

# Personality Change During Depression Treatment

## A Placebo-Controlled Trial

Tony Z. Tang, PhD; Robert J. DeRubeis, PhD; Steven D. Hollon, PhD;  
Jay Amsterdam, MD; Richard Shelton, MD; Benjamin Schalet, MA

**Context:** High neuroticism is a personality risk factor that reflects much of the genetic vulnerability to major depressive disorder (MDD), and low extraversion may increase risk as well. Both have been linked to the serotonin system.

**Objectives:** To test whether patients with MDD taking selective serotonin reuptake inhibitors (SSRIs) report greater changes in neuroticism and extraversion than patients receiving inert placebo, and to examine the state effect hypothesis that self-reported personality change during SSRI treatment is merely a change of depression-related measurement bias.

**Design:** A placebo-controlled trial.

**Setting:** Research clinics.

**Patients:** Adult patients with moderate to severe MDD randomized to receive paroxetine (n=120), placebo (n=60), or cognitive therapy (n=60).

**Outcome Measures:** NEO Five-Factor Inventory and Hamilton Rating Scale for Depression.

**Results:** Patients who took paroxetine reported greater personality change than placebo patients, even after controlling for depression improvement (neuroticism,

$P < .001$ ; extraversion,  $P = .002$ ). The advantage of paroxetine over placebo in antidepressant efficacy was no longer significant after controlling for change in neuroticism ( $P = .46$ ) or extraversion ( $P = .14$ ). Patients taking paroxetine reported 6.8 times as much change on neuroticism and 3.5 times as much change on extraversion as placebo patients matched for depression improvement. Although placebo patients exhibited substantial depression improvement (Hamilton Rating Scale for Depression score,  $-1.2$  SD,  $P < .001$ ), they reported little change on neuroticism ( $-0.18$  SD,  $P = .08$ ) or extraversion ( $0.08$  SD,  $P = .50$ ). Cognitive therapy produced greater personality change than placebo ( $P \leq .01$ ); but its advantage on neuroticism was no longer significant after controlling for depression ( $P = .14$ ). Neuroticism reduction during treatment predicted lower relapse rates among paroxetine responders ( $P = .003$ ) but not among cognitive therapy responders ( $P = .86$ ).

**Conclusions:** Paroxetine appears to have a specific pharmacological effect on personality that is distinct from its effect on depression. If replicated, this pattern would disconfirm the state effect hypothesis and instead support the notion that SSRIs' effects on personality go beyond and perhaps contribute to their antidepressant effects.

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### Author Affiliations:

Northwestern University, Evanston, Illinois (Dr Tang and Mr Schalet); University of Pennsylvania, Philadelphia (Drs DeRubeis and Amsterdam); and Vanderbilt University, Nashville, Tennessee (Drs Hollon and Shelton).

**N**EUROTICISM AND EXTRAVERSION are 2 of the 5 primary personality dimensions in the Five-Factor Model of Personality.<sup>1-3</sup>

Neuroticism refers to a tendency to experience negative emotions and emotional instability; extraversion encompasses social extraversion, dominance, and a tendency to experience positive emotions.<sup>1-3</sup> Neuroticism and extraversion are largely independent constructs, as evidenced by correlations between them of  $-0.28$  and  $-0.38$  in 2 normative samples.<sup>4</sup>

Results from longitudinal studies have consistently shown that neuroticism predicts both the onset and the chronicity of

major depressive disorder (MDD).<sup>5-11</sup> For example, in a study of more than 800 children, precursors of neuroticism measured at age 3 years predicted whether these children would develop MDD at age 21 years.<sup>11</sup> In some longitudinal studies, lower levels of extraversion have also predicted the onset of MDD,<sup>9,12</sup> but this pattern has not been replicated in other studies.<sup>8,10</sup>

Neuroticism and extraversion are both moderately heritable, with genetic factors determining 50% to 60% of their variance.<sup>2,13</sup> Twin studies have found substantial overlap in the genetic factors that are associated with high neuroticism and those that predispose persons to MDD.<sup>10,14-17</sup> Neuroticism, therefore,

appears to reflect much of the genetic vulnerability to MDD.<sup>10,16,17</sup>

Research on medical disorders with known causes often focuses on the impact of treatments on these causal factors. Despite the accumulating evidence associating neuroticism and extraversion with a causal path to MDD, little research exists on how selective serotonin reuptake inhibitor (SSRI) treatment affects these personality risk factors. Patients have reported that SSRIs make them less reactive to stress, less sensitive to rejection, and more outgoing and vivacious.<sup>18-23</sup> These descriptions are consistent with decreases in neuroticism and increases in extraversion, but these reports have not come from patients in double-blind, placebo-controlled studies.<sup>18-22</sup> In the one published placebo-controlled study of change in neuroticism during SSRI treatment of MDD, Agosti and McGrath<sup>24</sup> did not find that patients taking fluoxetine reported significantly greater neuroticism reduction than placebo patients. However, fewer than half of the patients in that study (42%) completed both treatment and assessment, making these findings difficult to interpret. Thus, it remains unclear whether neuroticism and extraversion change in response to SSRI treatment of MDD above and beyond their natural history and the placebo effect.

When change in personality is reported during SSRI treatment, it is usually assumed to reflect nothing more than the state effect of depression on personality measurement.<sup>21,25,26</sup> When in depressive episodes, patients often describe themselves as more neurotic and less extroverted than they are in their intermorbid or premorbid states. This is consistent with the idea that there is a state effect of depression on personality measurement.<sup>5,6,8</sup> The state effect hypothesis holds that reported personality change during SSRI treatment is just change in state effect: as depression improves, the state effect of depression will decline, and personality measurement will change as a consequence.<sup>21,25,26</sup> This hypothesis thus regards reported personality change as an inconsequential byproduct of depression improvement. The main evidence for this hypothesis is the finding that personality change correlates with depression improvement during SSRI treatment.<sup>18,21</sup>

Two studies of healthy subjects without current MDD reported findings that are inconsistent with the state effect hypothesis. In both studies, SSRIs were found to influence behaviors and affects that are closely associated with neuroticism and extraversion.<sup>27,28</sup> Recent findings from neuroscience investigations also support associations between these personality dimensions and the serotonin system. For example, molecular genetic and positron emission tomography studies have associated neuroticism with serotonin receptor polymorphisms and binding.<sup>29-31</sup> Individual studies of neuroticism and the functional polymorphic variants of the serotonin transporter gene have yielded mixed results, but 2 meta-analyses of these studies have converged on the conclusion that the link is statistically significant.<sup>32,33</sup> Moreover, the serotonin system has been implicated as a substrate for behaviors related to extraversion in numerous animal and human studies.<sup>27,28,34-36</sup> Selective serotonin reuptake inhibitor treatment, which targets the serotonin system, might thus affect neuroticism and extraversion directly, in a manner that does not depend on its antidepressant effects.

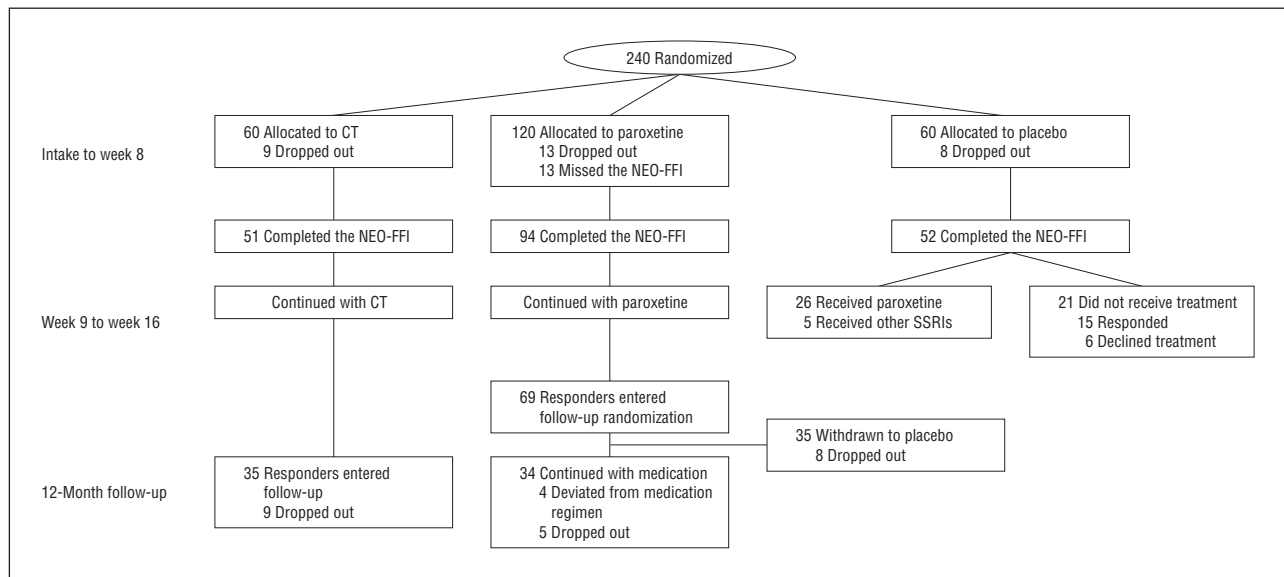
Cognitive therapy (CT), a leading psychosocial treatment of MDD, has been shown to reduce depression symptom severity to a degree similar to that produced by SSRIs.<sup>37-39</sup> While some studies of CT have examined pretreatment personality as predictors of outcome,<sup>40,41</sup> very little theoretical or empirical work exists on how CT might impact neuroticism and extraversion. Although the state effect hypothesis might also apply to personality changes reported in CT, it is also plausible that CT changes personality through cognitive or behavioral pathways. For example, CT therapists routinely encourage socially withdrawn patients to seek out social interactions and to test whether these interactions are as unpleasant as they predict. Cognitive therapy also teaches patients to challenge internal and stable negative attributions, such as "I am an inferior person." Such interventions, if successful, might result in changes in neuroticism and extraversion.

This project examined self-reported personality changes in a randomized, placebo-controlled clinical trial of MDD. In the trial, 240 patients were randomized such that 60 patients received placebo for 8 weeks, 120 patients received paroxetine for 16 weeks, and 60 patients received CT for 16 weeks.<sup>37</sup> Our first goal was to test whether patients treated with either paroxetine or CT reported greater changes in neuroticism and extraversion at week 8 relative to patients taking placebo.

If paroxetine or CT was observed to produce significantly greater personality change than placebo, our second goal was to test whether such effects could be attributed to between-group differences in depression improvement. We examined this in 2 ways: (1) a linear regression that accounted for depression improvement statistically, and (2) a matching analysis in which patients taking placebo were compared with patients taking paroxetine matched on amount of depression improvement. The state effect hypothesis would predict that the between-group differences in personality change would be largely eliminated in both of these analyses.

Our third goal was to examine the state-effect hypothesis by analyzing data obtained from the patients assigned to 8 weeks of treatment with placebo. In studies of MDD treatments, placebo patients tend to experience substantial improvement in depression.<sup>42-46</sup> Thus, their personality data provide a direct test of the state effect hypothesis, which predicts that these placebo patients should also report substantial change in personality. Because this test is not confounded by the effects of active treatments, it might be the purest method to test this hypothesis. Moreover, during the 8 weeks that followed the placebo phase, 31 patients treated with placebo accepted the offer of free subsequent treatment with an SSRI. This set up a within-subject comparison between their placebo phase and SSRI phase. The state effect hypothesis predicts that the magnitude of reported personality change during each phase should be roughly proportional to the magnitude of depression improvement during that same phase.

Our final goal was to examine whether reported neuroticism reduction during SSRI (or CT) treatment predicted subsequent relapse, since neuroticism is a key risk factor that reflects much of the genetic cause of MDD. If reported neuroticism reduction during active treatment was merely a change in the state effect of depression, then it should have no long-term clinical consequences.



**Figure 1.** Flowchart of the clinical trial patients. CT indicates cognitive therapy; NEO-FFI, NEO Five-Factor Inventory; and SSRI, selective serotonin reuptake inhibitor.

## METHODS

### PARTICIPANTS

Institutional review boards approved the clinical trial protocol, and written informed consent was obtained from all participants. Participants were 240 moderate to severely depressed adult outpatients; patient characteristics, as well as the procedures of the trial, have been detailed elsewhere.<sup>37,47</sup> All patients met criteria for MDD and scored 20 or higher at both screening and intake evaluations on the Hamilton Scale for Depression (HAM-D).<sup>42</sup> Inclusion criteria were (1) *DSM-IV* MDD diagnosis<sup>48</sup>; (2) age 18 to 70 years; (3) fluency in English; 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 60 patients into the CT group, 120 patients into the paroxetine group, and 60 patients into the placebo group (**Figure 1**). The patients who dropped out or who did not complete the personality assessments did not differ significantly from the other patients at intake on depression severity, neuroticism, or extraversion.

For patients in the paroxetine or CT conditions, response was defined in terms of HAM-D scores using the following criteria: (1) week 16 HAM-D score of 12 or less, and either week 14 HAM-D score of 14 or less or week 10 and week 12 HAM-D scores of 12 or less; or (2) week 12, week 14, and week 18 HAM-D scores of 12 or less.<sup>37</sup> These criteria prevented a transient exacerbation of depressive symptoms at week 14 or 16 from precluding a patient as being recognized as a responder.

After acute treatment, responders to paroxetine or CT entered the 12-month continuation phase (**Figure 1**). Paroxetine responders were randomly assigned to 2 subgroups: 34 con-

tinued taking medication at the same dosage, and 35 were withdrawn to placebo pills. The 35 CT responders were allowed 3 booster sessions, scheduled at least 1 month apart. Responders were asked not to pursue depression treatment outside the research protocol during this continuation phase.

The patients who had initially been assigned to placebo completed participation in the study at week 8. Thirty-one of these placebo patients then opted for subsequent SSRI treatment (**Figure 1**).

### MEASUREMENTS

Personality variables were assessed with the NEO Five-Factor Inventory (NEO-FFI), a widely used self-report measure based on the Five-Factor Model of Personality,<sup>3</sup> the dominant paradigm in current personality research.<sup>1-3</sup> The NEO-FFI has been validated by spouse and peer ratings,<sup>3</sup> and 3-month test-retest reliability coefficients of 0.79 have been reported for both neuroticism and extraversion.<sup>3</sup> The NEO-FFI scales have well-established normative sample mean scores (neuroticism: mean, 19.1; standard deviation [SD], 7.7; extraversion: mean, 27.7; SD, 5.8).<sup>3</sup> In this article, SD for neuroticism and extraversion refers to the SD estimates obtained in the normative sample.

Depression was measured with the 17-item version of the HAM-D, modified to assess atypical symptoms.<sup>42</sup> Longitudinal Interval Follow-Up Evaluation II was the primary means of evaluation during follow-up.<sup>49</sup> Longitudinal Interval Follow-Up Evaluation II tracks whether patients have reentered treatment and whether they had depressive episodes between evaluations.<sup>49</sup> Patients met criteria for relapse if (1) they had a HAM-D score of 14 or more for 2 consecutive weeks (3 weeks during the period of medication withdrawal) or (2) if Longitudinal Interval Follow-Up Evaluation II interviews yielded a diagnosis of MDD.

### STATISTICAL ANALYSIS

The main effects were tested by regressing week 8 scores against treatment assignment in a standard linear regression, with intake scores as covariates. All main-effect analyses used last available observations as week 8 scores for patients who dropped out or missed assessments. We also conducted analyses re-

**Table 1. Clinical Trial Main Effects From Intake to Week 8**

Measure	Treatment Assignment		Paroxetine vs CT			CT vs Placebo			Paroxetine vs Placebo		
	F	P Value	F	P Value	Effect Size	F	P Value	Effect Size	F	P Value	Effect Size
HAM-D	3.2	.04	0.0044	.95	0.01	5.6	.02	0.37	5.3	.02	0.38
Neuroticism	6.4	.002	0.41	.52	0.10	6.5	.01	0.46	13	<.001	0.57
Extraversion	7.7	<.001	0.13	.71	0.07	3.0	<.001	0.56	14	<.001	0.63

Abbreviations: CT, cognitive therapy; HAM-D, Hamilton Scale for Depression.

**Table 2. Change From Intake to Week 8 Among Patients Who Completed the NEO-FFI at Intake and Week 8**

Measure	Placebo (n=52)		CT (n=51)		Paroxetine (n=94)	
	SD	P Value	SD	P Value	SD	P Value
HAM-D	-1.2	<.001	-1.6	<.001	-1.6	<.001
Neuroticism	-0.18	.08	-0.54	<.001	-0.80	<.001
Extraversion	0.08	.50	0.49	<.001	0.64	<.001

Abbreviations: CT, cognitive therapy; HAM-D, Hamilton Scale for Depression; NEO-FFI, NEO Five-Factor Inventory.

stricted to only patients with both intake and week 8 scores, and no notable differences emerged. Effect sizes for main effects were estimated by dividing the difference in the respective least squares mean at week 8 with the pooled SD of the respective mean. They are basically Cohen *d* for least squares means, and effect sizes above 0.8 can be considered large; between 0.5 and 0.8, medium; and between 0.2 and 0.5, small.<sup>50</sup> Unless otherwise specified, multiple regressions results reported reflect the incremental changes attributed to the predictor variable in question and not to the full model. Within-subject comparisons between 2 times were examined with paired *t* tests. Repeated-measure analysis of variance was used to evaluate whether the placebo patients showed greater changes during their placebo phase than their SSRI phase. Survival curves and relapse rates were estimated using the Cox proportional hazards model,<sup>51</sup> and the observations that reflected patients who dropped out, deviated from medication regimen, or sought outside treatment prior to relapse were censored.

### MATCHING ANALYSIS

In an exploratory analysis, we identified placebo patients for whom we could find a paroxetine patient with matching amounts of depression improvement from intake to week 8. When such a match could not be found for a placebo patient, that patient was dropped. When a placebo patient could be matched with more than 1 paroxetine patient, the paroxetine patient whose intake HAM-D score was closest to the placebo patient's was chosen. If more than 1 match remained, the paroxetine patient with the closest study identification number to that of the placebo patient was chosen. This matching algorithm eliminated subjective choices, and it was unaffected by personality scores. It successfully matched 44 of the 52 placebo patients (85%) with intake and week 8 personality data with 44 paroxetine patients. Rather than conducting paired comparisons of these matched groups, we analyzed for the differences in group means. (While we attempted the same analysis with placebo and CT, we will not detail the results in this article because matching CT patients were found for only 28 of the 52 placebo patients [54%], and results from these 28 pairs were perfectly consistent with the results of regression analyses.)

## RESULTS

### MAIN EFFECTS

At intake, the mean neuroticism score was 34 (1.9 SD above the normative sample mean) and the mean extraversion score was 20 (1.3 SD below the normative sample mean). The treatment groups did not differ significantly on neuroticism ( $P=.27$ ) or extraversion ( $P=.84$ ) at intake. At week 8, treatment assignment (placebo, paroxetine, and CT) significantly predicted depression severity, neuroticism, and extraversion. The main-effect statistics are presented in **Table 1**; although no significant differences emerged between the 2 active treatment groups, paroxetine and CT each outperformed placebo in changing depression, neuroticism, and extraversion. Interestingly, in the comparisons with placebo, the effect sizes on depression improvement were smaller than those on neuroticism and extraversion for both paroxetine and CT (Table 1).

### PERSONALITY CHANGE FROM INTAKE TO WEEK 8

**Table 2** presents the magnitude of change (in SD) among patients who completed both intake and week 8 personality measurements, and **Table 3** compares reported personality change across the 3 groups after accounting for change in depression. Changes reported in all groups are in the direction of normalization: HAM-D scores and neuroticism decreased and extraversion increased. Consistent with prior studies,<sup>43-46</sup> placebo patients reported substantial depression improvement (1.2 SD), equal to 75% of the depression improvement shown by patients receiving either CT or paroxetine (1.6 SD each). Contrary to the prediction of the state effect hypothesis, placebo patients reported little change in neuroticism (0.18 SD,



**Table 3. Between-Group Comparisons of Personality Change From Intake to Week 8 After Accounting for Depression Improvement**

Measure	P Value		
	Paroxetine vs Placebo	CT vs Paroxetine	CT vs Placebo
Neuroticism	<.001	.07	.14
Extraversion	.002	.50	.05

Abbreviation: CT, cognitive therapy.

$P=.08$ ) or extraversion (0.08 SD,  $P=.50$ ) despite considerable depression improvement.

From intake to week 8, CT patients reported substantial changes on neuroticism and extraversion (Table 2). After accounting for depression improvement, CT patients still reported significantly greater improvement than placebo on extraversion, but the 2 groups' difference on neuroticism was no longer significant (Table 3). Furthermore, after accounting for depression improvement, CT patients reported less change on neuroticism than paroxetine patients, at the level of a nonsignificant trend (Table 3).

Paroxetine patients reported changes in neuroticism and extraversion that were 4 to 8 times as large as the changes reported by placebo patients (Table 2). Regression analyses suggested that such large differences were unlikely to be explained by the modest between-group difference on depression improvement (1.2 SD vs 1.6 SD): after accounting for depression improvement, paroxetine still significantly outperformed placebo in changing both neuroticism and extraversion (Table 3). Furthermore, the difference between paroxetine and placebo in depression reduction was no longer significant after controlling for neuroticism reduction ( $F_{1,145}=0.74$ ,  $P=.46$ , effect size=0.19) or change in extraversion ( $F_{1,145}=1.5$ ,  $P=.14$ , effect size=0.23).

#### MATCHING ANALYSIS

As linear regression approaches might model the nonlinear relationships between depression and personality poorly, we reexamined these variables in the paroxetine and placebo patients in an exploratory matching analysis. For each placebo patient, we attempted to identify a paroxetine patient with the same amount of depression improvement. We found matching paroxetine patients for 44 of the 52 placebo patients with intake and week 8 personality data.

Personality change in these patients from intake to week 8 are presented in **Table 4**. Although matched on depression improvement (and thus the state effect of depression), these paroxetine patients still reported far greater personality change than placebo patients. On neuroticism, the matched paroxetine patients showed 3.5 times as much reduction as the placebo patients; on extraversion, the matched paroxetine patients showed 6.8 times as much improvement as the placebo patients.

**Table 4. Personality Change From Intake to Week 8 of the Placebo Patients and Paroxetine Patients Matched on Depression Improvement**

Measure	SD		Magnitude Ratio, Paroxetine vs Placebo, %	P Value, Placebo vs Paroxetine
	Placebo (n=44)	Paroxetine (n=44)		
HAM-D	-1.4	-1.4	100	
Neuroticism	-0.23	-0.80	347	<.001
Extraversion	0.08	0.54	675	.006

Abbreviation: HAM-D, Hamilton Scale for Depression.

#### PLACEBO PATIENTS' WITHIN-SUBJECT COMPARISON

**Figure 2** shows the pattern of change for the 31 placebo patients who opted for subsequent SSRI treatment after week 8. Their HAM-D scores decreased by an average of 6.4 points during the placebo phase (from intake to week 8) compared with 2.4 points during the subsequent SSRI phase (from week 8 to week 16) (Figure 2A). A repeated-measure analysis of variance confirmed that HAM-D scores changed significantly more during the placebo phase than during the subsequent SSRI phase:  $F_{2,28}=9.0$ ,  $P=.005$ .

Based on this pattern of depression improvement, the state effect hypothesis predicts that personality measurements should change considerably more during the placebo phase than during the SSRI phase. However, the mean neuroticism score of these patients did not decrease at all during the placebo phase (it increased slightly instead), but it decreased 0.66 SD during the subsequent SSRI phase (Figure 2B). Similarly, their mean extraversion score increased only 0.12 SD during the placebo phase, but it increased 0.34 SD during the subsequent SSRI phase (Figure 2C). Repeated-measures analysis of variance confirmed that neuroticism and extraversion changed less during the placebo phase than during the subsequent SSRI phase (neuroticism,  $F_{2,28}=11.5$ ,  $P=.002$ ; extraversion,  $F_{2,28}=4.2$ ,  $P=.03$ ).

#### LONG-TERM CLINICAL CONSEQUENCE

Among the 69 paroxetine responders, extraversion improvement during acute treatment did not predict relapse rates ( $\chi^2=0.27$ ,  $P=.60$ ). However, greater neuroticism reduction predicted a significantly lower likelihood of relapse ( $\chi^2=8.6$ ,  $P=.003$ ). This relationship remained statistically significant even after accounting for pretreatment and end-of-treatment HAM-D scores, pretreatment neuroticism, and whether the responder was assigned to active medication or placebo during the continuation phase ( $\chi^2=12$ ,  $P<.001$ ). (While medication continuation vs withdrawal to placebo predicted lower relapse rates,<sup>47</sup> it did not interact with neuroticism improvement in predicting relapse:  $\chi^2=0.025$ ,  $P=.87$ .) To better understand the strength of this relationship between neuroticism improvement and relapse, we divided the paroxetine responders into 3 subgroups based on the magnitude of their neuroticism reduction: top third, neuroticism reduction by 15 or more points; middle third, reduction of more than 9 points and

less than 15 points; and bottom third, reduction of 9 points or less. The relapse rate was 35% in the top third ( $n=23$ ), 54% in the middle third ( $n=23$ ), and 84% in the bottom third ( $n=23$ ). Among the 35 CT responders, personality change during treatment did not predict relapse rates (neuroticism,  $\chi^2=0.028, P=.86$ ; extraversion,  $\chi^2=0.12, P=.73$ ).

### COMMENT

To the best of our knowledge, these are the first findings from a randomized placebo-controlled trial to suggest that an SSRI treatment of MDD produces greater changes in neuroticism and extraversion than an inert placebo. In other words, paroxetine demonstrated a true drug effect on neuroticism and extraversion scores, reflecting pharmacological specificity.

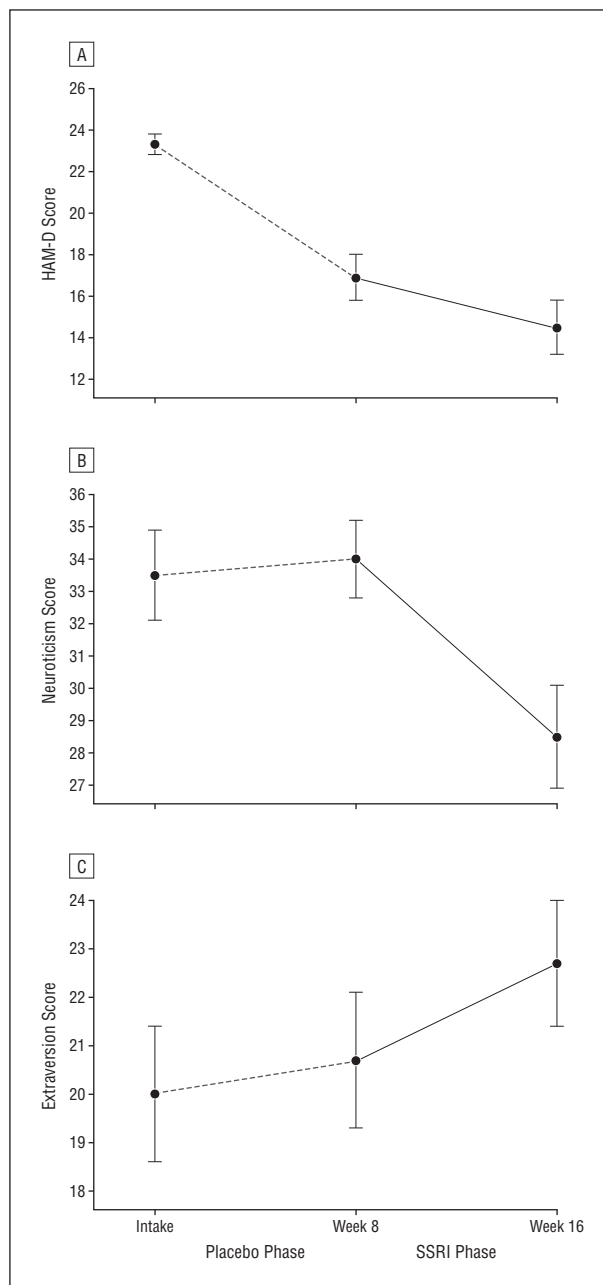
The state effect hypothesis predicts that differences between medications and placebo in reported personality change should largely disappear after controlling for depression improvement. However, after accounting for depression improvement in regression analyses and in a procedure that matched paroxetine and placebo patients on depression improvement, paroxetine patients still reported far greater personality change than did the placebo patients. This pattern of findings should not occur if personality change conformed to the state effect hypothesis.

The observed course of change in patients who were given placebo for 8 weeks followed by 8 weeks of SSRIs would likewise not be predicted by the state effect hypothesis. Depression reduction was substantial during the placebo phase and was much less so during the paroxetine phase. Personality change showed the opposite pattern. Perhaps the most surprising pattern we observed was the relation between neuroticism reduction during acute SSRI treatment and subsequent resistance to relapse. This finding is not in line with the state effect hypothesis either.

### THE CAUSE-CORRECTION MODEL

If the state effect hypothesis (**Figure 3A**) proves incorrect in future research, then what alternatives should be considered? One possibility is that the biochemical properties of SSRIs directly produce real personality change. Furthermore, because neuroticism is an important risk factor that captures much of the genetic vulnerability for MDD, change in neuroticism (and in neurobiological factors underlying neuroticism) might have contributed to depression improvement. Indeed, our regression analyses suggest that personality change can explain the advantage of paroxetine over placebo in antidepressant efficacy, rather than vice versa.

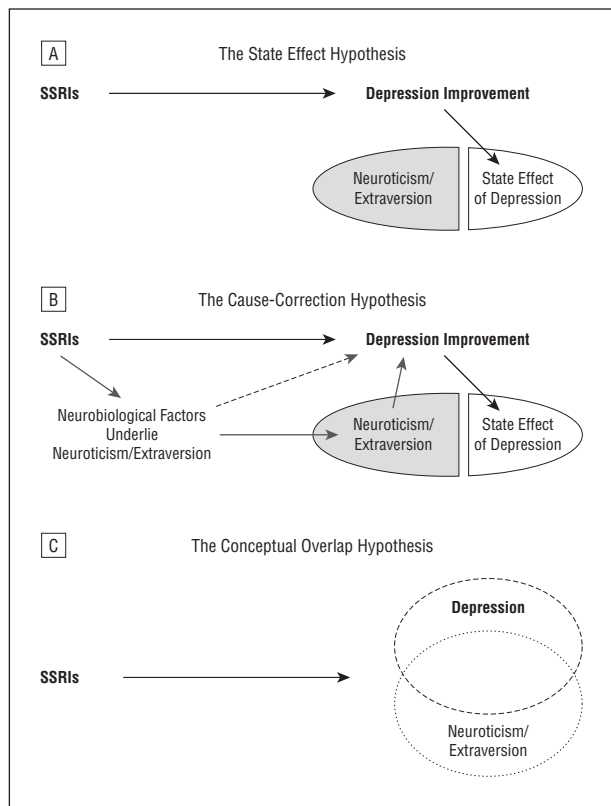
These possibilities can be integrated into the cause-correction model (**Figure 3B**): SSRI treatment produces changes in neuroticism/extraversion and the neurobiological factors underlying them; these changes then contribute to depression improvement. This model could be directly tested by tracking a large sample of premorbid subjects, waiting for them to develop MDD, and then treating them in an SSRI clinical trial. How much SSRI treatment changes personality could then be measured by comparing the premorbid and posttreatment personality scores



**Figure 2.** Courses of depression, neuroticism, and extraversion for patients taking placebo who opted for subsequent selective serotonin reuptake inhibitor (SSRI) treatment after week 8. Thirty-one patients took placebo from intake to week 8 and then opted for SSRI treatment from week 8 to week 16. Error bars reflect standard errors.

of responders in full remission. It would be challenging to obtain an adequate sample for such a study: a recent study found that only 262 subjects developed their first episode of MDD after tracking 4263 subjects for 2 years.<sup>6</sup>

Among responders to paroxetine, those for whom neuroticism changed the most during treatment were also those least likely to relapse. The predictive power of change in neuroticism was not accounted for by pretreatment levels of neuroticism or by posttreatment levels of depressive symptoms. It would appear, then, that change in neuroticism—or in a phenomenon related to self-reported neuroticism—served to reduce vulnerabil-



**Figure 3.** The state effect hypothesis and 2 alternative hypotheses. Depression etiology research has not determined whether neuroticism and extraversion are causes of depression or risk factors reflecting other underlying causes of depression. The cause-correction hypothesis retains this ambiguity: changes in neuroticism/extraversion and changes in factors underlying neuroticism/extraversion might both contribute to depression improvement. SSRIs indicates selective serotonin reuptake inhibitors.

ity to relapse. This explanation of the relapse prediction finding is consistent with the cause-correction model. In this model, greater neuroticism reduction reflects more correction of the personality risk factors of depression, which then reduces the risk for relapse. From this perspective, the paroxetine responders who recovered without experiencing much neuroticism reduction resembled the placebo patients in that they might not have benefited much from the biochemical properties of SSRIs. The alternative explanation of the relapse prediction finding is that confounding variables might have influenced both neuroticism and relapse rates; as a result, patients with lower relapse risk also happened to show greater neuroticism improvement during treatment.

### CONCEPTUAL OVERLAP

The state effect hypothesis exemplifies one causal interpretation of the correlation between depression and personality: depression improvement directly causes personality change. The cause-correction model integrates the 2 other possible causal interpretations, which in the context of our findings would be (1) reverse causation (personality change caused depression improvement) and (2) causation by a third variable (changes in underlying neurobiological factors caused both depression improvement and personality change). However, statistical as-

sociations that do not reflect causal relations might also exist among these variables. Depression, neuroticism, and extraversion probably overlap conceptually, which could lead to apparent correlations. For example, if SSRIs primarily change depression, but the definitions of depression and neuroticism overlap extensively, then neuroticism would also appear to change (Figure 3C). Nevertheless, such a conceptual overlap hypothesis cannot explain the dissociations we observed between depression change and neuroticism change with respect to paroxetine and placebo.

### CT AND PERSONALITY

This study is also the first clinical trial to show that CT can produce significantly greater change in neuroticism and extraversion than placebo. However, it remains unclear whether this effect reflects personality change, change in state effect, or measurement artifact related to cognitive therapists' explicit efforts to address thoughts and behaviors related to high neuroticism and low extraversion.

Cognitive therapy did not produce greater change in neuroticism than placebo after controlling for change in depression, and neuroticism improvement during CT did not predict subsequent relapse as it did among paroxetine responders. These findings suggest that the nature of reported neuroticism reduction in CT might differ from that in SSRI treatment and that it might be more closely associated with depression improvement. The fact that rates of subsequent relapse were relatively low in CT regardless of the amount of change in neuroticism suggests that it works through mechanisms other than neuroticism to produce its enduring effect.<sup>47</sup>

On extraversion, CT outperformed placebo even after controlling for depression improvement. This suggests that extraversion improvement in CT may be independent of depression improvement, which contradicts the state effect hypothesis (and the conceptual overlap hypothesis). Cognitive therapy showed no significant differences with paroxetine on extraversion, even after controlling for depression. However, the lack of difference between 2 active treatments on a process variable is often uninformative in testing mechanism models.<sup>52</sup> The lack of difference between CT and paroxetine on extraversion can be consistent with the state effect hypothesis, the conceptual overlap hypothesis, and even the cause-correction hypothesis. For example, if both CT and paroxetine first change extraversion, which then cause depression to improve (ie, the cause-correction model), then the 2 treatments may still appear similar on extraversion improvement. (Presumably, paroxetine and CT would change extraversion via distinct pathways.<sup>53</sup>)

### LIMITATIONS

The present findings need to be replicated with paroxetine, other SSRIs, and other antidepressant medications to determine whether the effects we observed are reliable and whether they are limited to the medication or medication class that we tested.<sup>18</sup> In previous research on the effects of antidepressant medications, other

temperament variables such as harm avoidance, novelty seeking, and reward dependence<sup>54</sup> have been used. It remains unclear how these variables relate to the personality dimensions of the Five-Factor Model of Personality. In addition, because this clinical trial measured personality with the more abbreviated NEO-FFI, rather than the Revised NEO Personality Inventory, we could not distinguish the different facets of neuroticism and extraversion.<sup>3</sup> We also did not investigate which underlying neurobiological system is involved in the cause-correction model. While the serotonin system is a natural candidate, other possibilities should be carefully considered in future research as well. Furthermore, although our main-effects analyses were obtained in the context of a placebo-controlled randomized clinical trial, our secondary analyses were nonexperimental and may therefore be open to alternative interpretations. Finally, there were a number of dropouts in this trial, and the sample sizes for some analyses were modest.

### IMPLICATIONS

In this study, patients with MDD reported substantial personality change during SSRI treatment; such personality change was not dependent upon depression improvement; and it might have contributed to acute and long-term treatment outcomes. Although SSRIs are the most widely used treatment of MDD, our understanding of their mechanisms remains limited.<sup>55</sup> Selective serotonin reuptake inhibitors are also effective in treating several anxiety disorders and eating disorders,<sup>56,57</sup> and recent studies have suggested that high neuroticism and low extraversion may be general risk factors for these disorders as well.<sup>5,58,59</sup> Investigating how SSRIs affect neuroticism and extraversion may thus lead toward a more parsimonious understanding of the mechanisms of SSRIs.

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**Correspondence:** Tony Z. Tang, PhD, Northwestern University, 2029 Sheridan Rd, Evanston, IL 60208 (ttang@northwestern.edu).

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