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Subchronic SSRI administration attenuates insula response during affective anticipation

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Abstract

Context—The anterior cingulate cortex (ACC) and insula are important neural substrates for the integration of cognitive, emotional, and physiological information, as well as the coordination of responses to anticipated stimuli. Increased neural activation within these structures has been observed in individuals with anxiety and depressive disorders. Selective serotonin reuptake inhibitors (SSRIs) are among the most effective and frequently prescribed anxiolytic agents, yet it is not known whether ACC or insula underlie the effects of these drugs. We examined whether subchronic administration of an SSRI to healthy volunteers attenuate activation in ACC or insula during anticipation, an important emotional process underlying anxiety. Support for this hypothesis would help to understand where and by what process SSRIs may exert beneficial effects as anxiolytics and would provide further mechanistic evidence for functional magnetic resonance imaging (fMRI) as a biomarker for the development of anxiolytics.

Participants and Design—15 volunteers participated in a double-blind, placebo-controlled, randomized cross-over study. Participants completed a pleasant and aversive picture cued anticipation task during fMRI after taking either escitalopram (10 mg) or placebo for 21 days.

Main Outcome Measure—Percent BOLD signal change during SSRI administration.

Results—Escitalopram significantly decreased activation in bilateral posterior and middle insula during the anticipation condition irrespective of stimulus valence and in medial prefrontal and ACC during anticipation of aversive versus pleasant images.

Conclusion—Reduced insular and ACC activation during anticipation may be integral to the therapeutic efficacy of SSRIs and provide a mechanistic approach for the use of pharmacofMRI in the identification of novel pharmacotherapeutic agents.

Keywords

SSRI; escitalopram; insula; fMRI; anticipation

Introduction

Increased emotionality associated with the anticipation of future events is a key feature of anxiety disorders [1, 2]. Related evidence indicates that heightened anticipatory anxiety is associated with deleterious psychophysiological stress responses [3, 4]. Serotonin may well be an important neurotransmitter in this, and other, affective processes [5], as well as playing a role in modulating both psychological [6–9] and physiological [10–12] aspects of anticipatory anxiety. Serotonin receptors are widely expressed within the amygdala [13], the ventral anterior cingulate (ACC) and insula [14], neural substrates that play a critical role in regulating psychological well-being and physiological homeostasis [15, 16].

Functional neuroimaging studies have shown that the medial prefrontal gyrus (MPFG), ACC [17–19] and insula [19, 20] are activated during anticipation of an electric shock or a noxious thermal stimulus, and during anticipation of feedback in a decision-making task [21]. Previously [22], we examined anticipation of aversive images (i.e., spiders and snakes) in healthy volunteers and found anticipation-related activation within the right insula. Furthermore, using that task, we observed greater insula activity in subjects with high trait anxiety [23], as well as in patients with PTSD (Simmons et al., submitted). In a similar study, Nitschke and colleagues displayed aversive and non-aversive pictures to healthy volunteers and found anticipation-related activation in ventral and dorsal ACC, bilateral insula, and bilateral amygdala [24]. In addition, Bermpohl and colleagues have found that the dorsal MPFG/ACC are particularly sensitive to expectancy while other regions such as the insula and amygdala are more sensitive to emotion intensity of the stimulus[25, 26]. The dorsal ACC has strong connections with the insula and these areas are often described as being part of a primary "default mode" network [27].

The insula, a part of the extended limbic system, can be subdivided into anterior agranular (Ia), central/middle dysgranular (Id) and posterior granular (Ig) subregions based on function and cytoarchitectural structure [28, 29]. The anterior insula has efferent connections with ventral frontal brain regions such as the ACC and orbital frontal cortex (OFC), as well as with periamygdaliod areas. Its middle region has strong connections with the amygdala body, OFC and secondary somatosensory areas [28, 30, 31]. The posterior insula has afferent projections from the frontal cortex, the temporopolar cortex, and secondary somatosensory area [29]. Recent literature has suggested that the rostral parts of the insula (Ia and anterior Id) motivates action while the caudal insula (Ig and posterior Id) is involved in monitoring the physiological condition of the body [32, 33]. In comparison, the ACC—particularly the ventral subdivision—plays a similar role in emotional and physiological processing (Brodmann Area, BA 24a). Its ventral region has projections to the anterior insula [28, 29, 34–36] and the amygdala, [34, 37–40] exerting top-down regulation on these structures [38, 40]. The ventral ACC is involved in fear conditioning [40–42], in the pathophysiology of anxiety disorders [41, 43], self-relevant cognition [44–52], and error processing [49, 53–55]. Given the importance of the various subdivisions of the ACC in the integration of physiological and psychological processes, changes in their activity are potentially useful neural biomarkers for the efficacy of pharmacotherapies [56].

Altered anticipatory processing is a key feature of many of the anxiety disorders, reflected by greater activation in the insula [19, 23, 24, 57], medial frontal gyrus [23, 24, 57–59], and amygdala [4, 24, 57]. Although anticipation may be less pertinent to depression than to anxiety, the high comorbidity of anxiety and depressive symptoms[60] suggests that elevating anticipatory symptoms may be relevant to both conditions. SSRIs are among the first-line treatments for anxiety and depression [5, 13, 61–68]. Although SSRIs block synaptic neuronal reuptake of secreted serotonin [69, 70], current theories posit that the antidepressant (and, possibly, the anxiolytic) actions of SSRIs involve effects that extend beyond serotonin reuptake [65, 66, 71]. The effects of SSRIs in affective disorders may be the result of modulation by serotonin pathways of the cortical and subcortical circuitry involved in the processing of emotional stimuli [72]. The acute effects of SSRIs are sometimes opposite the chronic effects in that an early elevation of anxiety symptoms is often followed by an anxiolytic effect if treatment is continued [13, 73]. Acute oral [74] and intravenous [75] administration of an SSRI (i.e., citalopram) has been shown to increase the processing of anxiety-related stimuli in healthy volunteers. Acute SSRI administration has been associated with decreased activation during affective image processing [76] and during a go-nogo task [77], whereas more prolonged administration has more consistently been associated with attenuation of the recognition of fearful stimuli [78] and amygdala activation [73]. Thus the role of SSRIs in brain may be highly dependent on the task used to probe the brain and the length of drug administration. Although effects of SSRIs on emotion processing networks are under intense investigation, much is still unknown about how these substances work to normalize abnormal cognitive and emotional processes.

In an effort to better understand the mechanism (and brain localization) of SSRI treatments, fMRI techniques have recently been applied to measure their effect on neural processing [73, 79, 80]. We have previously shown that acute administration of a benzodiazepine anxiolytic (lorazepam) attenuates activity of the amygdala, ACC, and insula during risk-taking decision making [81] and emotional face processing [56]. Acute doses of SSRI treatment can increase anxiety whereas prolonged administration can attenuate amygdala activation [73] and decrease anxious distress. Although several studies have used pharmaco-fMRI to assess the neural correlates of certain antidepressant agents [72, 73, 77, 82–86], to our knowledge, this is the first study to implement a sub-chronic, placebo-control cross-over (i.e., within subjects) design using a cohort of healthy volunteers to assess the effects of SSRIs on emotion anticipation. Considering the pivotal role of the insula and ACC in subjective feeling states and interoceptive awareness [32, 87] and their implication in the pathophysiology of anxiety disorders [87–89], we hypothesized that subchronic administration (3 weeks) of the SSRI escitalopram would be associated with attenuated activation in the ACC and insula during an emotional anticipation task. Confirmation of this hypothesis would provide further evidence of the utility of pharmacofMRI as a tool to identify the neural substrates important for anxiety and depression [90]. Once neural substrates are established, changes in their activity can be used as biomarkers for the measurement of efficacy of novel anxiolytics or antidepressants.

Methods

Subjects

Sixteen healthy, nonsmoking females provided written informed consent and were paid for their participation in this study, which was approved by the University of California San Diego School of Medicine institutional review board. One subject was excluded because her urine escitalopram level was undetectable during the period of time when she was to have been taking escitalopram, suggesting non-adherence to the protocol. The remaining 15 subjects were females of ages 19 to 27 years (mean ± SD, 22.3 ± 2.3 years) with 11 to 17 years of education (mean ± SD, 15.5 ± 1.8 years). Participants did not have medical or psychiatric disorders as determined by medical history and diagnoses according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition [91]. Subjects had no history of drug or alcohol abuse and no history of previously taking benzodiazepines, SSRIs, monoamine oxidase inhibitors (MAOIs), or neuroleptics. All participants had a negative urine drug screen at baseline. EKG and routine laboratory blood tests, which included a CBC, electrolytes, and liver function tests, were within normal limits. Subjects were instructed to maintain their regular bedtimes and wake times for 1 week before and throughout the study period.

Study design

This study used a randomized, cross-over, double blind design (see Figure 1). Once it was determined that a subject was eligible for the study, and informed written consent was obtained, the subject was randomized to receive either escitalopram (5 mg/d for the first 3 days, then 10 mg/d for another 18 days) or placebo, administered in identical, capsular form. Subjects were instructed to take the medication each morning throughout each 21 day arm of the study. In between arms, there was a 14–28 day tapered wash-out period, during which the medication was reduced from 10 mg/d to 5 mg/d for 3 days, and then discontinued. The study physician (MPP) also met with subjects weekly in order to address any concerns and to ensure that compliance with the medication was maintained.

At the end of each 21-day medication arm (prior to taper), subjects were scheduled for an fMRI visit. During this visit, and prior to the scanning session, subjects completed several self-report questionnaires, including the State-Trait Anxiety Inventory (STAI-S) [92], Beck Depression

Inventory (BDI) [93], Social Interaction Anxiety Scale SIAS [94], and the Brief Symptom Inventory BSI [95] to evaluate their psychological state at that time and provided a urine sample for escitalopram measurement.

Task

The task combined a continuous performance task (CPT), similar to a task described previously [96], with the interspersed presentation of aversive affective stimuli. During the CPT, subjects were asked to press a LEFT mouse button whenever they saw a blue circle and a RIGHT mouse button whenever they saw a blue square on the screen. Stimuli were presented at a visual angle of 4 degrees at a rate of 0.5 Hz. Simultaneously, a 250 msec long 500 Hz tone was presented every 2 seconds. Subjects were instructed prior to the task that a switch from a blue to a green circle or square accompanied by a 250 Hz tone would indicate that a positive image was going to appear on the screen. In contrast, a switch from blue to red stimuli together with a 1000 Hz tone signaled an impending negative image. The picture stimuli were comprised of 17 positive (i.e., pleasant) and 17 negative (i.e., unpleasant, or aversive) images taken from the International Affective Picture System (IAPS) [97], which consisted of superficial physical injuries, assaults, traffic accidents or other common traumatic events. The anticipation periods during the task (red and green shapes) lasted 6 seconds and the image presentation lasted 2 seconds. The baseline CPT task was interspersed for variable duration averaging about 8 seconds in between these task components. The total duration of the task was 580 seconds. No response from subjects was required when a picture stimulus was presented on the screen.

Response accuracy and response latency were obtained for the CPT, anticipation of a positive image (API), and anticipation of a negative image (ANI). To examine the behavioral effect of anticipation, we examined the difference between behavioral measures during the API and ANI.

Image Acquisition

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 = 250 × 250 mm^3, 64 × 64 matrix, 30 2.6mm axial slices with a 1.4mm gap, 290 scans). fMRI acquisitions were time-locked to the onset of each trial. 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 mm^3 voxels) was obtained for anatomical reference.

Data were preprocessed and analyzed with the Analysis of Functional NeuroImages (AFNI) software package [98]. Preprocessed time series data for each individual were analyzed using a multiple regression model. Regressors of interest included four orthogonal regressors that were constructed to quantify the neural substrates contributing to the different components of the task: 1) the API, capturing the anticipation of a positive image, 2) the ANI, capturing the anticipation of a negative image, 3) the positive image (PI) phase, which assesses the processing of positive stimuli, and 4) the negative image (NI) phase, which assesses the processing of negative stimuli. In addition, six nuisance regressors were entered into the linear regression model: three movement-related regressors used to account for residual motion (in the roll, pitch, and yaw direction), a white matter mask to control for physiological noise [99], and regressors for baseline and linear trends used to eliminate slow signal drifts. The CPT task (blue shapes) provided the baseline condition and was accounted for by the baseline regressor. Percent signal change was calculated by dividing the regressor of interest by the baseline regressor. Subsequently, simple contrasts were constructed on an individual subject level for all anticipation (ANI+API) and differential anticipation (DA) of negative versus positive (ANI −API). A Gaussian filter with full width- half maximum 6 mm was applied to the voxel-wise

percent signal change data to account for individual variations in the anatomical landmarks. Data of each subject were normalized to Talairach coordinates.

Voxel-wise percent signal change data for whole brain were entered into a paired samples t-test for drug effects during anticipation and image presentation between SSRI dosing and placebo dosing. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation [100]. A prior voxel-wise probability of $p< 0.05$ in a cluster of 1440 μL resulted in whole brain corrected probability of $p <0.05$. Finally, the average percent signal difference was extracted from regions of activation that were found to survive this threshold/cluster method and the t-values were calculated with and without education as a covariate. All analyses for the behavioral data were carried out with SPSS 12.0 [101].

In addition, a region of interest (ROI) based analysis was performed on several *apriori* areas of interest: the bilateral insula, bilateral amygdala, ventral ACC, and dorsal ACC. These corrected voxel probabilities are based on Monte Carlo simulations via AFNI's program AlphaSim, using the filtered data and the a-priori defined regions of interest. Stereotactic coordinates of the ROIs were based on standardized Talairach atlas locations [102]. This resulted in minimum clusters sizes of 128 μL for the amygdala ROIs and 256 μL for all remaining ROIs. While the cluster significance is $p<.05$ for the ROIs, the corrected voxel-wise probabilities are as follows: amygdala $p < 0.012$, insular cortex $p < 0.00007$, ventral medial prefrontal cortex $p < 0.00014$, and dorsal medial prefrontal cortex $p < 0.00014$.

Correlational analyses were also conducted for the placebo minus escitalopram effects for particular contrasts of interest, including imaging, behavioral, and self-report data.

Results

Behavioral Analysis

Subchronic administration of escitalopram had no significant effect on task performance during the different task conditions (CPT, ANI, and API) as measured by response latency or accuracy ($F(1,14)=2.303$, p = ns; $F(1,14)=0.007$, p = ns, respectively). Escitalopram did not alter self report measures of various types of anxiety symptoms or depression (i.e., BDI, BSI, SIAS, STAIS; data not shown) in this group of healthy volunteers.

Brain Activation Analysis

Task Effect—ROI analysis of the task related activation (combined placebo and SSRI) was observed for differential anticipation (DA; ANI−API) in the bilateral anterior insula (Ia) (right Ia: $F(1,14)=4.645$, $p=0.001$; left Ia: $F(1,14)=4.005$, $p=0.001$; see Figure 2) in the ROI analysis. The bilateral anterior insula regions did not differ significantly across conditions.

SSRI Effect—There was a main effect of subchronic administration of escitalopram, which was seen as a relative deactivation during differential anticipation (ANI−API) in the ventral ACC (2624μl, x=5, y=32, z=−12; $F(1,14)=3.259$, $p=0.005$; see Figure 2). Moreover, individuals after escitalopram administration relative to the placebo condition showed relative deactivation for all anticipation (ANI+API) trials in the right posterior insula (1344μl, x=42, y=−19, z=3; $F(1,14)=4.496$, $p=0.001$), left inferior posterior insula (1088μl, x=−42, y=−17, z=2; $F(1,14)=2.855$, $p=0.05$), left superior posterior insula (832μl, x=−41, y=−13, z=25; $F(1,14)=3.028$, $p=0.01$), and left middle insula (1216μl, x=−40, y=6, z=−9; $F(1,14)=3.011$, $p=0.01$) (see Figure 3).

Correlations—There were no significant correlations between the change in response latency or accuracy, any self-report measures (i.e., BDI, BSI, SIAS, STAIS), or the change in the degree of activation in the insula or cingulate during the task across drug conditions (data not shown).

Discussion

This experiment yielded three main findings. First, sub-chronic administration of "therapeutic doses" of the SSRI escitalopram resulted in significant relative deactivation of the ventral ACC during anticipation of negative compared to positive visual stimuli. Second, escitalopram reduced middle to posterior bilateral insula activation during anticipation regardless of the valence of the stimulus. Third, we confirmed previous observations[22, 23] that bilateral anterior insula is important for anticipation of negative (aversive) compared to positive (pleasant) visual stimuli. Taken together, these results show that escitalopram influences anticipatory processing by modulating insula and ventral ACC activity during emotion processing. This is a compelling hypothetical mechanism by which SSRIs may act as anxiolytics. Therapeutic effects of SSRIs may involve modulation of cues that signal expected emotional states such that they contribute less significantly to emotion processing. These observations add to the growing literature that pharmacofMRI may be useful in revealing effects of well-established anxiolytics and antidepressants in the brain and could thus be a useful tool in the development of novel therapeutics [90].

The current study replicated the relative increases in the bilateral insula during anticipation seen in our prior work [22, 23]. The insula has been suggested to play a key role in evaluating the impact that environmental stimuli may have on the interoceptive body state [15, 88]. Activity in this region relates to anxiety during risk-taking decision making [103], is elevated in individuals with specific phobia when viewing fearful faces [104], is increased during anticipation of emotion face processing in those with high trait anxiety [23, 105], relates to anticipatory anxiety in those with social phobia [57], and is associated with increased perfusion in patients with panic disorder [106]. Taken in combination, these studies suggest that altered insula activity may be a common denominator that could be used as a biomarker for treatment effects. The anterior subdivision of the insula has been highlighted as an important region for the integration of physiological and psychological self [32, 88], and is of particular importance in down-modulating the posterior insula [28]. In the present study, activity in the posterior insula was reduced by the administration of escitalopram, suggesting that SSRIs may contribute to central reduction in physiological reactivity during emotional anticipation. Escitalopram did not affect processing within the anterior insula, which is important for the integration of cognitive, affective, and physiological processes. In comparison, escitalopram attenuated the more posterior aspects of the insula, which are important for the physiological representation of potentially aversive emotional experiences. Therefore, escitalopram (and, by inference, other SSRIs) may have a more subtle "bottom up" effect, i.e., modulating the physiological associations of anticipatory stimuli, rather than a "top-down" modulation, i.e., modulating the cognitive attributes of anticipatory stimuli, which is consistent with models proposed by Mayberg and colleagues [107, 108]. In fact the model proposed by Mayberg focus3w on the subgenual cingulate, directly inferior to the region found in this study, as being in the critical path for the treatment effects of SSRIs due to the serotonin density of this region [107–111]. Slight discrepancy in location of the effects of SSRI in the current study may be due in part to the selection of an anticipatory task to probe brain functioning. As a cautionary note, however, it is important to point out that activation differences between the anticipation and baseline condition in posterior insula regions were mostly negative. This may be due to uncorrected physiological effects such as breathing [99] or alternatively there may be a dampening of somatic information during anticipation[112].

We also found a significant attenuation of the ventral ACC during anticipation of negative versus positive visual stimuli. This region is often linked with self-focus and emotional

evaluation [44–52], as well as anticipatory processing [19, 24, 59, 113]. Thus, the attenuating effects of escitalopram in this region may reflect decreases in self-focus during the anticipation of aversive stimuli. Numerous studies have found an anticipatory activation in the dorsal ACC particularly in contrast with uncued anticipatory phases [25, 26]; considering the strong connections between the insula and dorsal ACC/MPFG [29] this relationship may play a part in top-down modulation of interoceptive processing.

Our findings are based on results from healthy volunteers who did not report significant subjective changes during subchronic escitalopram administration. Nevertheless, imaging of healthy volunteers is an important step in proof of concept in drug discovery [114]. In particular, the use of a relatively homogenous, healthy population may allow for the use of smaller groups to detect neural effects of a compound. It should be noted that healthy volunteers may show brain changes without behavioral changes [114]. Although escitalopram is an approved, marketed drug, proving that sub-chronic doses of SSRIs act on specific neural pathways can provide biomarkers for efficacy in similar drugs entering phase I or II (i.e., safety/efficacy studies). In comparison, the advantage of using patient samples may be the ability to determine the relationship between the neural substrate effects of potential therapeutics and subjective or objective changes in disorder symptoms.

In terms of the mechanistic actions of SSRIs, these findings suggest that direct or indirect serotonergic modulation of insular cortex, among other regions, results in relative deactivation of affective neural substrates during anticipation. Specifically, the mechanism of action could be explained as a reduction of the affective/physiological reactivity to anticipation that may then result in decreased feelings of anxiety and/or depression. Reduction of self-focused attention during negative anticipation may relate to less concern about the internal body state. Given the importance of somatic reactivity in both anxiety and anticipatory processing [3, 4, 115], this mechanism may be considered as a potentially effective way to modulate affect through particular pharmacological interventions. This model would help explain why SSRIs are effective at modification of mood only in conditions of distress, such as anxiety, and in the current study are only seen when the individual is momentarily provoked by an affective anticipatory task that can induce physiological or homeostatic distress.

The current study has several limitations. First, as noted above, this study was conducted with healthy volunteers and generalizability to patient samples still need to be established. In particular, we did not observe changes in subjective ratings on scales measuring anxiety or depression. This range restriction in the emotional state of healthy volunteers may explain the lack of significant correlations between change in psychological measures and change in BOLD signal in functional ROIs during SSRI treatment. Because physiologic reactivity to anticipatory anxiety is greater in anxious individuals [4, 115], future studies with patients suffering from anxiety disorders may reveal even larger BOLD changes during SSRI treatment. Also the neural expression of escitalopram appears to be task dependant both in the mechanism and strength of the effect [116], so these findings should not be over-generalized in its effects.

In summary, our results suggest that treatment with escitalopram results in attenuation of the neural response to affective anticipation in brain regions responsible for the integration of physiological and affective well-being. Specifically, sub-chronic SSRI treatment may reduce the anticipatory reactivity to emotional—especially aversive—stimuli. These findings can have important implications for the development of pharmacological interventions to treat anxiety disorders, suggesting that BOLD signal in the insula and ACC during anticipatory anxiety may be a useful biomarker for measuring psychopharmacological effects of extant and novel anxiolytic agents.

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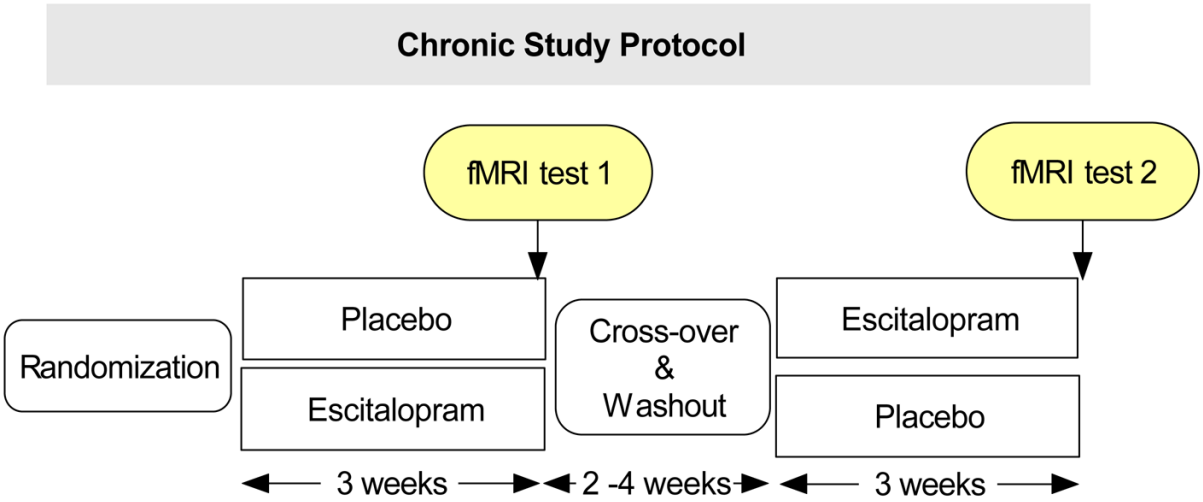

Figure 1.
Study design

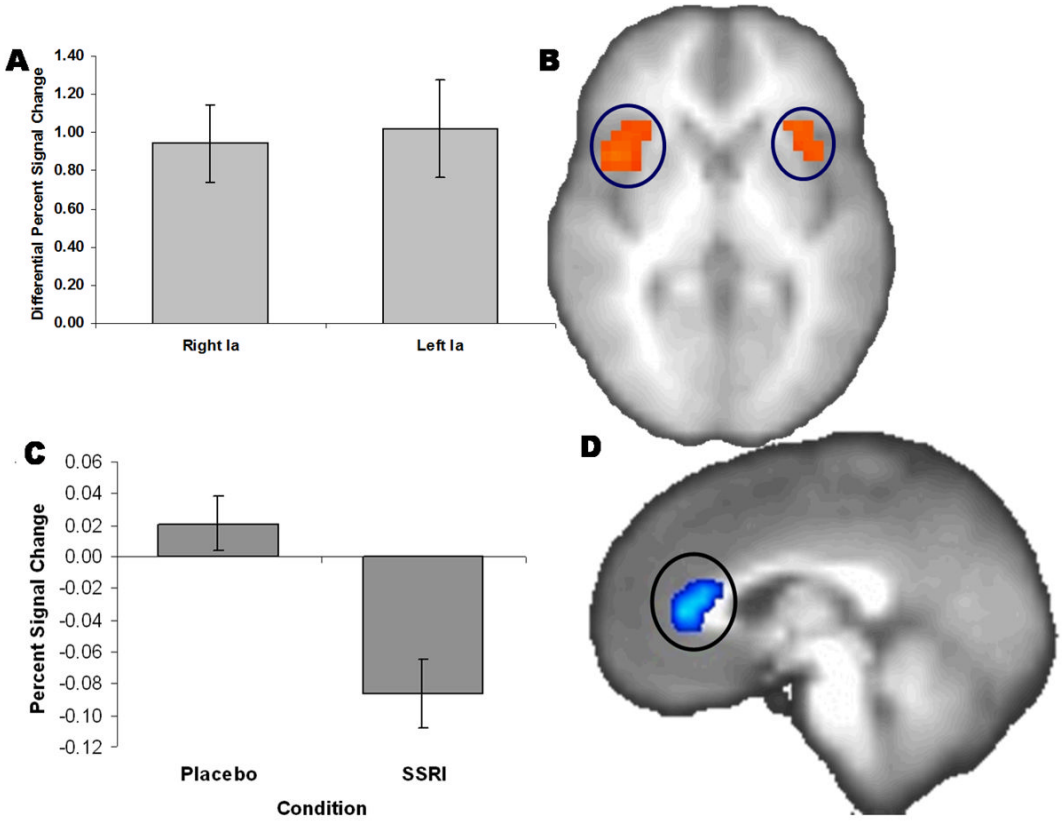

Figure 2.

Task activation: greater activation (% signal change) in the bilateral anterior insula for negative anticipation minus positive anticipation [A] shown at . Condition activation: deactivation (% signal change in ventral anterior cingulate [C]) in negative minus positive anticipation during escitalopram versus placebo conditions shown at x=0 [D].

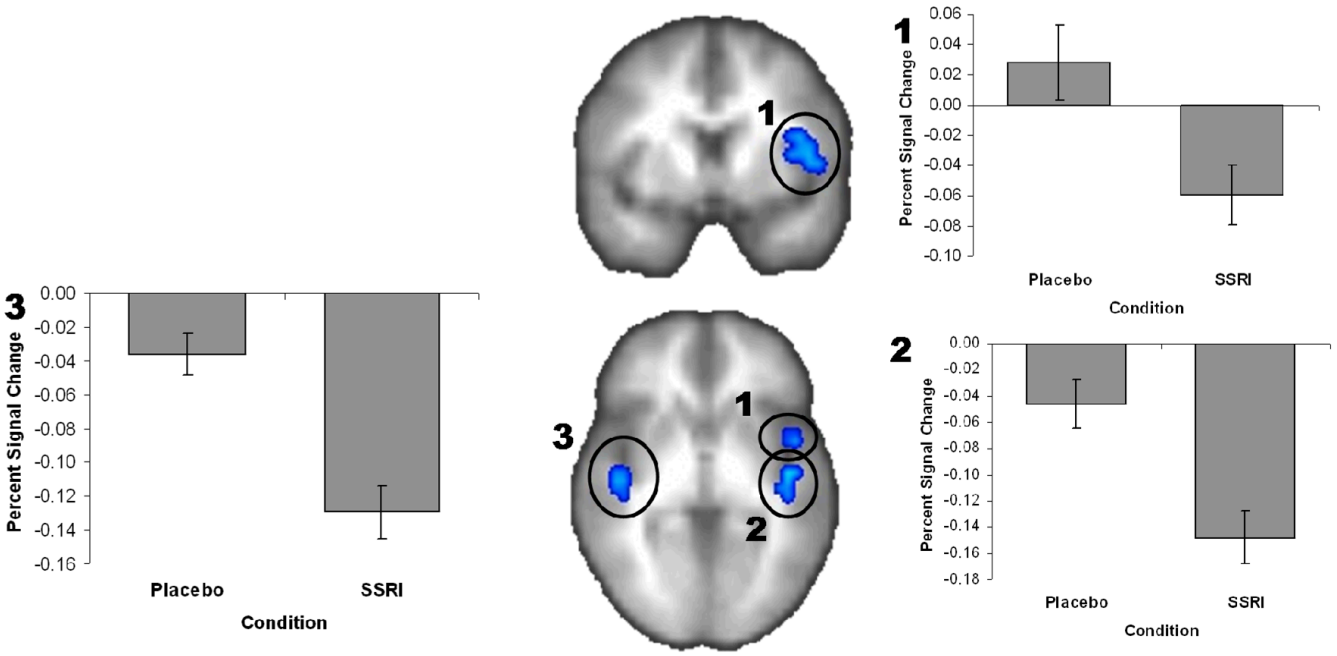

Figure 3.
Deactivation (% signal change) in positive and negative anticipation during escitalopram versus placebo conditions in the (1) left middle (2) left posterior, and (3) right posterior insula.