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The Effects of Sertraline on Psychopathic Traits

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Abstract

Objective—To evaluate whether antidepressants alter expression of psychopathic personality traits in patients with major depressive disorder (MDD).

Methods—Data were collected from a double-blind, placebo-controlled 8-week trial evaluating the efficacy of sertraline (50–200 mg/d) combined with either tri-iodothyronine (T3) or matching placebo in adult outpatients with MDD. Administration of sertraline was open-label; T3/placebo was double-blind. At the baseline and week 8 visits, patients completed the short form of the Psychopathic Personality Inventory (PPI), a well-validated self-report measure assessing two major factors of psychopathy: Fearless Dominance (PPI-1) and Self-centered Impulsivity (PPI-2). Change in PPI scores were assessed using paired t-tests for all subjects who completed a baseline and post-randomization PPI.

Results—Ninety patients (84 completers and 6 who terminated the trial early) were eligible for the analysis. Both PPI factors changed significantly from baseline to endpoint, but in opposing directions. The mean score on PPI-1 increased significantly during treatment; this change was weakly correlated with change in depression scores. In contrast, the mean score on PPI-2 decreased significantly, but these changes were not correlated with changes in depression scores.

Conclusion—Independent of their effects on depression, antidepressants increase adaptive traits traditionally observed in psychopathic individuals, such as social charm and interpersonal and physical boldness. Antidepressants reduce other, more maladaptive, traits associated with psychopathy, including dysregulated impulsivity and externalization.

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DISCLOSURES

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Dr. DeFife reports no conflicts.

Ms. Marx reports no conflicts.

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Dr. Nemeroff has served on the scientific advisory boards of American Foundation for Suicide Prevention (AFSP); AstraZeneca; Forest Laboratories; NARSAD; Quintiles; Janssen/Ortho-McNeil, PharmaNeuroboost, and Mt. Cook Pharma, Inc. He holds stock/equity in Corcept; Revaax; NovaDel Pharma; CeNeRx, and PharmaNeuroboost. He is on the board of directors of the AFSP; George West Mental Health Foundation; NovaDel Pharma, and Mt. Cook Pharma, Inc. Dr. Nemeroff holds a patent on the method and devices for transdermal delivery of lithium (US 6,375,990 B1) and the method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing April, 2001).

Dr. Lilienfeld is the co-author on the Psychopathic Personality Inventory-Revised (PPI-R), published by Psychological Assessment Resources (PAR).

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INTRODUCTION

There is increasing evidence that antidepressant medications can alter long-standing personality traits independent of their therapeutic effects in patients with Axis I disorders. Patients with MDD treated with selective serotonin reuptake inhibitors (SSRIs) show reductions in neuroticism and aggression, and increases in extraversion, social desirability and affiliativeness (Brody AL *et al.*, 2000; Ekselius L, Von Knorring L, 1999; Tang TZ *et al.*, 2009). Some have attributed personality changes during SSRI treatment to improvement in depressive symptoms (Du L *et al.*, 2002), but more recent work derived from placebo-controlled studies indicate that reduced neuroticism and increased extraversion are independent from depression improvement, and are temporally dissociated from depression score change (Tang TZ *et al.*, 2009). Moreover, the reduction in neuroticism occurring with paroxetine treatment is associated with lower risk of relapse, an effect not observed among patients treated successfully with cognitive-behavioral therapy (Fournier JC *et al.*, 2008).

Bolstering findings of personality change with SSRIs in depressed patients, several studies have explored the effects of SSRIs on healthy subjects. Compared with placebo treatment, SSRI treatment is associated with reduced hostility and attention to negative stimuli, and increased affiliative behaviors and self-directedness (Harmer CJ *et al.*, 2003; Knutson B *et al.*, 1998; Tse WS, Bond AJ, 2001), although some have found no effects (Gelfin Y *et al.*, 1998). To date, these personality changes with treatment have been viewed as positive enhancements of maladaptive personality styles, and have produced discussion of “cosmetic psychopharmacology,” in which antidepressants could be used to change undesirable personality features (Kramer PD, 1993). Whether certain maladaptive personality traits may worsen with antidepressant treatment has not been explored.

Psychopathy is a particularly destructive form of personality pathology, characterized as “a socially devastating disorder defined by a constellation of affective, interpersonal, and behavioral characteristics including egocentricity, impulsivity, irresponsibility, shallow emotions, lack of empathy, guilt, or remorse, pathological lying, manipulativeness, and the persistent violation of social norms and expectations” (Hare RD, 1998). Psychopathy, operationalized using the Psychopathy Checklist-Revised (PCL-R), is estimated to be present in 15% of male prisoners, 3.5% of businessmen, and 1% of the general US population (Coid JW *et al.*, 2009; Hare RD, 2003). The frequency of psychopathic traits that fall short of the full syndrome are significantly more common, as psychopathy, like many or most other forms of personality, appears to lie on a spectrum of expression in the population (Lilienfeld SO, Andrews BP, 1996). Indeed, recent findings using taxometric techniques suggest that psychopathy is best defined dimensionally rather than categorically (Edens JF *et al.*, 2006; Marcus DK *et al.*, 2004). As a consequence, the field of psychopathy has increasingly turned to examining psychopathic personality traits along a continuum in both normal and abnormal populations (Benning SD *et al.*, 2005).

Factor analyses of the PCL-R, the most commonly used instrument to assess psychopathy, have often identified two moderately correlated dimensions underpinning the psychopathy construct. Factor 1 captures the affective and interpersonal traits that reflect a callous and remorseless exploitative style of interaction with others. Factor 2, which is closely related to the diagnostic features of ASPD, reflects the criminal and impulsive features sometimes associated with psychopathy. Conceptually, these two factors parallel the classic distinction between “primary” or classic psychopathy, which is marked by the core emotional and social features of the condition (e.g., lack of guilt, immunity to anxiety and fear, callousness, narcissism), and “secondary” psychopathy, which is marked by poor impulse control and a propensity toward anxiety and other negative emotions (Karpman B, 1941; Levenson MR *et al.*, 1996).

The Psychopathic Personality Inventory (PPI) is a commonly used self-report instrument that identifies two broadly similar factors of psychopathy (Benning SD *et al.*, 2005; Lilienfeld SO, Andrews BP, 1996; Poythress NG *et al.*, 2010). In contrast to the PCL-R, however, the first major factor of the PPI, often termed Fearless Dominance, PPI-1, assesses attributes of primary psychopathy that are commonly regarded as adaptive, such as social poise, low anxiety, and interpersonal and social boldness (Lilienfeld SO, Widows MR, 2005). Healthy control subjects scoring highly on the second PPI factor ("Self-Centered Impulsivity"), PPI-2, demonstrate hyper-reactivity in dopaminergic reward pathways in response to pharmacological and monetary reinforcers, suggesting that response to reward cues may be a stable trait characteristic detectable by the PPI (Buckholz JW *et al.*, 2010).

The rationale for examining the effects of SSRI on psychopathic personality traits derives from recent studies of the neurobiology of psychopathy and the effects of SSRIs on normal-range personality traits in healthy and ill populations. The PPI-1 captures features of extraversion, interpersonal and physical boldness, and stress immunity. Changes in these largely adaptive characteristics of psychopathy may be predicted by extrapolating from the demonstrated effects of SSRIs on social phobia (Ninan PT, Dunlop BW, 2006) and from work in depressed patients suggesting that extraversion increases with SSRI treatment independently of depressive symptoms (Bagby RM *et al.*, 1999; Tang TZ *et al.*, 2009). Moreover, 3-weeks of SSRI treatment reduced anticipatory anxiety in healthy controls, and this change was correlated with reductions of activity in the anterior insula and ventromedial prefrontal cortex (Simmons AN *et al.*, 2009). Social anxiety and psychopathy are negatively correlated (Hofmann SG *et al.*, 2009); SSRI-induced reduction of social inhibition may thus further enhance this feature of psychopathy.

The PPI-2 characteristics of hostility, externalization, and behavioral dyscontrol may improve with SSRI treatment. Reductions in hostility and anger occur in both healthy controls and depressed patients taking antidepressants (Harmer CJ *et al.*, 2004; Bagby RM *et al.*, 1999). Additionally, social affiliativeness in healthy controls increases with SSRI treatment (Knutson B *et al.*, 1998). Finally, impulsivity, which contributes to behavioral dyscontrol, improves in patients with borderline personality disorder patients treated with SSRIs (Bellino S *et al.*, 2008). Open-label data suggest that SSRIs reduce impulsivity among repeat violent offenders (Butler T *et al.*, 2010). Taken together, existing data support the hypothesis that SSRIs may mitigate these maladaptive components of psychopathy.

Depressed patients frequently demonstrate high levels of guilt, sensitivity to criticism, and low levels of sensation-seeking, which may improve with SSRI treatment. This constellation of characteristics is the inverse of those typically observed in primary psychopathy. In his seminal writings on primary psychopathy, Cleckley (1941) referred to the apparent absence of "valid depression" (p. 339) among individuals with this disorder. Indeed, at least some data support the contention that indicators of psychopathy and depression are negatively correlated (Lovelace L, Gannon L, 1999). That SSRIs are demonstrated to improve such symptoms as guilt and oversensitivity to criticism in depressed individuals raises the possibility that SSRIs may, paradoxically, enhance these aspects of psychopathy. Reduction of impulsivity with SSRI treatment has the potential to produce both positive and negative effects: SSRIs may lower levels of impulsive violence, but permit greater levels of planned exploitation of others ("instrumental aggression") (Cornell DG *et al.*, 1996).

The effects of SSRI treatment on antisocial personality disorder (ASPD), which captures some significant aspects of psychopathy (e.g., lack of remorse, poor impulse control), has been evaluated to a limited degree. Whether depressed patients with ASPD respond to antidepressant treatment equally well as non-ASPD patients is unclear (Fava M *et al.*, 2002; Joyce PR *et al.*, 1994; Mulder RT *et al.*, 2006). Rates of ASPD among patients enrolling in

clinical trials of antidepressants for MDD or anxiety disorders are generally low, although ASPD was present in 18 of 378 (4.7%) patients with MDD treated with fluoxetine for 8 weeks (Fava M *et al.*, 2002). In that study, 5 patients who had not met criteria for ASPD at baseline fulfilled criteria after treatment, raising the possibility that SSRIs may increase the levels of certain antisocial traits in some individuals. Such findings are especially striking given that ASPD, in contrast to other Axis II disorders, is primarily an historical diagnosis that rests on the presence of antisocial and criminal behaviors dating to childhood or adolescence. Given the absence of research on the effect of antidepressants on psychopathic personality traits *per se*, we examined the change in psychopathy levels during treatment with an SSRI, sertraline, among MDD outpatients. The data reported here were derived from additional exploratory measures from a trial designed to evaluate the antidepressant efficacy of tri-iodothyronine (T3, Cytomel®) when co-initiated with sertraline in the treatment of MDD. We hypothesized that psychopathy scores, as assessed by the short-version of the PPI, would change during 8 weeks of sertraline treatment, but in opposing directions. Specifically, we predicted that scores on Factor 1 (“Fearless Dominance”; PPI-1) of the PPI, associated with such adaptive traits as social command and absence of interpersonal and physical fear and anxiety (ostensibly reflecting many of the features of primary psychopathy), would increase with treatment independently of depression improvement. Conversely, we hypothesized that scores on PPI Factor 2 (“Self-centered Impulsivity”; PPI-2), which is associated with the maladaptive psychopathy characteristics of failing to plan for events, a selfish and manipulative interpersonal style, and a tendency to externalize blame (ostensibly reflecting many of the features of secondary psychopathy), would decrease with treatment. We expected T3 to have no effect on the psychopathy measures.

METHODS

Procedure

The Institutional Review Board of Emory University reviewed and approved the conduct of this clinical investigation. All subjects were provided with and signed written informed consent to participate. This study was conducted at the Mood and Anxiety Disorders Program in the Department of Psychiatry and Behavioral Sciences at Emory University School of Medicine between 1998 and 2003. The data reported here are derived from the full sample of patients who participated in a placebo-controlled, double-blind clinical trial designed to assess the efficacy of tri-iodothyronine (T3) combined with sertraline from the beginning of treatment for major depressive disorder (MDD). A full description of the study design is reported elsewhere (Garlow SJ *et al.*, 2007), and will be reviewed here briefly.

Patients

Male and female patients meeting Structured Clinical Interview for DSM-IV (SCID) criteria for non-psychotic major depressive disorder (MDD) between the ages of 18 and 60 were eligible for the study. SCID interviews were conducted by study psychiatrists, fourth-year psychiatric residents, or PhD-level psychologists. For inclusion, patients had to score ≥ 18 on the 21-item Hamilton Depression Rating Scale for Depression (HRSD-21) (Hamilton M, 1960) at the screening visit, and at the baseline assessment, which occurred after a one-week single-blind placebo lead-in. Any current medical conditions had to be stable, except for thyroid disease, which was exclusionary. Exclusionary criteria included clinically significant active suicidality, lifetime bipolar disorder, schizophrenia, schizoaffective disorder, and substance abuse or dependence in the past year (excluding nicotine and caffeine). Comorbid anxiety disorders were permitted so long as they were not the primary focus of treatment. Patients who had previously failed treatment with sertraline and those who had received ECT in the previous 6 months were excluded, as were women who were pregnant or breast-feeding. Concurrent depression-specific psychotherapy was prohibited during the trial.

Study Design

Following a one-week placebo lead-in, all patients received open-label sertraline, 50 mg/day (Baseline visit). Patients were also simultaneously randomized to receive either T3, 25 µg/day, or matching pill placebo at the baseline visit. Treatment lasted 8 weeks, during which the sertraline (50-200 mg/d) and T3/placebo (25-50 µg/d) were flexibly dosed based on tolerability and response. Assessment and medication adjustment visits occurred 1, 2, 3, 4, 6, and 8 weeks after randomization.

Measures

Depression severity measures—The primary outcome variable was change on the HRSD-21 total score. Secondary efficacy variables included the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg A, 1979) and Clinical Global Impression- Severity (CGI-S) (Guy W, 1976). The Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR) (Rush *et al.*, 2003) was also collected at each study visit.

Personality Measures—Psychopathy was assessed with the short version of the Psychopathic Personality Inventory (PPI), a 56-item self-report instrument with demonstrated validity for detecting psychopathic personality traits in non-criminal populations (Lilienfeld SO, Andrews BP, 1996). The scale asks participants to rate on a 4-point scale how true each of 56 statements is for themselves. The PPI does not explicitly ask about antisocial or criminal behaviors, yet it correlates moderately to highly with self-report, structured, and peer-rated measures of antisocial behavior and psychopathy, including the PCL-R (Lilienfeld SO, Andrews BP, 1996; Poythress NG *et al.*, 1998). This scale identifies two main psychopathy factors: Factor 1, “Fearless Dominance,” captures many of the characteristics of primary psychopathy, including social skillfulness, general fearlessness, and stress immunity; and Factor 2, “Self-Centered Impulsivity,” captures many of the characteristics of secondary psychopathy, including a Machiavellian and narcissistic interpersonal style, hostility, blame externalization, impulsive nonconformity, and failure to plan. In contrast to the two major factors of the PCL-R, these factors are weakly or even negligibly correlated (Benning SD *et al.*, 2005).

A short version of the Multidimensional Personality Questionnaire (MPQ) was also completed at baseline by participants to supplement our assessment of personality traits relevant to psychopathy and allied constructs. This self-report scale assesses three broad traits of personality: positive emotion (PEM, tendency to experience joy, activity and reward), negative emotion (NEM, proneness to anger, anxiety, and withdrawal) and constraint (CON, tendency to inhibit impulses and risk taking). The MPQ scales relate in predictable ways to psychopathy; for example, primary psychopaths tend to be lower in NEM and higher in PEM than secondary psychopaths and perhaps non-psychopaths (Hicks BM *et al.*, 2004).

Statistical Analysis

The Total Sample (n=144) included all patients who completed a PPI at baseline. The Test-Retest sample (n=90) included all patients who completed a baseline and endpoint PPI. Response was defined as an endpoint HDRS score reduction of ≥50% from the baseline HDRS score. Remission was defined as a final visit HDRS score ≤ 7. Analyses were performed in SPSS version 17.0. Differences and changes in mean scores were assessed using two-tailed t-tests using a p<.05 level of significance. Hierarchical linear modeling (HLM) was used to examine the relationship of PPI baseline variables with change in depression symptoms over time and separated by gender. HLM is appropriate for use with nested data (in this case, with individuals completing repeated symptom measurements over

multiple units of time) and instead of utilizing summary pre-post scores, allows for inclusion of all available data points in a regression model.

RESULTS

The addition of T3 produced no differences versus placebo on the primary outcome variables in the study, and is not considered further in the analysis. The final visit mean sertraline dose was 151.1 mg/d (SD: 46.2 mg/d).

The baseline demographic, depression and psychopathy characteristics of the sample are presented in Table 1. There were no significant differences in these characteristics between the Total sample who completed the PPI at baseline and the Test-Retest sample who completed both a baseline and endpoint PPI (N=90). Of the Test-Retest sample, 84 completed all 8 weeks of the trial, and 6 terminated the trial early.

Total Sample

PPI factors 1 (“Fearless Dominance”) and 2 (“Self-centered Impulsivity”) were not significantly correlated ($r=.02$, $p=.ns$). Baseline PPI total and factor scores were not significantly correlated with age, recurrent episodes of depression, or lifetime substance abuse diagnosis. Correlations of PPI factors with levels of clinician-rated depressive symptoms (HDRS, MADRS), self-rated depressive symptoms (QIDS-SR) and the CGI-Severity scores at baseline were all low and non-significant (r s ranged from $-.16$ to $.02$, p s $> .05$), except for the correlation between the QIDS-SR correlation and Self-centered Impulsivity ($r=.18$, $p=.035$).

None of the MPQ broad traits were significantly correlated with the depression measures at baseline. MPQ PEM scores were positively correlated with PPI Fearless Dominance scores ($r=.55$, $p<.001$), but not correlated with PPI Self-Centered Impulsivity. MPQ NEM scores were negatively correlated with PPI Fearless Dominance ($r=-.34$, $p<.001$), and positively correlated with Self-Centered Impulsivity ($r=.48$, $p<.001$). MPQ CON scores were not correlated with either PPI factor.

Table 2 demonstrates characteristics associated with baseline differences on PPI scores. Men scored significantly higher than women on both PPI factor scores. Patients with a current anxiety disorder scored significantly lower on Fearless Dominance and PPI total at baseline than those without, but their Self-Centered Impulsivity scores were not significantly different. Conversely, melancholic patients scored significantly higher on Self-Centered Impulsivity than non-melancholic patients, but did not differ significantly on Fearless Dominance. Years of education were significantly correlated with Fearless Dominance scores ($r=.19$, $p=.026$), but not Self-centered Impulsivity scores ($r=-.08$, $p=.ns$).

Of the Total sample, an intent-to-treat (ITT) sample of 134 patients who initiated treatment with sertraline and returned to complete at least one post-randomization HDRS efficacy rating was identified. For this population, the baseline means ($\pm$ s.d.) were 101.1 (13.9); 46.5 (9.4), and 55.0 (9.9), for PPI total, Fearless Dominance, and Self-Centered Impulsivity, respectively. These scores were not significantly different from the Total sample or Test-Retest sample scores. A median split of baseline PPI-1, PPI-2 and PPI total scores did not yield significant differences in rates of response or remission at Visit 8.

Test-Retest Sample

Of the 134 patients in the ITT sample, 97 completed the 8 week trial. Thirteen of these did not complete a repeat PPI, resulting in 84 completing subjects who had both pre- and post-

treatment PPIs. In addition, six early terminating subjects also performed a repeat PPI at their final study visit, resulting in a total Test-Retest sample size of 90.

Figure 1 shows the change in PPI Factor scores from baseline to endpoint. Both PPI factors showed significant changes of small-to-moderate effect size: Fearless Dominance scores significantly increased by study completion (Cohen's $d = .32$), whereas Self-centered Impulsivity scores decreased significantly ($d = .44$). Compared with non-completers, study completers demonstrated a non-significant but medium-to-large effect size trend in Fearless Dominance increases [Non-completers: -0.8 (2.9); Completers: 3.4 (6.0), $p = .09$, $d = .74$] with significant and large effect decreases in Self-centered Impulsivity ratings [Non-completers: 1.33 (6.0); Completers: -4.6 (7.0), $p < .05$, $d = .86$]. Changes in PPI scores were not significantly associated with the presence or absence of an anxiety disorder at baseline.

Fearless Dominance increases were significantly correlated with improvements in depressive symptoms and clinically-rated impairment (HDRS, $r = -.32$, $p < .05$; MADRS change, $r = -.29$, $p < .01$; CGI-Severity, $r = -.34$, $p = .001$; QIDS-SR change $r = -.30$, $p = .005$). Self-centered Impulsivity changes were not significantly related to depression score changes ($r_s = .10$, $.04$, and $-.07$, respectively).

Gender was not significantly related to PPI changes (Fearless Dominance change, $t(88) = -.60$, $p = .55$; Self-centered Impulsivity change, $t(88) = .54$, $p = .59$). However, depressive symptom scores were significantly moderated by a three-way interaction of study week by gender by Fearless Dominance-Baseline score (HDRS, $\gamma_{13} = .08$, $t(808) = 3.9$, $p < .001$; MADRS, $\gamma_{13} = .09$, $t(806) = 3.44$, $p < .001$; CGI-Severity, $\gamma_{13} = .02$, $t(804) = 4.13$, $p < .001$), such that men with higher Fearless Dominance factor scores at baseline exhibited poorer treatment response across outcome measures. **Figures 2a and 2b** illustrates this interaction effect on HDRS scores over time stratified by gender and baseline Fearless Dominance scores (low scorers defined as a PPI-1 baseline score ≤ 1 SD below the sample mean [males $n = 9$, females $n = 14$] and high scorers defined as a PPI-1 baseline score ≥ 1 SD above the sample mean [males $n = 5$, females $n = 12$]). Moreover, high PPI-1 men had significantly greater scores on the MPQ positive emotion ($p < .05$) and significantly lower MPQ Constraint scores ($p < .05$) compared to the rest of the sample. This pattern of MPQ scores is consistent with the greater levels of psychopathy identified by the PPI scores in these men.

DISCUSSION

Consistent with our hypotheses, personality traits of psychopathy as measured by the PPI changed during 8 weeks of treatment with sertraline, but in opposing directions. Specifically, PPI-1, "Fearless Dominance" scores increased whereas PPI-2, "Self-centered Impulsivity" scores decreased. These findings bolster recent suggestions that psychopathy is not a unitary syndrome, but instead may reflect a configuration of at least two independent causal processes, namely fearless dominance (boldness) and disinhibition (Fowles DC, Dindo L, 2009; Patrick CJ *et al.*, 2009). The changes in psychopathy scores were only weakly correlated with changes in depressive symptoms. Our findings suggest that, in addition to improving symptoms of depressive symptoms, SSRIs may enhance adaptive personality traits traditionally observed in psychopathic individuals, such as social charm and interpersonal and physical boldness. Conversely, psychopathic traits often considered maladaptive, such as dysregulated impulsivity and externalization of blame, were reduced by SSRI treatment.

These data contribute to the growing literature on antidepressant modulation of personality traits. Previous work has demonstrated the effects of antidepressants on reducing neuroticism and increasing extroversion (Fournier JC *et al.*, 2008; Tang TZ *et al.*, 2009).

That these personality changes do not merely reflect depression improvement is demonstrated by the differing temporal course for improvement of depressive versus personality factors. Although our dataset did not permit such a time-course analysis, the low correlation between PPI change and depression severity change suggests that the PPI captures aspects of psychopathology above and beyond the mood and anxiety symptoms captured by the depression rating scales.

Previous work evaluating outcomes of depressed patients with personality disorders have yielded mixed results. ASPD encompasses primarily the behavioral traits sometimes associated with psychopathy, and in that sense is probably the DSM-IV personality disorder most closely aligned with psychopathy. In general, depression in patients with cluster B personality disorders appears to respond well to antidepressant medication treatment, with particular benefit noted from SSRIs as opposed to TCAs (Fournier JC *et al.*, 2008; Mulder RT *et al.*, 2003; Newton-Howes G *et al.*, 2006). However, the number of ASPD subjects in these samples is small, and the results are mixed (Fava M *et al.*, 2002; Joyce PR *et al.*, 1994; Mulder RT *et al.*, 2006). Treatment with medication appears superior to psychotherapy in depressed patients with cluster B personality disorders (Newton-Hayes G *et al.*, 2006). Emotional lability and impulsivity are common features of cluster B disorders, and are aspects of personality that may contribute to depression and be particularly responsive to serotonergic modulation.

We found no relationship between PPI scores at baseline and response or remission rates, although men with the highest PPI scores benefited significantly less from treatment with sertraline. This finding, which requires replication, raises the possibility that greater levels of psychopathy predict poorer outcomes with antidepressant treatment, perhaps indicating a variant of depression in these individuals (Lovelace L, Gannon L, 1999). Additionally, some evidence suggests that many psychopaths have low levels of anxiety sensitivity (fear of one's own anxiety and anxiety symptoms), which is often elevated in patients with MDD, and the reduction of which may be one mechanism of action for SSRIs (Lilienfeld SO, Penna S, 2001).

Previous work has identified relationships between serotonin function and psychopathy factors, but not psychopathy overall. Using a fenfluramine challenge paradigm in personality-disordered offenders, Dolan and Anderson (2003) identified a positive correlation between serotonin and the arrogant-deceitful factor on the Psychopathy Checklist-Screening Version, but a negative correlation between serotonin function and the impulsive-antisocial factor on this instrument. Our findings provide support for this biological separation of psychopathy factors, in that SSRI-treatment increased scores on PPI-1 and reduced scores on PPI-2. That men with high baseline PPI-1 fared less favorably with SSRI treatment, despite similar baseline depression severity levels, is consistent with the notion that serotonin dysfunction in these individuals was not a core contributor to their depression. Abnormalities in the structure or function of the prefrontal cortex, the amygdala, and their connections are frequently found in psychopathic individuals. Individuals with higher trait levels of psychopathy demonstrate lower levels of amygdala activation during decision-making about moral dilemmas (Glenn AL *et al.*, 2009). Psychopaths also exhibit thinner temporal and prefrontal grey-matter cortices compared with controls (Yang Y *et al.*, 2009), and reduced white matter connectivity between the amygdala and orbitofrontal cortex (OFC) (Craig MC *et al.*, 2009). These brain regions have all been associated with abnormal function in actively depressed patients, with reductions in amygdala and OFC activity after SSRI treatment (Ressler KJ, Mayberg HS, 2007). Thus, there is an intriguing overlap between the neurobiological effects of SSRIs and the neuroimaging findings in psychopathy. It is possible that in psychopaths these medications further reduce the activity of pre-existing hypoactive circuits.

An important limitation to this study is our reliance on a self-report measure of psychopathy. We did not collect any objective measures of change in antisocial and prosocial behaviors, such as criminal records or occupational and family functioning, although such objective changes may have been difficult to detect over the 8-week course of the trial. Without objective measures of change, it is possible that reported increases in some of the features of psychopathy were merely reflecting improvements in self-perception, in a manner consistent with the established negative perceptual bias in MDD patients (Beck, AT, 2008). Hence, we recommend that future research collect objective outcome measures of antisocial behavior, such as verbal and physical aggression, as well as measures of psychopathy as rated by external observers (see Lilienfeld, SO, 1998, for a review of such measures). Nevertheless, the fact that PPI-1 changes were significantly correlated with clinician-related improvements in depression symptoms strongly suggests that these changes at least partly reflected objective improvement. We caution against over-reaching in interpreting the findings we report here. The investigation did not include a placebo control condition with which to compare sertraline treatment, and its generalizability to other populations (e.g., prisoners or other individuals with severe antisocial and criminal behavior) is unknown. With these cautions in mind, we propose that these findings raise an intriguing and perhaps troubling possibility that requires systematic investigation. Specifically, antidepressant-induced reductions in amygdala activity in a psychopath with an already low level of amygdala function and fear responsiveness could produce pathologically lower levels of fearfulness and greater stress immunity. In one sense, our findings of reduction in Self-centered Impulsivity, reflecting improved self-control, would seem to suggest that SSRI treatment may reduce the potential for psychopaths to impulsively harm others or perform spontaneous criminal acts. Conversely our findings of increases in Fearless Dominance, reflecting heightened social confidence and diminished interpersonal and physical fear, may lessen any restraint psychopaths may experience prior to embarking on risky ploys. Whether our findings generalize to samples with more severe personality disorder pathology, however, is unclear.

Our results suggest that SSRI effects on personality traits in individuals who meet full criteria for psychopathic personality merit further study. Potential areas of future research include evaluating change in personality measures during SSRI treatment among psychopathic individuals with and without a current diagnosis of MDD. Similar studies of psychopathic patients with and without anxiety disorders also appear warranted. Better characterization of the subjective experience of “depression” among psychopathic and non-psychopathic MDD patients could be achieved through a combination of neuroimaging and qualitative research approaches. In particular, existing neuroimaging challenge paradigms for decision-making, risk-taking, and empathy could compare MDD patients before and after treatment, stratified by degree of psychopathy (Rangel A *et al.*, 2008; Masten CL *et al.*, 2011). For all such studies, incorporation of largely objective measures of psychopathic and antisocial behavior will be important to enhance validity of the findings. Finally, controlled studies of the impact of SSRI treatment on long-term outcomes of recidivism and social function among criminals with psychopathy would be of great public importance.

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Figure 1.
Change in Psychopathic Personality Inventory (PPI) scales after 8 weeks of sertraline treatment (N=90)
P-value for change for both scales: $p < .001$; Data expressed as mean $\pm$ SD

Figure 2a.

Change in depression severity during sertraline treatment among men with high versus low Fearless Dominance factor (PPI-1) scores at baseline.

Figure 2b.

Change in depression severity during sertraline treatment among women with high versus low Fearless Dominance factor (PPI-1) scores at baseline.

Table 1

Baseline demographic and clinical characteristics of the Baseline and Test-Retest Samples

Characteristic	Baseline Sample (N=144)		Test/Retest Sample (N=90)	
	Mean	SD	Mean	SD
Age (years)	42.0	11.0	42.4	10.6
Education (years)	15.2	1.9	15.4	1.9
HDRS Baseline	22.5	4.2	22.1	4.0
MADRS Baseline	26.8	5.6	26.3	5.5
QIDS-SR Baseline	14.4	3.8	14.4	4.0
CGI-Severity	4.5	0.6	4.5	0.6
PPI - Factor 1	45.8	9.4	44.7	9.4
PPI - Factor 2	55.4	9.9	55.4	9.8
PPI Total Score	101.1	13.7	100.1	13.7
	N	%	N	%
Sex				
Male	56	38.9	33	36.7
Female	88	61.1	57	63.3
Race				
Caucasian	115	79.9	74	82.2
Black	24	16.7	13	14.4
Other	5	3.5	3	3.3
Current Anxiety Disorder	51	35.4	29	32.2
Lifetime substance abuse disorder	34	23.6	19	21.1
Recurrent Depression	95	66.0	63	70.0
Melancholic Depression	66	45.8	41	45.6

Table 2

Baseline differences in PPI scores by gender and presence of current anxiety disorder and melancholia.

	N	PPI-1 Mean (SD)	p	d	PPI-2 Mean (SD)	p	d	PPI-Total Mean (SD)	p	d
Sex										
Women	88	44.0 (9.2)			53.7 (8.3)			97.7 (11.7)		
Men	56	48.5 (9.1)	.005	.49	58.0 (11.5)	.018	.45	106.5 (15.1)	<.001	.68
Current Anxiety Disorder										
Yes	51	40.0 (8.7)			55.7 (9.1)			95.8 (13.8)		
No	93	48.9 (8.3)	<.001	1.06	55.2 (10.3)	.74	-.05	104.1 (12.9)	0.001	.63
Melancholic Features										
Yes	66	45.3 (8.4)			57.2 (10.2)			102.4 (13.9)		
No	78	46.2 (10.2)	.55	.10	53.8 (9.4)	.043	-.35	100.0 (13.6)	.29	-.18

d= effect size; p= p-value; PPI: Psychopathic personality inventory; PPI-1: Factor 1, Fearless Dominance; PPI-2: Factor 2, Self-Centered Impulsivity.