

The effects of sertraline on psychopathic traits

Boadie W. Dunlop^a, Jared A. DeFife^a, Lauren Marx^a, Steven J. Garlow^a, Charles B. Nemeroff^b and Scott O. Lilienfeld^a

We examined whether antidepressants alter expression of psychopathic personality traits in patients with major depressive disorder (MDD). Data were collected from a double-blind, placebo-controlled 8-week trial evaluating the efficacy of sertraline (50–200 mg/day) combined with either tri-iodothyronine (T3) or matching placebo in adult outpatients with major depressive disorder. 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 participants who completed a baseline and postrandomization PPI. Ninety patients (84 completers and six 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. 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. *Int Clin Psychopharmacol* 26:329–337 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2011, 26:329–337

Keywords: antidepressive agents, anxiety, depression, personality disorders, psychopathic personality

^aEmory University School of Medicine, Atlanta, Georgia and ^bMiller School of Medicine, University of Miami, Miami, Florida, USA

Correspondence to Dr Boadie W. Dunlop, MD, Emory University School of Medicine, 1256 Briarcliff Road NE, Building A, 3rd Floor, Atlanta, GA 30306, USA

Tel: +1 404 727 8474; fax: +1 404 727 3700; e-mail: bdunlop@emory.edu

Received 17 February 2011 Accepted 1 August 2011

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 major depressive disorder (MDD)-treated with selective serotonin reuptake inhibitors (SSRIs) show reductions in neuroticism and aggression, and increases in extraversion, social desirability, and affiliativeness (Ekselius and Von Knorring, 1999; Brody *et al.*, 2000; Tang *et al.*, 2009). Some have attributed personality changes during SSRI treatment to improvement in depressive symptoms (Du *et al.*, 2002), but a more recent study found that reduced neuroticism and increased extraversion are independent from depression improvement, and are temporally dissociated from depression score change (Tang *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 *et al.*, 2008).

Bolstering findings of personality change with SSRIs in depressed patients, several studies have explored the effects of SSRIs on healthy participants. Compared with placebo treatment, SSRI treatment is associated with reduced hostility and attention to negative stimuli, and

increased affiliative behaviors and self-directedness (Knutson *et al.*, 1998; Tse and Bond, 2001; Harmer *et al.*, 2003), although some have found no effects (Gelfin *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, 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, 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 (Hare, 2003; Coid *et al.*, 2009). 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 and Andrews, 1996). Indeed, recent findings using taxometric techniques suggest that psychopathy is best defined dimensionally rather than categorically (Marcus *et al.*, 2004; Edens *et al.*, 2006). 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 *et al.*, 2005a, 2005b).

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 antisocial personality disorder (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 (NEMs, Karpman, 1941; Levenson *et al.*, 1995).

The Psychopathic Personality Inventory (PPI) is a commonly used self-report instrument that identifies two broadly similar factors of psychopathy (Lilienfeld and Andrews, 1996; Benning *et al.*, 2005a, 2005b; Poythress *et al.*, 2010). In contrast to the PCL-R, however, the first major factor of the PPI, often termed as 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 and Widows, 2005). Healthy control participants scoring highly on the second PPI factor ('Self-Centered Impulsivity'), PPI-2, demonstrate hyperactivity 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 *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 and Dunlop, 2006) and from

study in depressed patients suggesting that extraversion increases with SSRI treatment independently of depressive symptoms (Bagby *et al.*, 1999; Tang *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 *et al.*, 2009). Social anxiety and psychopathy are negatively correlated (Hofmann *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 (Bagby *et al.*, 1999; Harmer *et al.*, 2004). In addition, social affiliativeness in healthy controls increases with SSRI treatment (Knutson *et al.*, 1998). Finally, impulsivity, which contributes to behavioral dyscontrol, improves in patients with borderline personality disorder patients treated with SSRIs (Bellino *et al.*, 2008). Open-label data suggest that SSRIs reduce impulsivity among repeat violent offenders (Butler *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 (1988) 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 and Gannon, 1999). That SSRIs are demonstrated to improve such symptoms as guilt and oversensitivity to criticism in depressed individuals raises the possibility that SSRIs may even further diminish 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 *et al.*, 1996).

The effects of SSRI treatment on 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 patients with non-ASPD is unclear (Joyce *et al.*, 1994; Fava *et al.*, 2002; Mulder *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

antisocial behavior and psychopathy, including the PCL-R (Lilienfeld and Andrews, 1996; Poythress *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 *et al.*, 2005a, 2005b).

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), 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 nonpsychopaths (Hicks *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 greater than or equal to 50%

from the baseline HDRS score. Remission was defined as a final visit HDRS score less than or equal to 7. Analyses were performed in SPSS version 17.0. (SPSS Inc., Chicago, Illinois, USA). Differences and changes in mean scores were assessed using two-tailed t -tests using a $P < 0.05$ level of significance. Hierarchical linear modeling was used to examine the relationship of PPI baseline variables with change in depression symptoms over time and separated by gender. Hierarchical linear modeling 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 prescore and postscores, 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/day [standard deviation (SD): 46.2 mg/day].

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 six terminated the trial early.

Total sample

PPI factors 1 ('Fearless Dominance') and 2 ('Self-Centered Impulsivity') were not significantly correlated ($r = 0.02$, $P = \text{NS}$). Baseline PPI total and factor scores

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-S	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
	<i>n</i>	%	<i>n</i>	%
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

CGI-S, Clinical Global Impression-Severity; HDRS, Hamilton Depression Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; PPI, Psychopathic Personality Inventory; QIDS-SR, Quick Inventory of Depressive Symptoms-Self Report.

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-S scores at baseline were all low and nonsignificant (r ranged from -0.16 to 0.02 , $P > 0.05$), except for the correlation between the QIDS-SR correlation and Self-Centered Impulsivity ($r = 0.18$, $P = 0.035$).

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 ($r = 0.55$, $P < 0.001$), but not correlated with PPI Self-Centered Impulsivity. MPQ NEM scores were negatively correlated with PPI Fearless Dominance ($r = 0.34$, $P < 0.001$), and positively correlated with Self-Centered Impulsivity ($r = 0.48$, $P < 0.001$). 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 nonmelancholic patients, but did not differ significantly on Fearless Dominance. Years of education were significantly correlated with Fearless Dominance scores ($r = 0.19$, $P = 0.026$), but not Self-Centered Impulsivity scores ($r = -0.08$, $P = \text{NS}$).

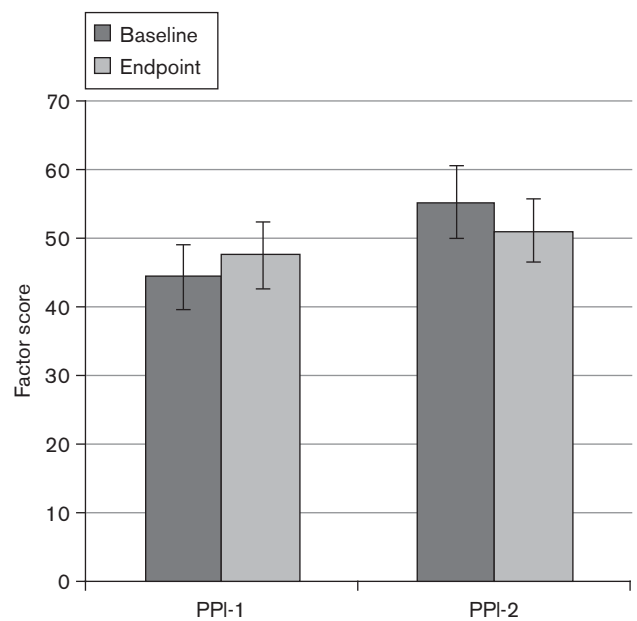
Of the total sample, an intent-to-treat sample of 134 patients who initiated treatment with sertraline and returned to complete at least one postrandomization HDRS efficacy rating was identified. For this population, the baseline means (\pm SD) were 101.1 (13.9); 46.5 (9.4), and 55.0 (9.9), for PPI total, 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 intent-to-treat sample, 97 completed the 8-week trial. Thirteen of these did not complete a repeat PPI, resulting in 84 completing participants who had both pretreatment and posttreatment PPIs. In addition, six early terminating participants 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 $d = 0.32$), whereas Self-Centered Impulsivity scores decreased significantly ($d = 0.44$). Compared with noncompleters, study completers demonstrated a nonsignificant but medium-to-large effect size trend in

Fig. 1



Change in Psychopathic Personality Inventory (PPI) scales after 8 weeks of sertraline treatment ($n = 90$). P -value for change for both scales: $P < 0.001$; data expressed as mean \pm standard deviation.

Table 2 Baseline differences in PPI scores by gender and presence of current anxiety disorder and melancholia

	<i>n</i>	PPI-1 Mean (SD)	<i>P</i>	<i>d</i>	PPI-2 Mean (SD)	<i>P</i>	<i>d</i>	PPI-total Mean (SD)	<i>P</i>	<i>d</i>
Sex										
Women	88	44.0 (9.2)			53.7 (8.3)			97.7 (11.7)		
Men	56	48.5 (9.1)	0.005	0.49	58.0 (11.5)	0.018	0.45	106.5 (15.1)	<0.001	0.68
Current anxiety disorder										
Yes	51	40.0 (8.7)			55.7 (9.1)			95.8 (13.8)		
No	93	48.9 (8.3)	<0.001	1.06	55.2 (10.3)	0.74	-0.05	104.1 (12.9)	0.001	0.63
Melancholic features										
Yes	66	45.3 (8.4)			57.2 (10.2)			102.4 (13.9)		
No	78	46.2 (10.2)	0.55	0.10	53.8 (9.4)	0.043	-0.35	100.0 (13.6)	0.29	-0.18

d, effect size; *P*, *P*-value; PPI, Psychopathic Personality Inventory; PPI-1, factor 1, Fearless Dominance; PPI-2, factor 2, Self-Centered Impulsivity.

Fearless Dominance increases [noncompleters: -0.8 (2.9); completers: 3.4 (6.0), $P = 0.09$, $d = 0.74$] with significant and large effect decreases in Self-Centered Impulsivity ratings [noncompleters: 1.33 (6.0); completers: -4.6 (7.0), $P < 0.05$, $d = 0.86$]. Changes in PPI scores were not significantly associated with the presence or absence of an anxiety disorder at baseline.

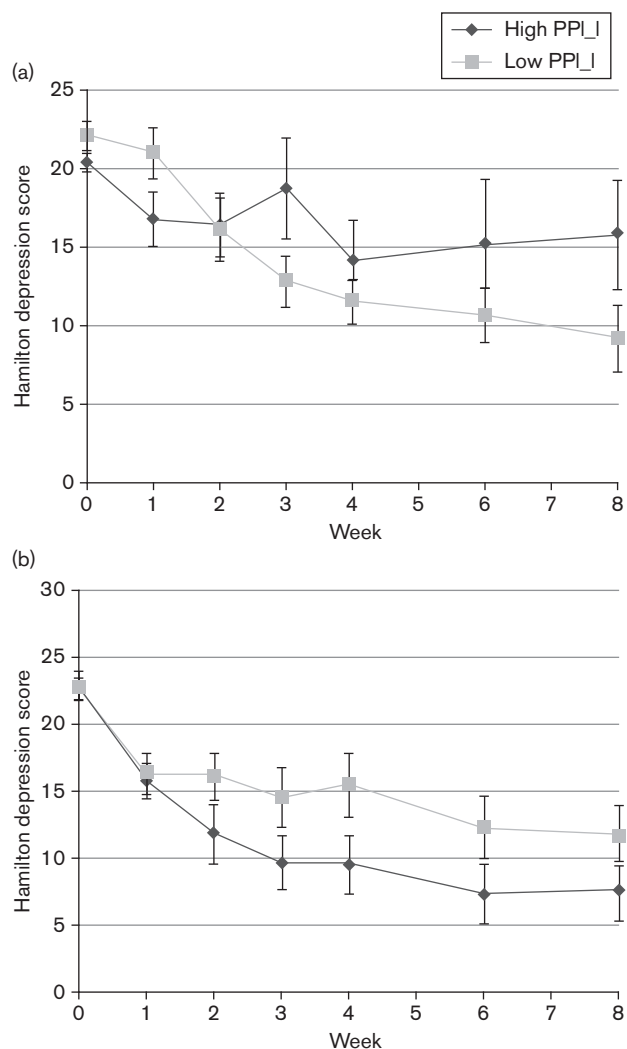
Fearless Dominance increases were significantly correlated with improvements in depressive symptoms and clinically rated impairment (HDRS, $r = -0.32$, $P < 0.05$; MADRS change, $r = -0.29$, $P < 0.01$; CGI-S, $r = -0.34$, $P = 0.001$; QIDS-SR change $r = -0.30$, $P = 0.005$). Self-Centered Impulsivity changes were not significantly related to depression score changes ($r = 0.10$, 0.04 , and -0.07 , respectively).

Gender was not significantly related to PPI changes [Fearless Dominance change, $t(88) = -0.60$, $P = 0.55$; Self-Centered Impulsivity change, $t(88) = 0.54$, $P = 0.59$]. However, depressive symptom scores were significantly moderated by a three-way interaction of study week by gender by Fearless Dominance-Baseline score [HDRS, $\gamma_{13} = 0.08$, $t(808) = 3.9$, $P < 0.001$; MADRS, $\gamma_{13} = 0.09$, $t(806) = 3.44$, $P < 0.001$; CGI-S, $\gamma_{13} = 0.02$, $t(804) = 4.13$, $P < 0.001$], such that men with higher Fearless Dominance factor scores at baseline exhibited poorer treatment response across outcome measures. Figure 2a and b 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 less than or equal to 1 SD below the sample mean (males $n = 9$, females $n = 14$) and high scorers defined as a PPI-1 baseline score greater than or equal to 1 SD above the sample mean (males $n = 5$, females $n = 12$)]. Moreover, high PPI-1 men had significantly greater scores on the MPQ PEM ($P < 0.05$) and significantly lower MPQ CON scores ($P < 0.05$) compared with 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 and Dindo, 2009; Patrick *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 tradition-

Fig. 2



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

ally 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 study has demonstrated the effects of antidepressants on reducing neuroticism and increasing extroversion (Fournier *et al.*, 2008; Tang *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 study 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 *Diagnostic and Statistical Manual of Mental Disorder, 4th edition* 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 (Mulder *et al.*, 2003; Newton-Howes *et al.*, 2006; Fournier *et al.*, 2008). However, the number of ASPD participants in these samples is small, and the results are mixed (Joyce *et al.*, 1994; Fava *et al.*, 2002; Mulder *et al.*, 2006). Treatment with medication appears superior to psychotherapy in depressed patients with cluster B personality disorders (Newton-Howes *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 and Gannon, 1999). In addition, 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 and Penna, 2001).

Previous study 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 *et al.*, 2009). Psychopaths also exhibit thinner temporal and prefrontal gray-matter cortices compared with controls (Yang *et al.*, 2009), and reduced white matter connectivity between the amygdala and orbitofrontal cortex (Craig *et al.*, 2009). These brain regions have all been associated with abnormal function in actively depressed patients, with reductions in amygdala and orbitofrontal cortex activity after SSRI treatment (Ressler and Mayberg, 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 preexisting 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 patients with MDD (Beck, 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, 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 overreaching 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 before 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 nonpsychopathic patients with MDD 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 patients with MDD before and after treatment, stratified by degree of psychopathy (Rangel *et al.*, 2008; Masten *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.

Acknowledgements

This research was funded by the National Institutes of Mental Health grants R01 MH56946 and K23 MH086690 (B.W.D.). Pfizer provided the sertraline used in the study.

Conflicts of interest

Dr Dunlop has received research support from Evotec, Forest, GSK, NIMH, Novartis, Ono, Pfizer. He has performed consulting with BMS, Imedex LLC, and Medavante. Dr DeFife reports no conflicts. Ms Marx reports no conflicts. Dr Garlow receives research support from Evotec. Dr Nemeroff has served on the scientific advisory boards of American Foundation for Suicide Prevention (AFSP); AstraZeneca; Forest Laboratories; NARSAD; Quintiles; Janssen/Ortho-McNeil; Pharma-Neuroboost; 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 coauthor on the Psychopathic Personality Inventory-Revised (PPI-R), published by Psychological Assessment Resources (PAR).

Clinicaltrials.gov: NCT0028702.

References

- Bagby RM, Levitan RD, Kennedy SH, Levitt AJ, Joffe RT (1999). Selective alteration of personality in response to noradrenergic and serotonergic antidepressant medication in depressed sample: evidence of non-specificity. *Psychiatry Res* **86**:211–216.
- Beck AT (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry* **165**:969–977.
- Bellino S, Paradiso E, Botetto F (2008). Efficacy and tolerability of pharmacotherapies for borderline personality disorder. *CNS Drugs* **22**:671–692.
- Benning SD, Patrick CJ, Blonigen DM, Hicks BM, Iacono WG (2005a). Estimating facets of psychopathy from normal personality traits: a step toward community epidemiological investigations. *Assessment* **12**:3–18.
- Benning SD, Patrick CJ, Salekin RT, Leistico AR (2005b). Convergent and discriminant validity of psychopathy factors assessed via self-report: a comparison of three instruments. *Psychol Assess* **15**:340–350.
- Brody AL, Saxena S, Fairbanks LA, Alborzian S, Demaree HA, Maidment KM, *et al.* (2000). Personality changes in adult subjects with major depressive disorder or obsessive-compulsive disorder treated with paroxetine. *J Clin Psychiatry* **61**:349–355.
- Buckholz JW, Treadway MT, Cowan RL, Woodward ND, Benning SD, Li R, Ansari MS (2010). Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nat Neurosci* **13**:419–421.
- Butler T, Schofield PW, Greenberg D, Allnutt SH, Indig D, Carr V, *et al.* (2010). Reducing impulsivity in repeat violent offenders: an open label trial of a selective serotonin reuptake inhibitor. *Aust N Z J Psychiatry* **44**:1137–1143.
- Cleckley H (1988). *The mask of sanity*. St Louis: Mosby.
- Coid JW, Yang M, Ullrich S, Roberts ADL, Hare RD (2009). Prevalence and correlates of psychopathic traits in the household population of Great Britain. *Int J Law Psychiatry* **32**:65–73.
- Cornell DG, Warren J, Hawk G, Stafford E, Oram G, Pine D (1996). Psychopathy in instrumental and reactive violent offenders. *J Consult Clin Psychol* **64**:783–790.
- Craig MC, Catani M, Deeley Q, Latham R, Daly E, Kanaan R, *et al.* (2009). Altered connections on the road to psychopathy. *Mol Psychiatry* **14**:946–953.
- Dolan MC, Anderson IM (2003). The relationship between serotonergic function and the psychopathy checklist: screening version. *J Psychopharmacol* **17**:216–222.
- Du L, Bakish D, Ravindran AV, Hrdina PD (2002). Does fluoxetine influence major depression by modifying five-factor personality traits? *J Affect Disord* **71**:235–241.
- Edens JF, Marcus DK, Lilienfeld SO, Poythress NG (2006). Psychopathic, not psychopath: taxometric evidence for the dimensional structure of psychopathy. *J Abnorm Psychol* **115**:131–144.
- Ekselius L, Von Knorring L (1999). Changes in personality traits during treatment with sertraline or citalopram. *Br J Psychiatry* **174**:444–448.
- Fava M, Farabaugh AH, Sickinger AH, Wright E, Alpert JE, Sonawalla S, *et al.* (2002). Personality disorders and depression. *Psychol Med* **32**:1049–1057.
- Fournier JC, DeRubeis RJ, Shelton RC, Gallop R, Amsterdam JD, Hollon SD (2008). Antidepressant medications v. cognitive therapy in people with depression with or without personality disorder. *Br J Psychiatry* **192**:124–129.
- Fowles DC, Dindo L (2009). Temperament and psychopathy: a dual-pathway model. *Curr Dir Psychol Sci* **18**:179–183.
- Garlow SJ, Dunlop BW, Neyman K, Ninan PT, Nemeroff CB (2007). The addition of tri-iodothyronine (T3) to sertraline does not enhance antidepressant response in patients with major depressive disorder. Poster presented at American College of Neuropsychopharmacology.
- Gelfin Y, Gorfine M, Lerer B (1998). Effect of clinical doses of fluoxetine on psychological variables in healthy volunteers. *Am J Psychiatry* **155**:290–292.
- Glenn AL, Raine A, Schug RA (2009). The neural correlates of moral decision-making in psychopathy. *Mol Psychiatry* **14**:5–9.
- Guy W (1976). ECDEU assessment manual for psychopharmacology. Rockville, MD: US Department of Health Education and Welfare. pp. 76–338.
- Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**:56–62.
- Hare RD (1998). *Without conscience: The disturbing world of the psychopaths among us*. New York: Guilford Press.

- Hare RD (2003). *The Hare psychopathy checklist-revised*. Toronto, Canada: Multi-Health System.
- Harmer CJ, Bhagwagar Z, Perrett DI, Völlm BA, Cowen PJ, Goodwin GM (2003). Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* **28**:148–152.
- Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004). Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry* **161**:1256–1263.
- Hicks BM, Markon KE, Patrick CJ, Krueger RF, Newman JP (2004). Identifying psychopathy subtypes based on personality structure. *Psychological Assess* **16**:276–288.
- Hofmann SG, Korte JK, Suvak MK (2009). The upside of being socially anxious: psychopathic attributes and social anxiety are negatively associated. *J Soc Clin Psychol* **28**:714–727.
- Joyce PR, Mulder RT, Cloninger CR (1994). Temperament predicts clomipramine and desipramine response in major depression. *J Affect Disord* **30**:35–46.
- Karpman B (1941). On the need of separating psychopathy into two distinct clinical types: the symptomatic and the idiopathic. *J Crim Psychopathology* **3**:112–137.
- Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC, *et al.* (1998). Selective alteration of personality and social behavior by serotonergic intervention. *Am J Psychiatry* **155**:373–379.
- Kramer PD (1993). *Listening to Prozac*. New York: Viking Press.
- Levenson MR, Kiehl KA, Fitzpatrick CM (1995). Assessing psychopathic attributes in a noninstitutionalized population. *J Pers Soc Psychol* **68**:151–158.
- Lilienfeld SO (1998). Methodological advances and developments in the assessment of psychopathy. *Beh Res Therapy* **36**:99–125.
- Lilienfeld SO, Andrews BP (1996). Development and preliminary validation of a self-report measure of psychopathic personality traits in noncriminal populations. *J Pers Assess* **66**:488–524.
- Lilienfeld SO, Perna S (2001). Anxiety sensitivity: relations to psychopathy, DSM-IV personality disorder features, and personality traits. *J Anxiety Disord* **15**:367–393.
- Lilienfeld SO, Widows MR (2005). *Psychopathic Personality Inventory-Revised: professional manual*. Lutz, FL: Psychological Assessment Resources.
- Lovelace L, Gannon L (1999). Psychopathy and depression: mutually exclusive constructs? *J Behav Ther Exp Psychiatry* **30**:169–176.
- Marcus DK, John SL, Edens JF (2004). A taxometric analysis of psychopathic personality. *J Abnorm Psychol* **113**:626–635.
- Masten CL, Morelli SA, Eisenberger SI (2011). An fMRI investigation of empathy for 'social pain' and subsequent prosocial behavior. *Neuroimage* **55**:381–388.
- Montgomery SA, Asberg A (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**:382–389.
- Mulder RT, Joyce PR, Luty SE (2003). The relationship of personality disorders to treatment outcome in depressed patients. *J Clin Psychiatry* **64**:259–264.
- Mulder RT, Joyce PR, Frampton CMA, Luty SE, Sullivan PF (2006). Six months of treatment for depression: outcome and predictors of the course of illness. *Am J Psychiatry* **163**:95–100.
- Newton-Howes G, Tyrer P, Johnson T (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. *Br J Psychiatry* **188**:13–20.
- Ninan PT, Dunlop BW (2006). *Contemporary diagnosis and management of anxiety disorders*. Newton, PA: HHC Books.
- Patrick CJ, Fowles DC, Krueger RF (2009). Triarchic conceptualization of psychopathy: developmental origins of disinhibition, boldness, and meanness. *Dev Psychopathol* **21**:913–938.
- Poythress NG, Edens JF, Lilienfeld SO (1998). Criterion-related validity of the Psychopathic Personality Inventory in a prison sample. *Psychol Assess* **10**:426–430.
- Poythress NG, Lilienfeld SO, Skeem JL, Douglas KS, Edens JF, Epstein M, *et al.* (2010). Using the PCL-R to help estimate the validity of two self-report measures of psychopathy with offenders. *Assessment* **17**:206–219.
- Rangel A, Camerer C, Montague PR (2008). A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* **9**:545–556.
- Ressler KJ, Mayberg HS (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat Neurosci* **10**:1116–1124.
- Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, *et al.* (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* **54**:573–583.
- Simmons AN, Arce E, Lovero KL, Stein MB, Paulus MP (2009). Subchronic SSRI administration reduces insula response during affective anticipation in healthy volunteers. *Int J Neuropsychopharmacol* **12**:1009–1020.
- Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B (2009). Personality change during depression treatment. *Arch Gen Psychiatry* **66**:1322–1330.
- Tse WS, Bond AJ (2001). Serotonergic involvement in the psychosocial dimension of personality. *J Psychopharmacol* **15**:195–198.
- Yang Y, Raine A, Colletti P, Toga AW, Narr KL (2009). Abnormal temporal and prefrontal cortical gray matter thinning in psychopaths. *Mol Psychiatry* **14**:561–562.