking benzodiazepines, SSRIs, monoamine oxidase inhibitors (MAOIs), or neuroleptics. All participants had a negative urine drug screen at baseline. electrocardiogram and routine laboratory blood tests, which included a complete blood count, electrolytes, and liver function tests, were within normal limits.

2.2. Study design

Once eligibility was determined and informed written consent was obtained, each subject was randomized to either the escitalopram first or placebo first group. All subjects received both placebo and escitalopram in a randomized, cross-over, double-blind design (see Figure 1). After randomization, individuals completed phase 1 during which they took either escitalopram (i.e., 5 mg/day for the first 3 days, then 10 mg/day for 18 days) or placebo (i.e., the placebo was an empty capsule manufactured by the UCSD pharmacy to match the capsules containing active drug) orally each morning. Escitalopram and placebo were administered in identical, capsular form. Following phase 1, all subjects completed several self-report questionnaires, including the State-Trait Anxiety Inventory (STAI-S) (Spielberger, 1983), Beck Depression Inventory (BDI) (Beck et al., 1961), Social Interaction Anxiety Scale (SIAS) (Mattick and Clarke, 1998), and the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983), and performed a self referential processing task (described below) during fMRI scan 1.

Subjects then completed a 14-28 day “wash-out” period during which individuals in the placebo first group continued to receive placebo for 3 days then discontinued the placebo, and subjects in the escitalopram first group took a reduced dose (i.e., 5 mg/day) of escitalopram for 3 days then discontinued escitalopram. Following the “wash-out” period was phase 2, which was identical to phase 1 but involved administration of whichever drug (escitalopram or placebo) had not been administered in phase 1. Four paired t-tests were performed using SPSS 14 software (Chicago, IL) to examine differences in scores on the STAI-S, BDI, SIAS and BSI between scan 1 and scan 2, i.e., before and after medication (either placebo or escitalopram).

2.3. Task

Each subject performed a self referential processing task during two separate fMRI sessions (see Figure 1). The task had three different types of trials: (1) self evaluation, (2) other evaluation, and (3) word evaluation. During each trial, the subject was first shown the type of trial, i.e., each subject viewed “I am...” for the self evaluation trials, “My best friend is...” for the other evaluation trials and “This word is positive/negative” for the word evaluation trials. Subsequently, each individual viewed at the top of the screen an adjective, which was drawn from the ANEW word list (Bradley, 1999) and two response options, i.e., “yes” or “no”, which were displayed on the left and right side of the bottom of the screen. Subjects were instructed to press the left mouse button for “yes” and the right mouse button for “no”, i.e., whether each adjective described the subject (i.e., self evaluation: “I am...?”), the subject’s best friend (other evaluation: “My best friend is...?”), or the general valence of the word (word evaluation: “The word is positive/negative ...?”). The adjectives for the self, other and word evaluation trials were matched for arousal, valence, and dominance. Once the subject’s response was recorded (as evidenced by the appearance of an “X” below the chosen response) a blank screen was presented for the remaining duration of the trial. Each trial was 6000ms long. Within each trial, the cue was first presented on the screen alone for 1500ms, then the words appeared on the screen and were presented together with the cue for 1500ms or until a response was provided, whichever was shorter. During the ITI, which was at least 3000ms long a fixation cross was presented on the screen. Sixteen 6-second trials were presented for each of the 6 possible trial

types resulting from 2 valence possibilities (i.e., positive and negative) and 3 evaluation conditions (i.e., self, other and word) yielding a total of 96 trials that were presented in pseudo-randomized order. The first trial of each run was preceded by a 0.5-second blank screen, and the last trial was followed by a 3.5-second blank screen. Total scan time was 580 seconds. Response selection (i.e., percent of “yes” responses) for all trials was recorded, and behavioral analyses were carried out with SPSS 14 (Chicago, IL). Four paired t-tests were used to compare response selection before and after drug related to: (a) positive self, (b) negative self, (c) positive other and (d) negative other. During the word evaluation trials, the correct valence (i.e., either positive or negative) was identified 100% of the time both before and after the drug.

2.4. fMRI Data Collection and Analysis

During the task, one fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast was collected for each subject using a Signa EXCITE (GE Healthcare, Milwaukee) 3.0T scanner (T2 * weighted echo planar imaging, TR = 2000 ms, TE = 32 ms, FOV = 230 × 230 mm, 64 × 64 matrix, 30 2.6mm axial slices with a 1.4mm gap, 290 scans). fMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a high resolution T1-weighted image (SPGR, TI = 450, TR = 8 ms, TE = 4 ms, flip angle = 12°, FOV = 250 × 250, ~1 mm³ voxels) was obtained for anatomical reference.

All structural and functional image processing was performed with the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). Preprocessed time series data for each individual were analyzed using a multiple regression model. Regressors were constructed for positive self, negative self, positive other, negative other, positive word and negative word. Additionally, five nuisance regressors were used to account for residual motion (roll, pitch, and yaw) and to eliminate slow signal drifts (baseline and linear trend). These 11 regressors were applied to the AFNI program 3dDeconvolve in order to calculate the estimated voxelwise response amplitude. To account for individual variation of anatomical landmarks, a Gaussian filter with 4mm full width at half maximum was applied to the voxelwise percent signal change data. Data for each subject were normalized to Talairach coordinates.

To test our a priori hypotheses regarding the effects of SSRI administration on medial cortical activation related to self referential processing, we performed a two-way ANOVA with task condition (self evaluation / word evaluation) and drug condition (placebo / escitalopram) as fixed within subject factors, subject number as a random factor, and sequence (i.e., placebo first-escitalopram second / escitalopram first-placebo second) as a between subjects factor. For the task effect, we examined brain activation related to self evaluation versus word evaluation across the drug conditions. For the task effect a whole brain analysis using a probability of 0.01 was performed to constrain the widespread areas of activation observed at 0.05. For the drug effect, we examined brain activation related to self and word evaluation trials after escitalopram administration relative to brain activation related to self and word evaluation trials after placebo administration. For the drug and the drug by task interaction, a whole brain analysis was performed with a probability of 0.05. Simulations using the AFNI function AlphaSim were performed to account for multiple comparisons. Clusters of adjacent voxels that maintained the thresholds for the task, drug and task x drug interaction effects were retained. A volume of 896μl was needed for the task effect and 704μl was required for the drug and interaction effects. Only activations which satisfied the volume and voxel connection criteria were extracted and used for post-hoc correlations between brain activation and behavioral performance (i.e., response selection), as well as between brain activation and self report measures of anxiety and depression.

In a subsequent exploratory analysis, we examined whether brain activation differed between the self and other evaluation conditions by performing a voxel-based two-way ANOVA with task condition (self evaluation / other evaluation) and drug condition (placebo / escitalopram)

as fixed within subject factors, subject number as a random factor, and sequence (i.e., placebo first-escitalopram second / escitalopram first-placebo second) as a between subjects factor.

3. Results

3.1. Behavioral

Escitalopram administration was associated with a significant change in how individuals responded to self-referential adjectives. Specifically, after 3 weeks of escitalopram but not placebo, subjects less frequently endorsed that negative adjectives described themselves, and also more frequently endorsed that positive adjectives described their best friend (see Table 1). Consistent with prior work from our group (Simmons et al., 2009a), there were no significant effects of escitalopram on any of the self report measures of anxiety and depression (see Table 1) in these healthy volunteers. However, there was a trend toward decreased STAI-S scores at the end of SSRI administration (see Table 1).

3.2. Functional Neuroimaging

A whole brain analysis of the task effect, drug effect, and the task x drug interaction was conducted within the primary ANOVA that included the self and word evaluation conditions. This provided three primary findings. First, the task effect (i.e., activation related to self evaluation versus word evaluation trials across the drug conditions) revealed several regions of differential activation (see Table 2). Specifically, the PCC and mPFC were significantly more activated during self minus word evaluation, which supports the hypothesis that anterior and posterior medial cortical structures are involved in emotional self judgments. The opposite comparison showed that regions in bilateral inferior and middle frontal gyri, right lingual gyrus, left precuneus, and right superior parietal lobule were significantly more activated during word minus self evaluation. Second, the drug effect (i.e. brain activation related to escitalopram minus placebo for self and word evaluation trials) revealed decreased activation of bilateral PCC / precuneus and increased activation of left inferior, medial and superior frontal gyri, left middle temporal gyrus and right cuneus (see Table 3 and Figure 2). Third, the task (self / word) x drug (placebo / escitalopram) interaction resulted in activation of left posterior insula, pre- and post-central gyri, cerebellum and left medial / superior frontal gyrus (see Table 4 and Figure 3).

The whole brain exploratory analysis of the neural correlates of self versus other evaluation revealed: (1) no task effect, as evidenced by no areas of significant activation related to self evaluation versus other evaluation trials across the drug conditions, (2) an effect of drug in the cingulate/precuneus, middle/superior frontal gyri, insula, and left PCC, and (3) a task x drug interaction whereby the left insula, thalamus and right medial/superior frontal gyrus were activated in the task (self / other) x drug (placebo / escitalopram) interaction (see Table 5). A subsequent analysis of the extracted region of interest averages yielded no significant main effect of sequence and no sequence by drug condition interaction on any of the reported activations, indicating that there were no significant order or carry over effects on any of the reported areas of brain activation.

3.3. Brain-Behavior Relationships

Because we observed a trend toward decreased STAI-S scores at the end of SSRI administration, we correlated this measure with the clusters of activation related to the drug effect. A significant positive correlation was observed between the escitalopram-related change in state anxiety (i.e., the difference in STAI-S scores before and after drug) and the escitalopram-related change in PCC activity (i.e., the difference in PCC activity related to self and word evaluation trials before and after drug) (Spearman's $\rho = 0.565$, $p < 0.05$). No

significant correlations were observed between brain activation and either baseline response selection scores or the drug-related change in response selection scores ($p = \text{N.S.}$).

4. Discussion

In this study, healthy female volunteers completed a randomized, cross-over, double-blind experiment during which they twice performed a self-referential processing task during fMRI, i.e., once after 3 weeks of placebo and once at the end of 3 weeks of escitalopram administration. The main goal of the current study was to examine the effect of escitalopram on medial cortical activity during self-referential processing. Supporting one aspect of our a priori hypothesis, we observed that administration of escitalopram for 3 weeks at doses that were in the therapeutic range for depression and anxiety was associated with a significant decrease in posterior medial cortical (i.e., PCC/precuneus) activity when task conditions that required self-evaluation were combined with task conditions that required evaluation of the valence of positive and negative words. Also related to the drug effect, increased activation was observed in the inferior, medial and superior frontal gyri, middle temporal gyrus and cuneus, regions that are involved in decision making (Simmons et al., 2008; Simmons et al., 2006) and self-control (Matthews et al., 2005). These results point to a network that is affected by SSRI administration during more general evaluative processing (i.e., self and word evaluation). The results of the drug $\times$ task interaction (see Figure 3) build on the drug effect findings and suggest that SSRI administration may primarily affect the left posterior insula and left middle frontal gyrus, as well as the pre- and post-central gyri and cerebellum specifically during self-referential processing. Taken together, these brain imaging findings may represent a neural correlate of more deliberative and controlled decision making, which may involve less focus on negative autobiographical thoughts and memories, after escitalopram administration. This interpretation is supported by the significant correlation that was observed between decreased state anxiety and decreased PCC/precuneus activity after SSRI administration. This formulation is also consistent with evidence that administration of fluoxetine 20 mg per day for 8 weeks increased PCC activity to happy faces in MDD subjects (Fu et al., 2007), and with prior research indicating that tryptophan depletion increases regional cerebral glucose utilization in the PCC, as well as a functionally connected network of emotion processing structures including the orbitofrontal cortex, medial thalamus, ACC and ventral striatum in patients with remitted MDD (Neumeister et al., 2004).

Our findings are also in line with evidence that SSRI administration is associated with interruption of rumination on negative thoughts and feelings, and consequent protection against the development of anxiety and depression (Siegle et al., 2007). Supporting this conceptualization is an emerging body of work indicating that individuals with MDD display an increased level of self-focused attention (Ingram, 1990) and dysregulated brain activity in fronto-insular circuitry (Matthews et al., 2009; Strigo et al., 2008). Moreover, our results are consistent with recent research indicating that greater PCC activity related to performance of memory encoding task, correlated positively with increased severity of subsyndromal depressive symptoms (Woo et al., 2009), and with several converging studies showing that functional activity in a network of medial cortical structures during self-referential processing is dysregulated in MDD individuals (Grimm et al., 2009; Johnson et al., 2009; Lemogne et al., 2009a).

Our finding that the PCC and mPFC were activated during self-evaluation relative to word evaluation is consistent with prior work (Yoshimura et al., 2009a) showing that self-referential processing activates a network of structures including: (a) PCC, which is thought to be involved in evaluating the affective valence of external stimuli (Maddock et al., 2003); (b) mPFC, which is activated when individuals reflect on their emotions, and; (c) inferior frontal gyrus, which has been shown to mediate the selection of the appropriate semantic description of an

individual's emotional state (Lane et al., 1997) and may underlie behavioral and emotional control (Ochsner and Gross, 2005). The PCC is a core component of the self referential processing network, which receives afferents primarily from the anterior thalamus as well as from extensive cortical areas in the frontal, parietal, and temporal lobes (Vogt et al., 1979) and medial orbitofrontal cortex (Cavada et al., 2000). Prior studies have shown increased PCC activation related to processing emotional (i.e., threatening, unpleasant and pleasant) words relative to neutral words (Maddock and Buonocore, 1997). Activity in this structure is strongly coupled with increased activity in the subgenual cingulate (i.e., an emotion processing structure that is hyperactive in individuals with MDD) and with decreased activity in the lateral prefrontal cortex (Greicius et al., 2003) (i.e., a structure that is critically involved in emotional control and is hypoactive in MDD). Our results extend this evidence by showing that the PCC as well as the mPFC are activated when subjects engage in self evaluation versus word evaluation.

Although we did not have a priori hypotheses about how escitalopram would differentially affect brain activity related to self versus other evaluation, our findings (see Table 5) suggest that SSRIs modulate activity in a network of structures that includes the PCC, as well as prefrontal cortex, cingulate/precuneus, middle/superior frontal gyri, and insula during both self and other evaluation, an interpretation that is in line with a recent study that showed no effect of antidepressant treatment on dorsal mPFC activity during self-referential processing (Lemogne et al., 2009b). Further research is needed to disambiguate this network and identify the common and unique neural networks involved in evaluation of self and other. The results of the interaction between task (self / other) and drug (placebo / escitalopram) suggest that SSRIs may differentially affect the left posterior insula, thalamus and right middle frontal gyrus during self versus other evaluation. Prior research has shown that escitalopram attenuates activity in the posterior insula during emotion processing (Arce et al., 2009; Simmons et al., 2009b), suggesting that SSRIs may modulate the impact of emotional stimuli by decreasing activity in neural circuitry such the posterior insula which drives physiological responses to aversive stimuli. Further studies are needed to examine the degree to which such a mechanism may be operating during self and other evaluation.

Behaviorally, subjects endorsed negative self statements significantly less often and positive friend statements significantly more often after drug administration. These novel findings are consistent with prior evidence that acute administration of SSRIs leads to increased recognition of happy facial expressions (Harmer et al., 2003) and increased attention to positive socially relevant stimuli (Browning et al., 2007). Although we did observe a trend toward decreased state anxiety at the end of SSRI administration, the lack of a significant effect of escitalopram on self report measures of anxiety and depression in the current study may suggest that the effects of escitalopram on response selection were independent of its effects on mood.

In summary, the current study provides the first evidence that 3-week administration of an SSRI is associated with increased positive self endorsement and also with attenuation of posterior medial cortex activity during self referential processing in healthy volunteers. Although our investigation was limited by a modest sized sample of healthy female subjects, our results represent the first evidence that modulating serotonin function alters behavioral and brain responses during self referential emotion processing. Future studies should examine the degree to which behavioral and brain responses during self-referential processing predict clinical course of illness in individuals with mood disorders and response to SSRI and more novel antidepressants.

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Figure 1.

Study Design-All subjects received both placebo and escitalopram in a randomized, cross-over, double-blind design. After randomization, individuals completed phase 1 during which they took either placebo or escitalopram for 18 days then completed self-report questionnaires and performed a self referential processing task during fMRI scan 1. Subsequently, subjects completed a 14-28 day “wash-out” period and then phase 2, which was identical to phase 1 but involved administration of whichever drug (escitalopram or placebo) had not been administered in phase 1.

Figure 2.

Functional brain activity during self and word evaluation Task Effect (panel 1). Examining activity for self minus word evaluation across drug conditions revealed increased activity in a cluster in the posterior cingulate. Drug Effect (panels 2 and 3). Administration of 3 weeks of escitalopram relative to placebo was associated with significantly decreased activity in bilateral posterior cingulate/precuneus related to self and word evaluation.

Figure 3. Functional brain activity related to the task (self/word) x drug (placebo/escitalopram) interaction.

Table 1
Symptom ratings and response selection before and after escitalopram

Symptom ratings	Placebo [†]	Escitalopram [†]	t-value	P
Beck Depression Inventory	0.38 (0.72)	0.56 (1.26)	-0.481	0.640
Social Interaction Anxiety Scale	6.44 (7.88)	6.81 (6.82)	-0.297	0.771
State Anxiety Inventory	24.63 (5.33)	23.31 (4.32)	1.470	0.162
Brief Symptom Inventory	36.19 (3.87)	36.56 (4.68)	-0.212	0.835

Response selection	Placebo [†]	Escitalopram [†]	t-value	P
Negative self	4.8% (7)	1.8% (5)	2.847	0.013
Positive self	88% (8)	90% (7)	-1.259	0.229
Negative other	3.8% (7)	2.5% (5)	0.937	0.365
Positive other	83% (10)	88% (8)	-2.157	0.049

[†] = Mean (SD)

Table 2
Brain activation related to self versus word evaluation trials across both drug conditions

Brain Area	Brodman Area	Volume	x	y	z	F (p)
Self > Word						
Right Posterior Cingulate	31	9152	1	-56	24	78.8 (<.001)
Right Medial Prefrontal Cortex	9	3904	3	52	15	47.6 (<.001)
Self < Word						
Right Middle/inferior Frontal Gyrus	9/44	5952	43	10	39	76.0 (<.001)
Left Inferior Frontal Gyrus	44	3840	-45	9	25	77.6 (<.001)
Left Middle Frontal Gyrus	6	2112	-35	-4	43	69.2 (<.001)
Right Lingual Gyrus	17	1792	4	-84	5	67.0 (<.001)
Right Inferior Frontal Gyrus	44	1664	45	11	19	44.8 (<.001)
Left Precuneus	19/7	1600	-25	-70	33	25.4 (<.001)
Right Middle Frontal Gyrus	10	960	41	40	21	38.3 (<.001)
Right angular gyrus/superior Parietal Lobule	7	960	37	-63	45	29.5 (<.001)

Table 3
Brain activation related to self and word evaluation trials before and after escitalopram

Brain Area	Brodmann Area	Volume	x	y	z	F (p)
Placebo > escitalopram						
Right Posterior Cingulate/Precuneus	31/7	896	23	-32	30	12.2 (<.005)
Left Posterior Cingulate/Precuneus	31/7	832	-19	-46	31	14.8 (<.005)
Escitalopram > placebo						
Left Inferior Frontal Gyrus	45	1344	-41	9	11	12.0 (<.005)
Left Middle/Superior Frontal Gyrus	8	1024	-5	20	47	21.5 (<.001)
Left Superior/Middle Frontal Gyrus	6	960	-15	6	56	14.7 (<.005)
Right Cuneus	19	832	6	-88	25	21.6 (<.001)
Left Middle Temporal Gyrus	39	832	-47	-65	25	22.9 (<.001)

Table 4
Brain activation related to the drug (escitalopram/placebo) by task (self/word) interaction

Brain Area	Brodmann Area	Volume	x	y	z	F (p)
Left Postcentral Gyrus	2	1152	-48	-17	29	7.5 (<.05)
Right Cerebellum		1024	7	-40	-32	10.9 (<.01)
Left Insula	13	1024	-43	-27	19	13.0 (<.005)
Left Medial/Superior Frontal Gyrus	6	960	-17	-2	53	7.1 (<.05)
Left Precentral Gyrus	4	960	-25	-26	55	9.1 (<.01)
Left Cerebellum		832	-7	-68	-14	6.0 (<.05)

Table 5

Neural correlates of self versus other evaluation

Brain Area	Brodmann Area	Volume	x	y	z	F (p)
Task effect (self versus other)						
No areas						
Drug effect						
Right Cingulate Gyrus/Precuneus **	31	2048	24	-33	29	15.7 (<0.005)
Right Cingulate Gyrus/Precuneus *	10	1728	40	40	23	34.4 (<0.001)
Right Cingulate Gyrus/Precuneus *	40	1728	-45	-47	46	9.5 (<0.01)
Left Middle Frontal Gyrus *	6	1344	-17	6	56	19.8 (<0.001)
Superior Frontal Gyrus *	8	1280	2	28	50	26.0 (<0.001)
Left Middle Frontal Gyrus *	9	1152	-34	35	24	20.8 (<0.001)
Left Insula *	13	1088	-44	8	12	8.8 (<0.05)
Right Superior/Medial Frontal Gyrus *	8	960	15	26	43	25.6 (<0.001)
Right Insula *	13	832	44	14	1	14.9 (<0.005)
Left Posterior Cingulate Gyrus *	31	768	-6	-70	25	7.4 (<0.05)
Medial/Superior Frontal Gyrus *	8	768	1	40	38	12.5 (<0.005)
Drug by Task Interaction						
Left Insula †	13	1280	-42	-26	18	5.7 (<0.05)
Right Thalamus †		1024	25	1	10	8.0 (<0.05)
Left Thalamus †		896	-20	2	8	6.9 (<0.05)
Right Medial/Superior Frontal Gyrus †	6	832	33	-7	54	5.7 (<0.05)

* = SSRI < Placebo

** = SSRI > Placebo

† = self < other during the SSRI condition and self > other during the placebo condition