Personality predictors of antiaggressive response to fluoxetine: inverse association with neuroticism and harm avoidance

K. Luan Phan[a,b], Royce Lee[c] and Emil F. Coccaro[c]

Although selective serotonin reuptake inhibitors (SSRI) are generally effective in reducing impulsive aggression in individuals with intermittent explosive disorder, a large proportion of intermittent explosive disorder patients fail to achieve full remission despite adequate dosage and duration of treatment. Temperament, specifically those associated with negative emotionality (neuroticism, harm avoidance) may predict response to SSRI treatment. The objective of this study was to determine whether baseline neuroticism and harm avoidance scores would be associated with reduced aggression (as measured by the Overt Aggression Scale-Modified [OAS-M] aggression scores) after SSRI treatment. Participants participating in a randomized, placebo-controlled clinical trial of fluoxetine completed the Eysenck Personality Questionnaire ($n=57$) and the Tridimensional Personality Questionnaire ($n=38$) before entering the treatment trial. Multiple regression analyses (accounting for baseline OAS-M aggression scores) revealed that pretreatment eysenck personality questionnaire neuroticism and tridimensional personality questionnaire harm avoidance independently and uniquely predicted OAS-M aggression scores at endpoint in the fluoxetine, but not placebo, treated group. These preliminary findings are the first from a placebo-controlled clinical trial to suggest that temperamental factors such as neuroticism and harm avoidance can partly explain the observed variability in treatment response in SSRI treated individuals with impulsive aggression and prompt future prospective studies examining personality dimensions as predictors of outcomes in clinical trials. *Int Clin Psychopharmacol* 26:278–283 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2011, **26**:278–283

Keywords: aggression, fluoxetine, harm avoidance, neuroticism

[a]Department of Psychiatry, University of Michigan, [b]Mental Health Service, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA and [c]Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, Clinical Neuroscience and Psychopharmacology Research Unit, University of Chicago, Chicago, Illinois, USA

Correspondence to Emil F. Coccaro, MD, Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA
Tel: +1 773 834 4083; fax: +1 773 834 7427;
e-mail: ecoccaro@yoda.bsd.uchicago.edu

Received 31 May 2011 **Accepted** 2 June 2011

Introduction

Intermittent Explosive Disorder (IED) is characterized by recurrent episodes of serious acts of aggression that are out of proportion to the provocation that are not better explained by another mental disorder, comorbid medical illness, or psychoactive substance (Coccaro, 2011). Current IED Research Criteria (Coccaro *et al.*, 2004), specify the frequency of assaultive acts (i.e., at least three serious assaults or destruction of property in a one-year period or two outbursts per week in no less than one month) and the nature of the aggression (i.e., impulsive, not premeditated). In the United States, the disorder is far more common than previously thought, with as many as 5–7% of the general population having IED over the course of their lifetime (Kessler *et al.*, 2006).

Among, empirically-validated treatments, SSRIs have been shown to reduce aggressive acts and irritability associated with IED from both open-label and double-blind, placebo-controlled clinical trials (RCT) (Fava *et al.*, 1993; Salzman *et al.*, 1995; Reist *et al.*, 2003; Coccaro *et al.*, 2009). However, in our recent RCT (Coccaro *et al.*, 2009), we observed that the SSRI fluoxetine's antiaggressive effects were more modest and variable than apparent from its effects on symptom severity (i.e., number and frequency of impulsive aggressive acts, irritability). Accounting for all fluoxetine treated patients in the study, only 29% had full remission and only 46% had achieved full or partial remission from IED at endpoint. Little is known about the clinical markers that mediate this variability in SSRI treatment response in individuals with impulsive aggression, and how to differentiate responders from nonresponders before treatment is initiated. Thus far, demographic and clinical measures have fared poorly as effective, reliable predictors of treatment response in patients with impulsive aggression, including those with IED and personality disorders (Coccaro, 2003).

Some clues do exist that personality variables may impact the likelihood of response to pharmacologic treatments that act on the serotonin system (e.g. SSRI or tricyclic antidepressants), mostly from antidepressant clinical trials. However, how 'personality' is measured has varied across studies and the results have been equivocal. For example, Peselow *et al.* (1992) had noted that the presence of personality disorders or higher personality

0268-1315 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/YIC.0b013e32834978ac

trait scores with depression was associated with a poorer antidepressant desipramine treatment outcomes. In contrast, Fava *et al.* (1994) reported that depressed patients who had cluster B personality disorders achieved a better fluoxetine treatment response compared with those without this personality comorbidity. More recent studies have employed temperament scales to directly measure and delineate different components of personality, such as the Tridimensional Personality Questionnaire (TPQ) (Cloninger *et al.*, 1991); the TPQ provides individual-specific scores on specific, separable traits such as harm avoidance, reward dependence, and novelty seeking that are known to be stable and heritable. For example, lower harm avoidance, but not reward dependence or novelty seeking, has been associated with better antidepressant treatment (Abrams *et al.*, 2004; Joffe *et al.*, 1993; Strakowski *et al.*, 1995). Petersen, *et al.* (2002) observed that neuroticism, which is correlated with harm avoidance and also measured by the Eysenck Personality Questionnaire (EPQ), at baseline (pretreatment) did not predict fluoxetine treatment response. Interestingly, Quilty, *et al.* (2008, 2010) have shown that neuroticism and harm avoidance serve as mediators of antidepressant treatment response in patients with major depression, such that the treatment effect (reduction in depressive symptoms) occurred through a reduction of these temperament variables. By extension, it would be of interest to examine if these personality variables in IED patients would help explain the variability of response to antiaggressive treatment.

There is other evidence to support the notion that temperament factors could influence the magnitude of improvement after SSRI treatment of impulsive aggression, related to the neurobiology of SSRI action and temperament. Two temperamental factors, neuroticism and harm avoidance, related to the general propensity to experience negative affect ('negative emotionality'; Lara *et al.*, 2006) are linked to serotonergic activity (Hansenne *et al.*, 1997; Sen *et al.*, 2004; Takano *et al.*, 2007), as has aggression, another expression of negative affect, in both animals and humans (Olivier, 2004). Specifically, converging evidence suggests an inverse correlation between 5-HT measures and impulsive aggressive behaviors in human patients (Coccaro *et al.*, 2010a, 2010b). Interestingly, neuroticism has been shown to be associated with aggressive behaviors and negatively correlated with serotonergic challenges with IED patients (Coccaro *et al.*, 2010a).

In this study we examined the relationship between pretreatment temperament and clinical response at posttreatment in the context of a large ($n = 100$) double-blind, RCT designed to evaluate the antiaggressive efficacy of the SSRI fluoxetine in a group of not depressed, personality-disordered individuals with prominent histories of impulsive aggression as defined by research criteria for IED. The efficacy results of fluoxetine on aggression and irritability from this RCT have been previously reported (Coccaro, *et al.*, 2009). On the basis of the extant literature, we hypothesized that the extent of neuroticism and harm avoidance in IED patients before SSRI treatment would predict the extent of treatment response in terms of reductions in impulsive aggression at posttreatment.

Methods

Patients

All men and women patients who enrolled in the Fluoxetine Treatment Study of IED (Coccaro, *et al.*, 2009) and who completed the EPQ (Eysenck and Eysenck, 1975) and/or TPQ (Cloninger, *et al.*, 1991) were included in this study. All patients met the Integrated Research Criteria for IED. Written informed consent, using an IRB-approved consent document, was obtained from all patients.

Diagnostic and medical evaluation

Axis I and Axis II personality disorder diagnoses were made according to diagnostic and statistical manual of mental disorders-IV criteria, and IED diagnosis was made by the Integrated Research Criteria (Coccaro *et al.*, 2004; Coccaro, 2011), by semi-structured interviews by masters or doctorate-level clinicians experienced in the administration of these assessments (Coccaro *et al.*, 2009).

Treatment patients were without a life history of mania/hypomania, schizophrenia, or delusional disorder or current alcohol or drug use disorders and current Major Depression; other Axis I disorders were not exclusionary. Current and Lifetime Axis I and Axis II disorders for the patients are displayed in Table 1.

Assessment of current and lifetime history of impulsive aggressive behavior, clinical response to treatment, and related behaviors

The history of impulsive aggression was assessed by interview assessments using Overt Aggression Scale-Modified (OAS-M). OAS-M aggression scores represent a frequency/severity weighted assessment of overt aggressive behavior for the past week (on a scale of 0 to > 999). OAS-M scores were determined by a trained behavioral assessor blind to treatment group assignment. Lifetime history of impulsive aggressive behaviors was assessed, blind to treatment group assignment, during the diagnostic assessment, using the Aggression Score from the Lifetime History of Aggression interview (scale of 0–25; Coccaro *et al.*, 1997).

General study design

The treatment study was a 14-week, double-blind, randomized, placebo-controlled trial to evaluate the safety and antiaggressive efficacy of fluoxetine (20–60 mg po) in patients meeting the Integrated

Research Criteria for IED. Randomized patients continued on in the protocol and received up to a 12-week course with fluoxetine (20–60 mg po qd) or placebo (1–3 capsules po qd) while undergoing OAS-M Aggression Assessments each week. For the first four weeks of the double-blind treatment phase, the fluoxetine dose was set at 20 mg po qd. At the end of week 4 (or later) fluoxetine (or placebo) could be raised to 40 mg (two placebo capsules) if the average OAS-M Aggression score for the previous two weeks had not decreased to less than 25% of the average OAS-M Aggression score during the placebo lead-in phase. Fluoxetine could be increased to a maximum of 60 mg qd (three placebo capsules) after week 8 if the average OAS-M Aggression score for the previous two weeks had not dropped to 25% of the average OAS-M 'Aggression' score at randomization. Details of the treatment protocol have been previously reported (Coccaro *et al.*, 2009).

Personality measures: EPQ and TPQ

The EPQ is a self-report questionnaire with three personality scales: neuroticism, extraversion, and psychoticism. Fifty-seven patients completed the EPQ before entering the treatment study. The TPQ is also a self report questionnaire but with three different personality scales: harm avoidance, novelty seeking, and reward dependence. Thirty-eight patients completed the TPQ prior to entering the treatment trial. Although 100 patients entered the overall clinical trial, these two measures were added at different times after the study began and so the number of patients who completed either assessment is less than 100 and not equal for each.

Statistical analysis

The primary outcome variable for impulsive aggressive behavior in this placebo-controlled trial was the mean OAS-M Aggression score over successive two-week windows at endpoint (whenever that was for the patient in question). Two-week windows were used because of the high intra-individual variability of OAS-M Aggression scores. As OAS-M Aggression scores were not normally distributed all scores were log-transformed. Multiple regression analyses were performed for EPQ and TPQ separately. In all these analyses, baseline OAS-M Aggression scores were included as a covariate. A subsequent analysis including the relevant EPQ/TPQ scales was then performed. Other statistical procedures included *t*-test (with correction for unequal variances where appropriate), Pearson correlation, and ANOVA, where appropriate. Probability values were set at a two-tail alpha level of 0.05.

Results

Demographic and behavioral of the treatment group randomized to fluoxetine ($n = 34$) and placebo ($n = 23$) are displayed in Table 2 with similar characteristics except for the modestly lower age of placebo patients.

Table 1 Current and lifetime axis I and axis II personality disorder diagnoses in the intermittent explosive disorder sample

	Current diagnosis	Lifetime diagnosis
Mood disorder:		
Major depression	0	14
Dysthymia	5	7
Depression disorder-NOS	9	14
Anxiety disorder	3	15
Substance dependence:		
Alcohol	0	19
Other drugs	0	21
Personality disorder (PD):		
PD-NOS	21	
Obsessive-compulsive PD	18	
Paranoid PD	17	
Borderline PD	9	
Antisocial PD	8	
Narcissistic PD	8	
Avoidant PD	3	
Histrionic PD	2	

NOS, not otherwise specified.

Table 2 Demographic, behavioral and diagnostic characteristics of sample and as a function of randomization to fluoxetine or placebo

	Fluoxetine ($N=34$)	Placebo ($N=23$)	*P*
Gender (% male/female):	77/23	78/22	0.87
Race (% white/nonwhite):	88/12	87/13	0.96
Age:	39.7 ± 8.4	35.2 ± 8.7	0.05*
Function (GAF):	55.6 ± 7.1	57.4 ± 5.6	0.29
LHA aggression:	17.0 ± 6.1	18.2 + 5.9	0.53
EPQ neuroticism	15.5 ± 4.5	14.4 ± 5.6	0.46
EPQ extraversion	11.1 ± 5.1	11.9 ± 6.6	0.65
EPQ psychoticism	4.9 ± 2.6	5.7 ± 3.1	0.29
TPQ harm avoidance	17.6 ± 6.2	18.1 ± 7.7	0.85
TPQ novelty seeking	17.7 ± 5.0	17.4 ± 6.1	0.90
TPQ reward dependence	18.1 ± 4.8	19.3 ± 5.3	0.49
Log baseline OAS-M aggression:	1.38 ± 0.31	1.43 ± 0.39	0.62
Log endpoint OAS-M aggression:	0.76 ± 0.51	1.04 ± 0.51	0.05*

EPQ, eysenck personality questionnaire; GAF, global assessment of function; LHA, Lifetime History of agression; OAS-M, Overt Aggression Scale-Modified; TPQ, tridimensional personality questionnaire.

Despite this, age did not correlate with OAS-M Aggression at baseline or at endpoint. In addition, the patients in this sample (i.e., those with EPQ/TPQ data) did not differ from the remaining patients in the overall clinical trial data set (i.e., those who did not have EPQ/TPQ data but entered the clinical trial) with regard to age, gender, race, socioeconomic status, or in their scores for Global Assessment of Function, Lifetime History of Aggression, or Baseline OAS-M Aggression.

Effect of fluoxetine versus placebo on endpoint OAS-M aggression scores

As in the larger group from which this sample was derived (Coccaro *et al.*, 2009), there was a significant reduction in OAS-M Aggression scores among Fluoxetine versus Placebo treated patients at endpoint (baseline OAS-M Aggression scores entered as a covariate). This was true for both the subsample with EPQ data [$n = 57$: $F(1,55) = 4.14$, $P < 0.05$] and the subsample with TPQ data [$n = 38$: $F(1,35) = 7.69$, $P < 0.01$]. Fluoxetine had no statistically significant effect on Hamilton Depression,

or Hamilton Anxiety, scores in patients with EPQ or TPQ data.

Effect of fluoxetine on OAS-M aggression scores as a function of EPQ scores

EPQ scores did not differ as a function of drug/placebo assignment. Multiple regression analysis of OAS-M Aggression scores at endpoint as dependent variable and EPQ neuroticism, Psychoticism, and Extraversion as predictor variables revealed a significant result for the model [$F(4,33) = 3.23$, $P = 0.026$] with only EPQ neuroticism as the unique inverse correlate to endpoint OAS-M Aggression Scores ($\beta = -0.44$, $t = -2.81$, $P = 0.009$); Fig. 1.

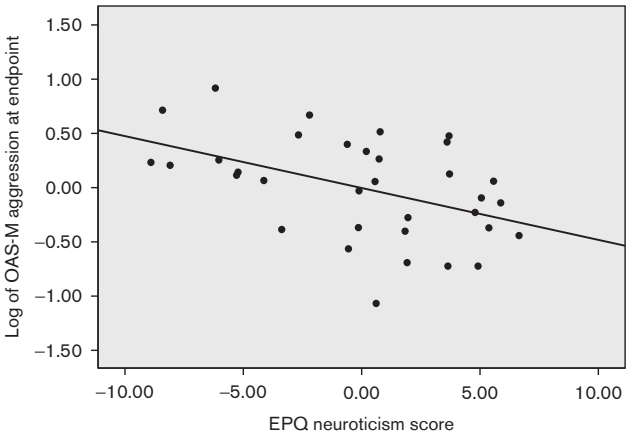
Effect of fluoxetine on OAS-M aggression scores as a function of TPQ scores

As with EPQ scores, TPQ scores did not differ as a function of drug/placebo assignment. A similar analysis of TPQ scales (Harm Avoidance, Novelty Seeking, and Reward Dependence) revealed a significant result for the model [$F(4,19) = 4.37$, $P = 0.011$] with only TPQ Harm Avoidance as the unique inverse correlate to endpoint OAS-M Aggression Scores ($\beta = -0.51$, $t = -2.95$, $P = 0.008$); Fig. 2. Placing both EPQ neuroticism and TPQ Harm Avoidance in the same model revealed a significant result for the model [$F(3,23) = 6.96$, $P = 0.002$]. However, neither EPQ neuroticism ($\beta = -0.35$, $t = -1.38$, $P = 0.182$) nor TPQ Harm Avoidance ($\beta = -0.28$, $t = -1.13$, $P = 0.273$) emerged as a unique inverse correlate to OAS-M Aggression scores at endpoint. This is likely because these two variables were highly correlated in these patients ($r = 0.65$, $n = 38$, $P < 0.001$).

Effect of placebo on OAS-M aggression scores as a function of EPQ and TPQ scores

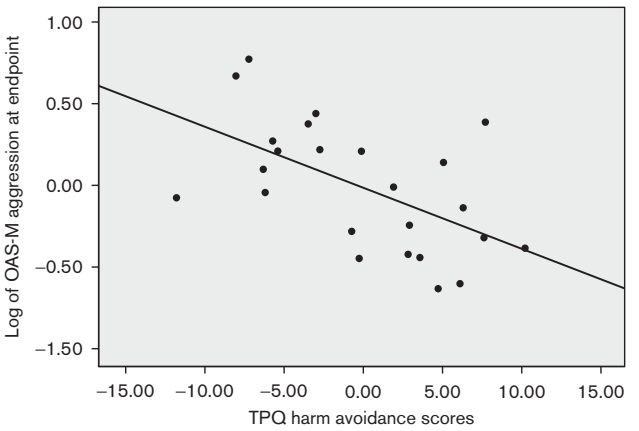
Similar multiple regression analysis of OAS-M Aggression scores in Placebo treated patients revealed no significant effect of EPQ or TPQ subscale scores, including neuroticism (e.g. $\beta = 0.22$, $t = 1.07$, $P = 0.298$) and TPQ Harm Avoidance (e.g. $\beta = 0.19$, $t = 0.70$, $P = 0.500$) on OAS-M Aggression scores in response to treatment with Placebo.

Fig. 1



Partial regression plot between Eysenck Personality Questionnaire (EPQ) neuroticism scores and Log of Overt Aggression Scale-Modified (OAS-M) aggression score at endpoint of trial in Intermittent Explosive Disorder (IED)-integrated research subjects treated with fluoxetine (partial $r = -0.46$, df = 29, $P = 0.009$).

Fig. 2



Partial regression plot between Tridimensional Personality Questionnaire (TPQ) harm avoidance scores and Log of Overt Aggression Scale-Modified (OAS-M) aggression score at endpoint of trial in Intermittent Explosive Disorder (IED)-IR subjects treated with fluoxetine (partial $r = -0.56$, df = 19, $P = 0.008$).

Discussion

In the context of a double-blind, RCT designed to evaluate the antiaggressive efficacy of the SSRI fluoxetine in a group of not depressed, personality-disordered, impulsive aggressive individuals, this study observed that neuroticism and Harm Avoidance were each inversely related to OAS-M Aggression scores at endpoint. Together, they contributed to predicting the antiaggressive response to fluoxetine in a way that was not unique to these measures specifically. The treatment relationship was specific for these two measures as it was not present for other remaining four personality domains on EPQ (Psychoticism and Extraversion) and TPQ (Novelty Seeking and Reward Dependence). In other words, higher levels of neuroticism and/or harm avoidance, prior to treatment, were associated with lower levels of aggression after treatment with fluoxetine. Moreover, the inverse correlation between pretreatment neuroticism and harm avoidance scores and endpoint aggression severity was observed only in patients treated with fluoxetine, and not in those treated with placebo. Importantly, baseline OAS-M Aggression scores were included as a covariate in all the multiple regression

analyses. To the best of our knowledge, these are the first findings from a RCT to suggest that temperamental factors such as neuroticism and harm avoidance can partly explain the observed variability in treatment response in SSRI-treated individuals with impulsive aggression. In addition, they add support to the utility of standardized, validated measures of personality dimensions as predictors of outcomes in clinical trials.

Prior findings on the effect of personality variables and personality disorder diagnosis or traits on SSRI treatment response in major depression have been mixed. Two reports (Newman *et al.*, 2000; Petersen, *et al.*, 2002) failed to observe a significant relationship between personality scores (neuroticism and harm avoidance, respectively) and improvement in depression after open-label SSRI treatment, whereas others showed that pretreatment reward dependence is related to antidepressant response (Joyce *et al.*, 1994; Nelson and Cloninger, 1995). Joffe *et al.*, (1993) found that *lower* harm avoidance was associated with better antidepressant treatment, an observation replicated in at least three other studies (Nelson and Cloninger, 1995; Strakowski, *et al.*, 1995; Abrams, *et al.*, 2004). Peselow *et al.* (1992) had noted that the presence of personality disorders or higher personality trait scores with depression was associated with poorer antidepressant desipramine treatment outcomes. In contrast, Fava *et al.* (1994) reported that depressed patients who had cluster B personality disorders achieved a better fluoxetine treatment response compared with those without this personality comorbidity. Taken together, these prior results do not fully explain the results observed in the current study.

Variables of temperament, particularly neuroticism and harm avoidance, may relate to depression and impulsive aggression in different ways. Neuroticism and harm avoidance are related to depression vulnerability (Duggan *et al.*, 1995) and symptomatology (Joffe, *et al.*, 1993; Strakowski, *et al.*, 1995; Farmer *et al.*, 2002). Interestingly, Tang *et al.* (2009) showed that SSRI treatment, unlike placebo, reduced levels of neuroticism and this change was independent of improvement in depression severity. Moreover, Quilty, *et al.* (2008, 2010) have shown that neuroticism and harm avoidance mediate antidepressant treatment response in patients with major depression, such that the treatment effect (reduction in depressive symptoms) occurred through a reduction of these temperament variables. In this context, it should be noted that patients with major depression were excluded from the current study and that Hamilton Depression scores in the patients included in these analyses were very low (Mean ± SD: 5.0 ± 3.5), suggesting only minimal depressive symptoms at study entry. In addition, fluoxetine had no effect on these low depression scores, while fluoxetine clearly had antiaggressive effects even after accounting for pretreatment depressive symptom severity (Coccaro, *et al.*, 2009). Further regression analyses, similar to those performed on EPQ and TPQ factor scores, did not reveal a significant association between pretreatment Hamilton Rating Scale for Depression scores and OAS-M Aggression scores at endpoint.

Recent pharmacogenetic studies raise intriguing possibilities that highly heritable temperament factors such as neuroticism and harm avoidance exert effects on SSRI actions through genetic mechanisms. For example, genetic variation in the functional serotonin transporter promoter polymorphism (5-HTTLPR) has been linked to NEO neuroticism and TPQ harm avoidance (Sen *et al.*, 2004). Others have observed similar findings with NEO neuroticism, but not with TPQ harm avoidance or EPQ neuroticism (Munafo *et al.*, 2009). Interestingly, 5-HTTLPR short alleles have also been linked to poorer SSRI treatment response in depression (Serretti *et al.*, 2007). A recent study also confirmed a similar pattern of 5-HTTLPR genotype and antiaggressive response to fluoxetine in personality disordered patients with impulsive aggression (Silva *et al.*, 2010). Moreover, neuroticism and harm avoidance appears to mediate the relationship between serotonin transporter gene variants in depression (Munafo *et al.*, 2006) and bipolar disorder (Mandelli *et al.*, 2009), respectively. Future studies are needed to clarify the role of genetic variation in 5-HTTLPR, negative emotionality temperaments, and SSRI treatment response in patients with impulsive aggression.

Several limitations exist which prompt some caution when interpreting these results. First, most of the enrolled patients in the clinical trial were men, so we cannot generalize across both genders. Second, we chose to exclude patients with current major depression, and the sample enrolled had very low levels of depression severity (similar to those in remission). Therefore, it remains unknown how the presence of more severe depressive symptoms at baseline and the reduction of depressive symptoms by treatment may affect the current findings. Finally, we did not obtain posttreatment EPQ or TPQ measures and cannot ascertain if fluoxetine, more so than inert placebo, would reduce neuroticism and/or harm avoidance as has been previously observed with SSRI antidepressant treatment (Tang *et al.*, 2009) or if the change in these variables would mediate antiaggressive SSRI response as previously observed in depression (Quilty *et al.*, 2008; 2010).

In summary, neuroticism and harm avoidance predicted antiaggressive response to fluoxetine, but not placebo, in impulsive aggressive individuals in the context of a large RCT demonstrating antiaggressive efficacy of the SSRI fluoxetine in a group of not depressed, personality-disordered, impulsive aggressive individuals. The link was observed independent of baseline levels of OAS-M Aggression and depression scores. These preliminary

findings are the first from a RCT to suggest that temperamental factors such as neuroticism and harm avoidance can partly explain the observe variability in treatment response in SSRI-treated individuals with impulsive aggression and prompt future prospective studies examining personality dimensions as predictors of outcomes in clinical trials.

Acknowledgements

Conflicts of interest

This project was supported in part by NIMH Grants R01MH47495, R01MH63262, K02MH00951 (EFC), K23MH076198 (KLP), and grant from the Eli Lilly Research Laboratories (EFC). Eli Lilly also provided the study drug and placebo. Dr Phan and Dr Lee report no competing interests.

References

Abrams KY, Yune SK, Kim SJ, Jeon HJ, Han SJ, Hwang J, Lyoo IK (2004). Trait and state aspects of harm avoidance and its implication for treatment in major depressive disorder, dysthymic disorder, and depressive personality disorder. *Psychiatry Clin Neurosci* **58**:240–248.

Cloninger CR, Przybeck TR, Svrakic DM (1991). The Tridimensional Personality Questionnaire: U.S. normative data. *Psychol Rep* **69 (3 Pt 1):**1047–1057.

Coccaro EF (2003). Intermittent Explosive Disorder. In: Coccaro EF, editor. *Aggression, Psychiatric Treatment and Assessment*. NY, NY: Marcel Dekker. pp. 149–166.

Coccaro EF (2011). Intermittent explosive disorder: development of integrated research criteria for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. *Compr Psychiatr* **52**:119–125.

Coccaro EF, Berman ME, Kavoussi RJ (1997). Assessment of life history of aggression: development and psychometric characteristics. *Psychiatry Res* **73**:147–157.

Coccaro EF, Schmidt CA, Samuels JF, Nestadt G (2004). Lifetime and 1-month prevalence rates of intermittent explosive disorder in a community sample. *J Clin Psychiatry* **65**:820–824.

Coccaro EF, Lee RJ, Kavoussi RJ (2009). A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *J Clin Psychiatry* **70**:653–662.

Coccaro EF, Lee R, Kavoussi RJ (2010a). Aggression, suicidality, and intermittent explosive disorder: serotonergic correlates in personality disorder and healthy control subjects. *Neuropsychopharmacology* **35**:435–444.

Coccaro EF, Lee R, Kavoussi RJ (2010b). Inverse relationship between numbers of 5-HT transporter binding sites and life history of aggression and intermittent explosive disorder. *J Psychiatr Res* **44**:137–142.

Diagnostic and Statistical Manual – Fourth Edition (DSM-IV) (1994).

Duggan C, Sham P, Lee A, Minne C, Murray R (1995). Neuroticism: a vulnerability marker for depression evidence from a family study. *J Affect Disord* **35**:139–143.

Eysenck HJ, Eysenck SBG (1975). *Manual of the Eysenck Personality Questionnaire*. Dunton Green, England: Hodder and Stoughton, Ltd.

Farmer A, Redman K, Harris T, Mahmood A, Sadler S, Pickering A, McGuffin P (2002). Neuroticism, extraversion, life events and depression. The Cardiff Depression Study. *Br J Psychiatry* **181**:118–122.

Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E (1993). Anger attacks in unipolar depression, part 1: clinical correlates and response to fluoxetine treatment. *Am J Psychiatry* **150**:1158–1163.

Fava M, Bouffides E, Pava JA, McCarthy MK, Steingard RJ, Rosenbaum JF (1994). Personality disorder comorbidity with major depression and response to fluoxetine treatment. *Psychother Psychosom* **62**:160–167.

Hansenne M, Pitchot W, Moreno AG, Reggers J, Machurot PY, Ansseau M (1997). Harm avoidance dimension of the Tridimensional Personality Questionnaire and serotonin-1A activity in depressed patients. *Biol Psychiatry* **42**:959–961.

Joffe RT, Bagby RM, Levitt AJ, Regan JJ, Parker JD (1993). The Tridimensional Personality Questionnaire in major depression. *Am J Psychiatry* **150**: 959–960.

Joyce PR, Mulder RT, Cloninger CR (1994). Temperament predicts clomipramine and desipramine responsedash; in major depression. *J Affect Disord* **30**:35–46.

Kessler RC, Coccaro EF, Fava M, Jaeger S, Jin R, Walters E (2006). The prevalence and correlates of DSM-IV intermittent explosive disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **63**:669–678.

Lara DR, Pinto O, Akiskal K, Akiskal HS (2006). Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: I. Clinical implications. *J Affect Disord* **94**:67–87.

Mandelli L, Mazza M, Martinotti G, Di Nicola M, Tavian D, Colombo E, Serretti A (2009). Harm avoidance moderates the influence of serotonin transporter gene variants on treatment outcome in bipolar patients. *J Affect Disord* **119**:205–209.

Munafo MR, Clark TG, Roberts KH, Johnstone EC (2006). Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. *Neuropsychobiology* **53**:1–8.

Munafo MR, Freimer NB, Ng W, Ophoff R, Veijola J, Miettunen J, Flint J (2009). 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am J Med Genet B Neuropsychiatr Genet* **150B**:271–281.

Nelson EC, Cloninger CR (1995). The tridimensional personality questionnaire as a predictor of response to nefazodone treatment of depression. *J Affect Disord* **35**:51–57.

Newman JR, Ewing SE, McColl RD, Borus JS, Nierenberg AA, Pava J, Fava M (2000). Tridimensional personality questionnaire and treatment response in major depressive disorder: a negative study. *J Affect Disord* **57**:241–247.

Olivier B (2004). Serotonin and aggression. *Ann N Y Acad Sci* **1036**:382–392.

Peselow ED, Fieve RR, DiFiglia C (1992). Personality traits and response to desipramine. *J Affect Disord* **24**:209–216.

Petersen T, Papakostas GI, Bottonari K, Iacoviello B, Alpert JE, Fava M, Nierenberg AA (2002). NEO-FFI factor scores as predictors of clinical response to fluoxetine in depressed outpatients. *Psychiatry Res* **109**:9–16.

Quilty LC, Meusel LA, Bagby RM (2008). Neuroticism as a mediator of treatment response to SSRIs in major depressive disorder. *J Affect Disord* **111**:67–73.

Quilty LC, Godfrey KM, Kennedy SH, Bagby RM (2010). Harm avoidance as a mediator of treatment response to antidepressant treatment of patients with major depression. *Psychother Psychosom* **79**:116–122.

Reist C, Nakamura K, Sagart E, Sokolski KN, Fujimoto KA (2003). Impulsive aggressive behavior: open-label treatment with citalopram. *J Clin Psychiatry* **64**:81–85.

Salzman C, Wolfson AN, Schatzberg A, Looper J, Henke R, Albanese M, Miyawaki E (1995). Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmacol* **15**:23–29.

Sen S, Villafuerte S, Nesse R, Stoltenberg SF, Hopcian J, Gleiberman L, Burmeister M (2004). Serotonin transporter and GABAA alpha 6 receptor variants are associated with neuroticism. *Biol Psychiatry* **55**:244–249.

Serretti A, Kato M, De Ronchi D, Kinoshita T (2007). Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry* **12**:247–257.

Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jimenez M, Bustamante ML (2010). Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. *Psychiatr Genet* **20**:25–30.

Strakowski SM, Dunayevich E, Keck PE Jr., McElroy SL (1995). Affective state dependence of the Tridimensional Personality Questionnaire. *Psychiatry Res* **57**:209–214.

Takano A, Arakawa R, Hayashi M, Takahashi H, Ito H, Suhara T (2007). Relationship between neuroticism personality trait and serotonin transporter binding. *Biol Psychiatry* **62**:588–592.

Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B (2009). Personality change during depression treatment: a placebo-controlled trial. *Arch Gen Psychiatry* **66**:1322–1330.