RESEARCH ARTICLE

Specific Pharmacological Effects of Paroxetine Comprise Psychological but Not Somatic Symptoms of Depression

Benjamin D. Schalet¹*, Tony Z. Tang², Robert J. DeRubeis², Steven D. Hollon³, Jay D. Amsterdam⁴, Richard C. Shelton⁵

¹ Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States of America, ² Department of Psychology, University of Pennsylvania, Philadelphia, PA, United States of America, ³ Department of Psychology, Vanderbilt University, Nashville, TN, United States of America, ⁴ Depression Research Unit, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America, ⁵ Department of Psychiatry and Behavioral Neurobiology, The University of Alabama at Birmingham, Birmingham, AL, United States of America

* b-schalet@northwestern.edu

Abstract

Background
Meta-analyses of placebo-controlled trials of SSRIs suggest that only a small portion of the observable change in depression may be attributed to "true" pharmacological effects. But depression is a multidimensional construct, so treatment effects may differ by symptom cluster. We tested the hypothesis that SSRIs uniquely alter psychological rather than somatic symptoms of depression and anxiety.

Method
Outpatients with moderate to severe MDD were randomly assigned to receive paroxetine (n = 120) or placebo (n = 60).

Results
Paroxetine significantly outperformed placebo on all psychological subscales of the syndrome measures, but not on any of the somatic subscales. The difference in score reduction between paroxetine and placebo was more than twice as great for the psychological symptoms compared to the somatic symptoms.

Conclusions
Paroxetine appears to have a “true” pharmacological effect on the psychological but not on the somatic symptoms of depression and anxiety. Paroxetine’s influence on somatic symptoms appears to be mostly duplicated by placebo.
Introduction

Depression is a multi-faceted disorder encompassing emotional, cognitive, behavioral, and somatic symptoms. Treatment for major depression may include various forms of psychotherapy, antidepressant medication (ADM), such as the selective serotonin reuptake inhibitors (SSRIs), or a combination of both. Placebo-controlled clinical trials typically show that SSRIs and cognitive-behavioral therapies outperform placebo [1] [2].

One striking aspect of these clinical trials is the large symptom improvement in the placebo group. Meta-analyses of placebo-controlled trials of most SSRIs estimate that placebo accounts for about 75% of the effects of ADM during the acute phase treatment [3, 4]. That is, these data suggest that no more than 25% of the observable change may be attributed to the pharmacological effects of SSRIs, whereas the majority of change is due to nonspecific placebo effects and natural course of the illness (spontaneous remission). In this light, the psychopharmacological effects of SSRIs appear rather unimpressive.

This conclusion, however, is based exclusively on reported changes in total scores on depression outcome measures and treatment effects may differ by symptom clusters. The effectiveness of SSRIs for a wide range of mental disorders [5–8] indicates that they provide relief on diverse sets of psychological symptoms, or, alternatively, that they may alter broader dispositions, such as maladaptive personality traits [9–11]. Secondly, patients in depression studies rarely present exclusively with a “pure” set of depression symptoms, but nearly always have clinical or subclinical manifestations of other disorders, particularly anxiety [12], which may also be altered by SSRI treatment [13]. Finally, depression itself is a psychometrically multidimensional construct [14, 15] and improvement in one dimensional symptom set (such as mood) will not automatically accompany change in another (such as insomnia). To understand the scope and the limits of SSRI effects, researchers must examine outcomes in greater detail and depth.

In one such example, Tang et al. [9] examined both the depression severity and the personality trait of neuroticism in a placebo-controlled trial of paroxetine for moderate to severely depressed patients. Neuroticism refers to one’s tendency to experience exaggerated negative emotions of sadness, anger, and anxiety under conditions of stress [16, 17]. While 75% of the improvement observed with paroxetine on the traditional depression measure, the Hamilton Rating Scale for Depression (HRSD) [18, 19] was accounted for by placebo effect, only 23% of the observed decrease in neuroticism was duplicated in the placebo condition. In addition, the specific advantage for paroxetine over placebo with respect to depression was no longer significant after controlling for change in neuroticism, whereas its specific advantage over placebo in reducing neuroticism remained significant after controlling for change in depression.

It is possible that ADM substantially changes some depression symptoms and has virtually no effect (or a negative effect) on others. Consistent with this notion, meta-analysis of placebo-controlled SSRI trials show a wide range of effect sizes for the individual depression symptoms [20, 21]. For example, in two separate meta-analyses of ADM treatment studies of depression—one with tricyclics and the other with fluoxetine—Faries et al. [20] found that five symptoms (depressed mood, guilt, suicidality, disinterest / reduction in work and activities, and psychic anxiety) were more sensitive to differences between placebo and SSRIs compared to the other symptoms on the HRSD. Given that the HRSD is a commonly used measure in clinical trials [22], several researchers have promoted the use of different subscales of HRSD items on the basis of greater responsiveness to ADM, improved psychometric properties of these scales, and the association of individual items with overall depression severity [14, 20, 23–29].

While these studies generally demonstrate superior ADM effects for certain HRSD subscales, a clearly stated theory for the observed differential symptom effect sizes is still absent...
For example, in a post-hoc analysis, Fairies et al. [20] described the five symptoms common to the most responsive HRSD subscales as “core symptoms” of depression. This is equivalent to defining depression as that which SSRIs reduce, and implies that non-core symptoms are unimportant. A clear conceptual distinction is needed between those symptoms on which SSRIs have a “true” pharmacological effect versus those symptoms on which their effects are largely nonspecific.

We hypothesize that the specific pharmacological advantage of SSRIs over placebo will be largely concentrated on the psychological symptoms of depression and anxiety and not on the somatic symptoms. This counterintuitive hypothesis is consistent with an earlier finding that paroxetine has a considerably larger specific effect on neuroticism than on depression [9]. While four out of the nine depression symptoms articulated in the DSM-IV may be characterized as somatic [30], and somatic symptoms make up as many as 11 out of 17 symptoms assessed by the HRSD, they are entirely absent in neuroticism measurement. Somatic complaints have been found to correlate weakly with neuroticism, whereas psychological symptoms of both depression and anxiety correlate moderately to strongly [31, 32]. Finally, psychometric analyses indicate that somatic symptoms—fatigue, appetite loss/gain, insomnia, and anxious arousal—show relatively distinct patterns of association relative to the more general affective symptoms common to both depression and anxiety [14, 33–35].

We test this hypothesis on data generated in a placebo-controlled randomized trial of 180 moderately to severely depressed patients [2]. In addition, we will also explore how changes in the psychological subscales of depression and anxiety relate to changes in neuroticism, given their conceptual overlap [36].

Method

Participants

The Institutional Review Board at the University of Pennsylvania and the Human Research Protection Program (Institutional Review Board) at Vanderbilt University approved the study protocol and written informed consent was obtained from all participants. Subjects were moderate-to-severely depressed adult outpatients; patient characteristics, treatment procedure, and depression outcome findings have been detailed elsewhere [2, 37]. All patients met criteria for MDD and scored 20 or higher at both screening and intake evaluations on the 17-item version of the Hamilton Rating Scale of Depression [18, 19], modified to incorporate atypical symptoms [38]. Inclusion criteria were: (1) DSM-IV MDD diagnosis; (2) aged 18 to 70; (3) English speaking; and (4) willingness and ability to give informed consent. Exclusion criteria were: (1) history of bipolar I disorder; (2) substance abuse or dependence judged to require treatment; (3) current or past psychosis; (4) another DSM-IV Axis I disorder judged to require priority treatment; (5) antisocial, borderline, and/or schizotypal disorders (all other Axis II disorders were permitted); (6) suicide risk requiring immediate hospitalization; (7) a medical condition that contraindicated study medications; or (8) nonresponse to an adequate trial of paroxetine in the preceding year.

Clinical Trial

The trial randomized 120 patients to paroxetine and 60 patients to pill-placebo. (Sixty patients were also randomized to a cognitive therapy group, but they are not included in this study of paroxetine mechanism). Thirteen paroxetine patients (11%) and eight placebo patients (13%) dropped out before week 8. The patients who dropped out did not differ significantly on depression or anxiety severity. Patients, psychiatrists, and evaluators were all blind as to whether the patients’ pills contained paroxetine. After week 8, the blind was broken and placebo patients were offered free medication treatment.
Measurements

The following three symptom measures were administered both at intake and week 8: 17-item modified Hamilton Rating Scale for Depression (HRSD) [18, 19], modified to incorporate atypical symptoms [38], the 14-item Hamilton Rating Scale for Anxiety (HRSA) [39] and the 21-item Beck Anxiety Inventory (BAI) [40]. Both the HRSD and HRSA are clinician-administered measurements, while the BAI is self-reported. To maximize objectivity, clinicians who administered the HRSD and HRSA provided neither psychotherapy nor ADM treatment to participants in this study. Neuroticism was assessed at intake and week 8 using a 12-item scale from the NEO-Five-Factor Inventory (NEO-FFI) [41], a widely-used self-report measure based on the Five-Factor Model of Personality [42].

Among patients who continued with the study, some data were nonetheless missing, mostly anxiety scores at week 8. Because we intended to compare the magnitude of change across multiple measures and treatment conditions, we limited our analyses to patients who completed the HRSD, HRSA, and BAI at both intake and week 8. We excluded 7 placebo and 21 paroxetine patients from analysis (12% and 17% of intake, respectively), because these patients did not complete one or more questionnaires at either time point. Final sample sizes for analysis were 45 participants in placebo and 86 in paroxetine. The patients with missing questionnaire data did not differ significantly on intake depression or anxiety severity from the completer sample we analyzed.

For each of these three measures, we divided symptoms into somatic and psychological groups (Table 1) following the classification of Simon et al. [30] of the basic nine DSM-IV criteria for major depression. We excluded the HRSD hypochondriasis (#15) and insight (#17) items from our analyses, as they appeared unrelated to current DSM-IV criteria for major depression. Following the logic of Simon et al.’s symptom division, we classified symptoms that primarily describe thoughts, moods, anxiety/fears, and interest/behaviour as psychological; symptoms that describe bodily manifestations were classified as somatic (e.g., fatigue, hypersomnia, changes in weight, heart racing).

Both libido (HRSD #14) and "unable to relax" (BAI #4) were classified as somatic; however, we recognize that these classifications might be challenged. Although we classified the HRSD libido item as somatic (as did Enns et al. [31]), the HRSD interview emphasizes interest in and thoughts about sex, not sexual performance. The BAI item "unable to relax" could possibly refer to cognitive manifestations rather than bodily tension. Nevertheless, placing these two items in the psychological subscales does not change the results; indeed, these items show changes that lie somewhere between the average changes we report for their respective somatic and psychological subscales (Fig 1).

Our modified HRSD [38] included the assessment of three atypical symptoms of depression: hypersomnia, weight gain, and appetite increase, along with their typical counterparts (insomnia, weight loss, and appetite decrease). Following Reimherr et al. [38] and DeRubeis et al. [2], only the maximum of each patient’s typical/atypical pair (e.g., weight gain or loss) was added into the total of both the HRSD full scale and the somatic subscale. We considered other scoring options, but this scoring method produced the result that was least favorable to our hypothesis. For example, if only the typical or the atypical symptoms are included in the subscale, the non-significant medication advantage over placebo (Fig 1) is further cut in half.

Descriptive Analysis

Typically, effect sizes in treatment studies are calculated by dividing the difference of two group means by the pooled standard deviation (SD) [43]. Unfortunately, standardized effects also pose several problems, especially when the purpose is to compare effects across different
measures, samples, or conditions. Effect sizes may be sensitive to particular sample characteristics (such as restricted range) and differences in the reliability of the measures [44]. In addition, standardizing essentially erases scale anchors (e.g., "not at all", "moderately", "severely"), which are still meaningful in average item scores. Reporting change in average symptom scores, however, is complicated by the fact that the rating scales of each symptom differ across the three measures and, in the case of the HRSD, also within the measure. Although HRSD total scores have established ranges corresponding to depression severity [45], these ranges have not been established for somatic and psychological subscales.

To place scores and changes therein on comparable units, we converted scores on the subscales of the HRSD, HRSA, and BAI to Percent of Maximum Possible (POMP) scores [46, 47]. POMP scores are calculated by linearly transforming each participant’s raw score into a

| Table 1. Classification of Depression and Anxiety Symptoms as Psychological or Somatic, by Instrument Item Numbers. |
|---------------------------------------------------------------|
| **Symptom**                              | **HRSD Item #** | **HRSA Item #** | **BAI Item #** |
| Psychological                        |                |                |                |
| Anxiety Psychic             | 10             | 1              | 10            |
| Concentration                | 5              |                |               |
| Depressed Mood               | 1              | 6              |               |
| Fears                        | 3              |                | 5, 9, 14, 16, 17 |
| Guilt                        | 2              |                |               |
| Suicide (thoughts and behavior) | 3              |                |               |
| Work & Activities (loss of interest) | 7              |                |               |
| Somatic                       |                |                |                |
| Agitation / Tension           | 9              | 2              | 4             |
| Anxiety Somatic              | 11             | 7, 8           |               |
| Appetite Decrease/Increase   | 12, 12A        |                |               |
| Autonomic (e.g., dry mouth)  | 13             | 20, 21         |               |
| Behavior at Interview (e.g., fidgeting, hand tremor) | 14 | |
| Cardiovascular (e.g., heart racing) | 9 | 7, 19 | |
| Dizzy/Lightheaded            |                | 6              |               |
| Fatigue/Energy Loss          | 13             |                |               |
| Feeling Hot                  |                | 2              |               |
| Gastrointestinal (e.g., abdominal pain) | 11 | 18 | |
| Genitourinary (e.g., frequent urination) | 12 | |
| Hands Trembling              |                | 12             |               |
| Hypersomnia                  | 4A-6A          |                |               |
| Insomnia                     | 4–6            | 4              |               |
| Libido / Interest in Sex     | 14             |                |               |
| Numbness / Tingling          | 1              |                |               |
| Respiratory (e.g., choking feeling) | 10 | 11, 15 | |
| Retardation                  | 8              |                |               |
| Shaky / Unsteady / Wobbliness|                | 3, 8, 13       |               |
| Weight Gain/Loss             | 16, 16A        |                |               |
| Residual                     |                |                |               |
| Hypochondriasis              | 15             |                |               |
| Insight                      | 17             |                |               |

Numbers represent the item number of the symptom in each scale. Abbreviations: BAI, Beck Anxiety Inventory; HRSA, Hamilton Rating Scale of Anxiety; HRSD, 17-item version of the Hamilton Rating Scale for Depression, modified to incorporate atypical symptoms.

doi:10.1371/journal.pone.0159647.t001
percentage of the maximum possible total score of the measure. Descriptive statistics of POMP scores are informative with respect to the range of all possible scores (and the implied severity), and readily comparable to POMP scores of other samples and similar measures [46, 47]. POMP scores do not alter inferential statistics like t- or F-tests and are increasingly applied in clinical research [17, 48–51]. To facilitate any possible direct comparison with other studies, we reported POMP scores separately for subscales of each measure, rather than combining similar subscales or items across measures.

Inferential Analysis

To test for significant differences among treatment conditions, we completed standard ANCOVA, with treatment condition as the independent variable, the symptom measures at week 8 as dependent variables, and intake symptom measures as a covariate. We completed these tests separately for the HRSD, HRSA, and BAI total scores, and the respective psychological and somatic subscales. Expecting significant differences for the psychological measures as dependent variables, we added neuroticism intake and week 8 scores as covariates. We also completed the reverse analysis to see if treatment assignment would still predict neuroticism reduction (relative to placebo) after controlling for psychological symptom improvement. Finally, we calculated Cohen’s d for placebo vs. active treatments by dividing the difference in
the respective least squares means at week 8 by the pooled SD of the respective means. Such effects can be considered large when they are 0.8 and above, medium between 0.5 and 0.8, and small between 0.2 and 0.5 [43].

## Results

### Main Effects

Fig 1 illustrates the discrepancy in the unique effect of paroxetine on psychological compared to somatic symptoms during the acute phase of therapy. (Table 2 also shows intake and week 8 means and standard deviations for the total scale measures and their somatic and psychological subscales). For depression, the difference in score reductions between paroxetine and placebo was more than twice as great for the psychological symptoms as for the somatic symptoms: 10.4% vs. 4.6% (of maximum possible scores). The contrast between the advantage for

|                | Total Scale | Psychological Subscales | Somatic Subscales |
|----------------|-------------|-------------------------|-------------------|
|                | Intake      | Week 8                  |                   |
|                | Placebo     | Paroxetine              | Placebo           | Paroxetine |
| HRSD Mean      | 44.6        | 44.5                    | 29.5              | 22.8       |
| HRSD SD       | 4.5         | 5.4                     | 12.2              | 12.5       |
| HRSA Mean     | 30.8        | 28.8                    | 20.7              | 16.3       |
| HRSA SD       | 10.1        | 9.3                     | 11.5              | 10.0       |
| BAI Mean      | 23.7        | 24.2                    | 13.6              | 9.4        |
| BAI SD        | 13.8        | 15.4                    | 13.8              | 10.1       |

Abbreviations: BAI, Beck Anxiety Inventory; HRSA, Hamilton Rating Scale of Anxiety; HRSD, 17-item version of the Hamilton Rating Scale for Depression, modified to incorporate atypical symptoms.

doi:10.1371/journal.pone.0159647.t002
paroxetine in psychological symptoms vs. somatic symptoms was even stronger for the anxiety scales: 12.2% vs. 1.7% on the BAI and 5.6% vs. 0.9% on the HRSA.

Table 3 shows the main effect statistics for the treatments on the symptom scales. F-tests on all symptom measures indicated that paroxetine significantly outperformed placebo on total HRSD scores ($p = .004$), BAI scores ($p = .03$), and marginally on total HRSA scores ($p = .054$). Paroxetine also significantly outperformed placebo on all psychological subscales, ($p < .001$ for HRSD, $p = .01$ for the HRSA, $p < .001$ for the BAI), but it did not show significant advantage over placebo on any of the somatic subscales ($p > .20$). In short, paroxetine outperformed placebo substantially on the psychological subscales, but it did not outperform placebo on the somatic subscales.

| Dependent Variable | Paroxetine vs. Placebo |
|--------------------|------------------------|
|                    | F          | P        | ES       |
| Total measures     |            |          |          |
| HRSD               | 8.7       | .004     | 0.54     |
| HRSA               | 3.8       | .05      | 0.36     |
| BAI                | 4.8       | .03      | 0.4      |
| Psychological Subscales |       |          |          |
| HRSD-psych.        | 15.9      | <.001    | 0.74     |
| HRSA-psych.        | 6.2       | .01      | 0.46     |
| BAI-psych.         | 15.3      | <.001    | 0.72     |
| Somatic Subscales  |            |          |          |
| HRSD-somatic       | 1.5       | .22      | 0.23     |
| HRSA-somatic       | 1.7       | .2       | 0.24     |
| BAI-somatic        | 0.5       | .47      | 0.13     |

Abbreviations: BAI, Beck Anxiety Inventory; HRSA, Hamilton Rating Scale of Anxiety; 17-item version of the Hamilton Rating Scale for Depression, modified to incorporate atypical symptoms; psych., psychological.

doi:10.1371/journal.pone.0159647.t003

Paroxetine in psychological symptoms vs. somatic symptoms was even stronger for the anxiety scales: 12.2% vs. 1.7% on the BAI and 5.6% vs. 0.9% on the HRSA.

Table 3 shows the main effect statistics for the treatments on the symptom scales. F-tests on all symptom measures indicated that paroxetine significantly outperformed placebo on total HRSD scores ($p = .004$), BAI scores ($p = .03$), and marginally on total HRSA scores ($p = .054$). Paroxetine also significantly outperformed placebo on all psychological subscales, ($p < .001$ for HRSD, $p = .01$ for the HRSA, $p < .001$ for the BAI), but it did not show significant advantage over placebo on any of the somatic subscales ($p > .20$). In short, paroxetine outperformed placebo substantially on the psychological subscales, but it did not outperform placebo on the somatic subscales.

Change in Psychological Symptoms vs. Neuroticism

Consistent with previous research [31, 32], we found that neuroticism correlated more closely with our psychological subscales than with somatic subscales, both at intake (Mean $r = .32$ vs. Mean $r = .07$) and at week 8 (Mean $r = .45$ vs. Mean $r = .29$), with all differences between corresponding psychological and somatic correlations being significant, all $p < .05$.

In an effort to understand the level of overlap between neuroticism and the psychological symptom scales, we repeated our ANCOVA of treatment assignment (paroxetine vs. placebo), but with additional covariates. First, we found that treatment assignment (paroxetine vs. placebo) had a unique effect on neuroticism reduction, even after controlling for the psychological symptoms ($p < .02$). (See Table 4 for details). Even when all three psychological symptom measures are entered simultaneously as covariates, paroxetine still significantly outperformed placebo in reducing neuroticism ($p = .01$) suggesting that paroxetine’s effect on neuroticism is not a mere byproduct of psychological symptom change. On the other hand, for the psychological symptoms of HRSD and BAI, the differences between reduction on paroxetine and placebo could not be entirely explained by neuroticism reduction either ($p = .03$ and $p = .02$, respectively). However, when controlling for neuroticism, treatment assignment no longer predicted reduction on the HRSA ($p = .65$).
Discussion

In this study, we analyzed symptom improvements in a moderately-to-severely depressed sample during placebo and paroxetine treatments. To our best knowledge, this study is the first to characterize the SSRI advantage over placebo as primarily psychological rather than somatic. In fact, differences in treatment assignment were not significant for any of the somatic subscales. In addition, differences between patients in the paroxetine condition and the placebo condition were much greater on psychological symptoms than on somatic symptoms, particularly for anxiety (Fig 1).

Our results are consistent with past research that empirically searched for HRSD items showing the largest treatment effects, typically without considering the nature of the HRSD items [20, 27]. For example, the top five items identified by Faries et al. [20] and Entsuah et al. [27], as well as five of the top six items identified by Santor et al. [29] belong to our psychological subscales of the HRSD. Our results extend these results beyond the HRSD to the HRSA and BAI. More importantly, it now gives a possible theoretical rationale to these past findings.

Fournier et al. [35] also analyzed the HRSD items of this clinical trial. Unlike this study, however, Fournier et al. [35] divided the 24-item version of the HRSD symptoms into five clusters using factor analysis. These empirically derived clusters show a somewhat complex relationship with the system of psychological vs. physiological items in this project. For example, their 3-item mood cluster includes depressed mood, anhedonia, and loss of energy. In this project, depressed mood and anhedonia are classified as psychological, but loss of energy is classified as a somatic symptom, consistent with the symptom divisions of Simon et al. [30], Shafer [15], and Enns et al. [31]. Fournier et al.’s [35] five-item suicide cluster included only items from our psychological symptom subscale: suicide and guilt, along with helplessness, hopelessness, and worthlessness from the 24-item HRSD. Consistent with our results and theory, this cluster showed the largest effect size in favor of paroxetine over placebo among the five clusters at week 8; and changes in the other clusters (all of which included one or more somatic symptoms) did not differ significantly from placebo.

Separate Neurobiological Correlates

Our findings indicate that SSRI treatment differentially impacts psychological and somatic symptoms of depression and anxiety, showing much greater specific effects (relative to
placebo) on psychological symptoms. One of the potential mechanisms for this finding is that separate neurobiological structures and pathways may be implicated in the expression of psychological versus somatic symptoms. Thus, while depressed mood may be marked by abnormal activation of the medial prefrontal cortex and difficulty concentrating is strongly associated with hypoactivity in the dorsolateral prefrontal cortex [52], motor retardation may be embodied by dysregulation in the striatum and physical tiredness may be associated with dopamine depletion in nucleus accumbens [53].

Antidepressant medications have been thought to act predominantly on neurovegetative symptoms of depression [54]. However, these effects are primarily associated with the older tricyclic antidepressants. Tricyclics block the reuptake of norepinephrine and serotonin, but more predominantly act on norepinephrine. Further, tricyclics are potent antagonists of histamine-1 receptors, conferring strong sedating properties. By contrast, SSRIs like paroxetine have little if any actions on either norepinephrine reuptake or histamine receptors [55]. Paroxetine is the most potent inhibitor of the norepinephrine transporter of all SSRIs but the actions on serotonin are 10-fold greater than on norepinephrine [55].

Why should SSRIs act preferentially on psychological symptoms of depression? In 1986 Depue and Spoont proposed that serotonin has an effect of constraining both behavioral inhibition and behavioral facilitation systems [56]. This concept was supported subsequently by Knutson et al. [57], who showed a general reduction in negative affect with paroxetine, and by Sheline et al. [58] who showed that the SSRI sertraline inhibited the excess left amygdala response to all faces, particularly fearful faces using fMRI. These effects are also consistent with the observations of Tang et al. of the effects of paroxetine on neuroticism noted above. This inhibiting effect of serotonin on amygdala reactivity and general distress symptoms is attributable to the actions on specific serotonin receptors on inhibitory, GABAergic interneurons [59]. Serotonin has a complex role in CNS function given the large number of serotonin receptors in brain and their sometimes opposing roles [60]. However, the current work continues to support the original Depue and Spoont [56] notion of an overall constraining effect on distress-inducing brain regional activity.

**Treatment Implications**

Our results suggest that the effects of SSRIs on somatic symptoms are not stronger than that of placebo. Researchers and clinicians may need to look towards additional medications to reduce these symptoms further. While neurological evidence for distinct systems is still limited, it stands to reason that improvement on somatic symptoms (such as fatigue) may require separate treatments from those that address psychological symptoms. One approach may be to target multiple neurotransmitter pathways; duel-acting medications (such as duloxetine and venlafaxine) may be more effective than SSRIs in treating some somatic symptoms of depression [61–64], though the advantage over SSRIs in total depression scores is rather modest [65].

Research on ADM treatment of low energy levels specifically in the context of depression has been limited, despite its apparent centrality to major depression. Not surprisingly, low energy (or fatigue) is among the most common residual symptom after acute SSRI treatment [66]. Buproprion, a norepinephrine and dopamine reuptake inhibitor that targets the frontal cortex may be more effective in improving energy levels than standard SSRIs [67, 68]. A meta-analysis of duloxetine trials shows a moderate improvement on the somatic HRSD symptoms of energy and retardation, though this holds primarily for moderate to severely depressed patients [64]. In addition, first-line ADM treatment may be augmented with modafinil or central nervous system stimulants, which promote wakefulness [66, 69].
The Role of Neuroticism

Our results are consistent with earlier findings that SSRIs may directly target neuroticism, a broad disposition to experience negative emotions [9, 10] that includes no somatic content [16, 41]. Our psychological subscales, therefore, show more efficient empirical and conceptual overlap with neuroticism compared to the full-length symptom scales. Although measures of neuroticism, depression, and anxiety exhibit considerable construct overlap, neuroticism (as a personality measure) is nevertheless crucially different from symptom measures because of the absence of any time-frame context [36]. A future area of investigation would be to further understand the extent to which treatment effects may be attributed to such unique aspects of personality assessment or to the intersection of personality and depression/anxiety symptoms.

Limitations

Our study needs to be replicated using both paroxetine and other SSRIs to determine if the effects are reliable and if they are limited to a single medication or medication class [70]. The use of multiple and more comprehensive measures of depression and anxiety would also have increased confidence in the finding. In addition, we did not directly measure the neurobiological systems underlying psychological and somatic symptoms. We also did not have plasma levels of paroxetine available to verify compliance. It is arguable that splitting each instrument into two subscales increased the type-1 error rate. However, setting alpha at 0.025 (instead of 0.05) for significance testing alters the conclusion of only one test, namely, that paroxetine no longer predicts change in psychological symptoms of the HRSD when controlling for Neuroticism change. Finally, there were a number of dropouts in the trial (11–13%) and our samples were modest and limited to those who completed assessments at both time points.

Significance

Although SSRIs are the most widely prescribed treatment for major depression, the field still needs a comprehensive description and clearly stated formulation of the symptom changes caused by SSRIs. Our results contribute to this effort by suggesting that SSRIs enact improvement beyond placebo mostly for psychological, but not somatic symptoms of depression and anxiety. To further improve somatic symptoms of depression, researchers may need to further explore how to improve treatments of somatic symptoms.

Supporting Information

S1 Data. SPSS data file containing variables used in analysis (deidentified data). (SAV)

S1 Data Syntax. Text file containing SPSS commands used in analysis. (TXT)

Author Contributions

Conceived and designed the experiments: RD SH JA RS. Performed the experiments: RD SH JA RS. Analyzed the data: BS TT. Wrote the paper: BS TT RD SH JA RS.

References

1. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. The American Journal of Psychiatry. 1999; 156(7):1007–13. PMID: 10401443
2. DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, et al. Cognitive Therapy vs Medications in the Treatment of Moderate to Severe Depression. Archives of General Psychiatry. 2005; 62(4):409–16. doi: 10.1001/archpsyc.62.4.409 PMID: 15809408

3. Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. Prevention & Treatment. 1998; 1(2). doi: 10.1037/1522-3736.1.1.12a

4. Kirsch I, Moore TJ, Scoboria A, Nicholls SS. The emperor’s new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. Prevention & Treatment. 2002; 5 (1):23.

5. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(1):85–102. PMID: 12551730

6. Zohar J, Sasson Y, Chopra M, Amital D, Iancu I. Pharmacological treatment of obsessive-compulsive disorder: a review. Obsessive-compulsive disorder. 2000:43–62.

7. Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: A randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. The American Journal of Psychiatry. 2002; 159(12):2048–54. doi: 10.1176/appi.ajp.159.12.2048 PMID: 12450955

8. Flament MF, Bissada H, Spettigue W. Evidence-based pharmacotherapy of eating disorders. Int J Neuropsychopharmacol. 2012; 15(2):189–207. doi: 10.1017/S1461145711000381 PMID: 21414249

9. Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B. Personality change during depression treatment: a placebo-controlled trial. Arch Gen Psychiatry. 2009; 66(12):1322–30. doi: 10.1001/archgenpsychiatry.2009.166 PubMed Central PMCID: PMCPMC2799251. PMID: 19996037

10. Quilty LC, Meusel L-AC, Bagby RM. Neuroticism as a mediator of treatment response to SSRIs in major depressive disorder. Journal of Affective Disorders. 2008; 111(1):67–73. doi: 10.1016/j.jad.2008.02.006 PMID: 18384882

11. Ripoll LH, Triebwasser J, Siever LJ. Evidence-based pharmacotherapy for personality disorders. Int J Neuropsychopharmacol. 2011; 14(9):1257–88. doi: 10.1017/S1461145711000071 PMID: 21320390

12. Rapaport MH. Prevalence, recognition, and treatment of comorbid depression and anxiety. Journal of Clinical Psychiatry. 2001; 62(Suppl24):6–10.

13. Ravindran LN, Stein MB. The pharmacological treatment of anxiety disorders: A review of progress. Journal of Clinical Psychiatry. 2010; 71(7):839–54. doi: 10.4088/JCP.10r06218blu PMID: 20667290

14. Gibbons RD, Clark DC, Kupfer DJ. Exactly what does the Hamilton Depression Rating Scale measure? Journal of Psychiatric Research. 1993; 27(3):259–73. doi: 10.1016/0022-3956(93)90037-3 PMID: 8295158

15. Shafer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. Journal of Clinical Psychology. 2006; 62(1):123–46. PMID: 16287149

16. Costa PT Jr., McCrae RR. The Five-Factor Model and the NEO Inventories. In: Butcher JN, editor. The Oxford handbook of personality assessment. Oxford library of psychology. New York, NY US: Oxford University Press; 2009. p. 299–322.

17. Griffith JW, Zimbarg RE, Craske MG, Mineka S, Rose RD, Waters AM, et al. Neuroticism as a common dimension in the internalizing disorders. Psychological Medicine. 2010; 40(7):1125–36. doi: 10.1017/S0033291709991449 PMID: 19903363

18. Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry. 1960; 23:56–61. doi: 10.1136/jnnp.23.1.56

19. Williams JB, A structured interview guide for the Hamilton Depression Rating Scale. Archives of General Psychiatry. 1988; 45(8):742–7. doi: 10.1001/archpsyc.1988.01800320058007 PMID: 3395203

20. Faries D, Herrera J, Rayamajhi J, DeBonta D, Demitrack M, Potter WZ. The responsiveness of the Hamilton Depression Rating Scale. Journal of Psychiatric Research. 2000; 34(1):3–10. doi: 10.1016/S0033-2917(99)00037-0 PMID: 10696827

21. Judge R, Plewes JM, Kumar V, Koke SC, Kopp JB. Changes in energy during treatment of depression: An analysis of fluoxetine in double-blind, placebo-controlled trials. Journal of Clinical Psychopharmacology. 2000; 20(6):666–72. PMID: 11106139

22. Demymtenaere K, De Fruyt J. Getting what you ask for: On the selectivity of depression rating scales. Psychotherapy and Psychosomatics. 2003; 72(2):61–70. doi: 10.1159/000068690 PMID: 12601223

23. Bech P, Allerup P, Gram L, Reisby N, Rosenberg R, Jacobsen O, et al. The Hamilton depression scale. Acta Psychiatrica Scandinavica. 1981; 63(3):290–9. PMID: 7015793

24. Maier W, Philipp M. Comparative analysis of observer depression scales. Acta Psychiatrica Scandinavica. 1985; 72(3):239–45. doi: 10.1111/j.1600-0447.1985.tb02601.x PMID: 4072721
25. Evans KR, Sills T, DeBrot DJ, Gelwicks S, Engelhardt N, Santor D. An Item Response analysis of the Hamilton Depression Rating Scale using shared data from two pharmaceutical companies. Journal of Psychiatric Research. 2004; 38(3):275–84. doi: 10.1016/j.jpsychires.2003.11.003 PMID: 15003433

26. McIntyre R, Kennedy S, Bagby M, Bakish D. Assessing full remission. Journal of Psychiatry & Neuroscience. 2002; 27(4):235–9.

27. Entsuah R, Shaffer M, Zhang J. A critical examination of the sensitivity of unidimensional subscales derived from the Hamilton Depression Rating Scale to antidepressant drug effects. Journal of Psychiatric Research. 2002; 36(6):437–48. doi: 10.1016/S0022-3956(02)00024-9 PMID: 12393314

28. Ballesteros J, Bobes J, Bulbena A, Luque A, Dalt-Ré R, Ibarra N, et al. Sensitivity to change, discriminative performance, and cutoff criteria to define remission for embedded short scales of the Hamilton depression rating scale (HAM-D). Journal of affective disorders. 2007; 102(1):93–9.

29. Santor DA, Debrota D, Engelhardt N, Gelwicks S. Optimizing the ability of the Hamilton Depression Rating Scale to discriminate across levels of severity and between antidepressants and placebos. Depression and Anxiety. 2008; 25(9):774–86. doi: 10.1002/da.20351 PMID: 17935212

30. Simon GE, Von Korff M, Piccinelli M, Fullerton C, Ormel J. An international study of the relation between somatic symptoms and depression. The New England Journal of Medicine. 1999; 341(18):1329–35. doi: 10.1056/NEJM199910283411801 PMID: 10536124

31. Enns MW, Larsen DK, Cox BJ. Discrepancies between self and observer ratings of depression. The relationship to demographic, clinical and personality variables. Journal of Affective Disorders. 2000; 60(1):33–41. doi: 10.1016/S0165-0327(99)00156-1 PMID: 10940445

32. de Beurs E, den Hollander-Gijsman ME, Helmich S, Zitman FG. The tripartite model for assessing symptoms of anxiety and depression: Psychometrics of the Dutch version of the mood and anxiety symptoms questionnaire. Behaviour Research and Therapy. 2007; 45(7):1609–17. doi: 10.1016/j.brat.2006.07.004 PMID: 16959211

33. Watson D, O’Hara MW, Simms LJ, Kotov R, Chmielewski M, McDade-Montez EA, et al. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychological Assessment. 2007; 19(3):253–68. doi: 10.1037/1040-3590.19.3.253 PMID: 17845118

34. Watson D, O’Hara MW, Chmielewski M, McDade-Montez EA, Koffel E, Naragon K, et al. Further validation of the IDAS: Evidence of convergent, discriminant, criterion, and incremental validity. Psychological Assessment. 2008; 20(3):248–59. doi: 10.1037/a0012570 PMID: 18778161

35. Fournier JC, DeRubeis RJ, Hollon SD, Gallop R, Shelton RC, Amsterdam JD. Differential change in specific depressive symptoms during antidepressant medication or cognitive therapy. Behaviour Research and Therapy. 2013; 51(7):392–8. doi: 10.1016/j.brat.2013.03.010 PMID: 23644038

36. Ormel J, Riese H, Rosmalen JGM. Interpreting neuroticism scores across the adult life course: Immutable or experience-dependent set points of negative affect? Clinical Psychology Review. 2012; 32(1):71–9. doi: 10.1016/j.cpr.2011.10.004 PMID: 22172577

37. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O’Reardon JP, et al. Prevention of Relapse Following Cognitive Therapy vs Medications in Moderate to Severe Depression. Archives of General Psychiatry. 2005; 62(4):417–22. doi: 10.1001/archpsyc.62.4.417 PMID: 15890409

38. Reimherr FW, Amsterdam JD, Quitkin FM, Rosenbaum JF, Favaz M, Zajecka J, et al. Optimal length of continuation therapy in depression: A prospective assessment during long-term fluoxetine treatment. The American Journal of Psychiatry. 1998; 155(9):1247–52. PMID: 9734550

39. Hamilton M. The assessment of anxiety states by rating. British Journal of Medical Psychology. 1959; 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x PMID: 13638508

40. Beck A, Epstein N, Brown G, Steer RA. (1988). An inventory for measuring clinical anxiety: Psychometric properties. Journal of Consulting & Clinical Psychology. 56:893–903.

41. Costa PT, McCrae RR. Professional manual: revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI). Odessa, FL: Psychological Assessment Resources. 1992.

42. McCrae RR, Costa PT. Jr. The five-factor theory of personality. In: John OP, Robins RW, Pervin LA, editors. Handbook of personality: Theory and research ( 3rd ed). New York, NY US: Guilford Press; 2008. p. 159–81.

43. Cohen J. Statistical power analysis for the behavioral sciences: Routledge Academic; 1988.

44. Baguley T. Standardized or simple effect size: What should be reported? British Journal of Psychology. 2009; 100(3):603–17. doi: 10.1348/000712608X377117 2009-25215-012. First Author & Affiliation: Baguley, Thom.

45. Pincus HA, Rush A, First M, McQueen L. Handbook of personality measures. American Psychiatric Association. 2000.

46. Cohen P, Cohen J, Aiken LS, West SG. The problem of units and the circumstances for POMP. Multivariate Behavioral Research. 1999; 34(3):315–46. doi: 10.1207/S15327906MBR3403_2
47. Cohen JC, West P, Aiken S. LS Applied multiple regression/correlation analysis for the behavioral sciences 3rd ed. Mahwah, NJ: Erlbaum; 2003.

48. Algorta GP, Youngstrom EA, Frazier TW, Freeman AJ, Youngstrom JK, Findling RL. Suicidality in pediatric bipolar disorder: predictor or outcome of family processes and mixed mood presentation? Bipolar Disord. 2011; 13(1):76–86. doi: 10.1111/j.1399-5618.2010.00886.x PMID: 21320255

49. Feinstein JS, Duff MC, Tranel D. Sustained experience of emotion after loss of memory in patients with amnesia. PNAS Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(17):7674–9. doi: 10.1073/pnas.0914054107

50. Mendenhall AN, Fristad MA, Early TJ. Factors influencing service utilization and mood symptom severity in children with mood disorders: Effects of multifamily psychoeducation groups (MFPGs). Journal of Consulting and Clinical Psychology. 2009; 77(3):463–73. doi: 10.1037/a0014527 PMID: 19485588

51. Gwadz MV, Leonard NR, Cleland CM, Riedel M, Arredondo GN, Wolfe H, et al. Behavioral interventions for HIV infected and uninfected mothers with problem drinking. Addiction Research & Theory. 2008; 16(1):47–65. doi: 10.1080/16066350701651214

52. Stahl SM, Zhang L, Damatarca C, Grady M. Brain Circuits Determine Destiny in Depression: A Novel Approach to the Psychopharmacology of Wakefulness, Fatigue, and Executive Dysfunction in Major Depressive Disorder. Journal of Clinical Psychiatry. 2003; 64(Suppl14):6–17.

53. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. International Journal of Neuropsychopharmacology. 2005; 8(1):93–105. PMID: 15482632

54. Akiskal HS. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. Am J Psychiatry. 1983; 140(1):11–20. Epub 1983/01/01. doi: 10.1176/ajp.140.1.11 PMID: 6336637

55. Owens MJ, Morgan WN, Pott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. JPharmacolExpTher. 1997; 283(3):1305–22.

56. Depue RA, Spoont MR. Conceptualizing a serotonin trait. A behavioral dimension of constraint. AnnNYAcadSci. 1986; 487:47–62.

57. Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC, et al. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry. 1998; 155(3):373–9. PMID: 9501748

58. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. BiolPsychiatry. 2001; 50(9):651–8.

59. Rainnie DG. Serotonergic modulation of neurotransmission in the rat basolateral amygdala. J Neurophysiol. 1999; 82(1):69–85. Epub 1999/07/13. PMID: 10400936

60. Palacios JM. Serotonin receptors in brain revisited. Brain Res. 2015. Epub 2016/01/08. doi: 10.1016/j.brainres.2015.12.042

61. Mallinckrodt CH, Prakash A, Houston JP, Swindle R, Detke MJ, Fava M. Differential antidepressant symptom efficacy: Placebo-controlled comparisons of duloxetine and SSRIIs (fluoxetine, paroxetine, escitalopram). Neuropsychobiology. 2007; 56(2–3):73–85. doi: 10.1159/000111537 PMID: 18037817

62. Delgado PL. Common pathways of depression and pain. Journal of Clinical Psychiatry. 2004; 65(Suppl12):16–9.

63. Kang E-H, Lee I-S, Chung S-K, Lee S-Y, Kim E-J, Hong J-P, et al. Mirtazapine versus venlafaxine for the treatment of somatic symptoms associated with major depressive disorder: A randomized, open-labeled trial. Psychiatry Research. 2009; 169(2):118–23. doi: 10.1016/j.psychres.2008.06.021 PMID: 19695711

64. Shelton RC, Andorn AC, Mallinckrodt CH, Wohreich MM, Raskin J, Watkin JG, et al. Evidence for the efficacy of duloxetine in treating mild, moderate, and severe depression. International Clinical Psychopharmacology. 2007; 22(6):348–55. PMID: 17917553

65. Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are Antidepressant Drugs That Combine Serotonergic and Noradrenergic Mechanisms of Action More Effective Than the Selective Serotonin Reuptake Inhibitors in Treating Major Depressive Disorder? A Meta-analysis of Studies of Newer Agents. Biological Psychiatry. 2007; 62(11):1217–27. PMID: 17588546

66. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. The International Journal of Neuropsychopharmacology. 2005; 8(1):93–105. PMID: 15482632

67. Bodkin JA, Lasser RA, Wines JD Jr, Gardner DM, Baldessarini RJ. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. The Journal of clinical psychiatry. 1997; 58(4):137. PMID: 9164423

68. Baldwin DS, Papakostas GI. Symptoms of fatigue and sleepiness in major depressive disorder. The Journal of clinical psychiatry. 2006; 67:9.
69. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry. 2005; 66(1):85–93. PMID: 15669893

70. Bagby RM, Levitan RD, Kennedy SH, Levitt AJ, Joffe RT. Selective alteration of personality in response to noradrenergic and serotonergic antidepressant medication in depressed sample: evidence of non-specificity. Psychiatry Research. 1999; 86(3):211–6. PMID: 10482340