2006

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Recommended Citation

Joyce, Peter R.; McHugh, Patrick C.; McKenzie, Janice M.; Sullivan, Patrick F.; Mulder, Roger T.; Luty, Suzanne E.; Carter, Janet D.; Frampton, Christopher M.; and Cloninger, C. R., "A dopamine transporter polymorphism is a risk factor for borderline personality disorder in depressed patients." Psychological Medicine. 36, 6. 807-813. (2006).
https://digitalcommons.wustl.edu/open_access_pubs/3870

Psychological Medicine, 2006, **36**, 807–813. © 2006 Cambridge University Press
doi:10.1017/S0033291706007288 First published online 20 April 2006 Printed in the United Kingdom

A dopamine transporter polymorphism is a risk factor for borderline personality disorder in depressed patients

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ABSTRACT

Background. Borderline personality disorder (BPD) is often co-morbid with major depression and may complicate its treatment. We were interested in differences in genetic and developmental risk factors between depressed patients with or without a co-morbid BPD.

Method. Out-patients with major depressive disorder were recruited for two treatment trials. Assessment of depressed patients included the assessment of personality disorders, developmental risk factors and DNA samples for genetic analyses.

Results. In each study there was a significant association between the 9-repeat allele of the dopamine transporter (DAT1) and BPD, with odds ratios (OR) >3 and $p \leqslant 0{\cdot}02$. This association remained significant when developmental risk factors for BPD (childhood abuse and neglect and borderline temperament) were also included in the analyses. The OR was even larger in the depressed patients aged $\geqslant 35$ years (OR 9·31, $p = 0{\cdot}005$).

Conclusion. This replicated association in depressed patients between the 9-repeat allele of DAT1 and BPD may provide clues to understanding the neurobiology of BPD. The finding that the association is larger in the older depressed patients, suggests that the 9-repeat allele may be associated with a poorer prognosis BPD, rather than a young adult limited variant of BPD.

INTRODUCTION

Borderline personality disorder (BPD) is a severe disorder of personality characterized by a pervasive and pathological pattern of affective instability, intense and unstable close relationships, instability of self-image, feelings of abandonment and boredom, and a range of impulsive behaviours including repeated suicide attempts and self-mutilation. Due to the intensity of emotions and the range of impulsive behaviours, patients with the disorder are often seen as among the most challenging to treat. In most instances, BPD is usually co-morbid with other mental disorders, especially mood and anxiety disorders and substance abuse (Hyman, 2002; Skodol *et al.* 2002*a*). There is no satisfactory neurobiological model of BPD, but there are suggestions that abnormalities of impulsive aggression reflect abnormalities of reduced serotonergic function, that affective instability may reflect increased responsivity of cholinergic

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systems (Skodol *et al.* 2002*b*), although there are grounds for implicating dopamine dysfunction in emotional dysregulation, impulsivity and cognitive-perceptual impairment (Friedel, 2004). Furthermore, traits such as high novelty-seeking which are associated with BPD may reflect altered dopaminergic function (Cloninger, 2000). The high co-morbidity of BPD with substance abuse also suggests that abnormalities of dopaminergic reward pathways could be implicated in both disorders (Ebstein *et al.* 2000).

The dopamine transporter gene *SLC6A3* (DAT1) contains 15 exons, is localized to chromosome 5p15.3 and is a member of the large Na^+/Cl^- dependent family of transporters (Vandenbergh *et al.* 1992; Giros *et al.* 1996). DAT1 functions to rapidly re-uptake dopamine from the synaptic cleft into the pre-synaptic terminals and thus acts as a key component in regulating dopaminergic neurotransmission (Kelsoe *et al.* 1996). Inactivation of the DAT1 gene in mice led to a prolonged persistence of dopamine in the extracellular space (Giros *et al.* 1996).

Genetic variation in *SLC6A3* may affect the expression of DAT1, impacting on the functioning of CNS dopaminergic systems. A 40-bp polymorphic variable number tandem repeats (VNTR) is present in the 3′ untranslated region of the gene and can vary from 3 to 12 repeatsDoucette-Stamm *et al.* 1995; Gelernter *et al.* 1998). Genetic association studies have inconsistently linked the 9-repeat allele to attention deficit hyperactivity disorder (ADHD) (Cook *et al.* 1995; Gill *et al.* 1997; Daly *et al.* 1999; Madras *et al.* 2005), the severity of alcohol withdrawal in alcohol-dependent subjects (Sander *et al.* 1997; Schmidt *et al.* 1998; Heinz *et al.* 2004), and to prolonged psychosis following stimulant withdrawal (Ujike *et al.* 2003). There is currently no consensus on how the 9- and 10-repeat alleles may affect the expression of *SLC6A3*. Due to the untranslated nature of the VNTR it cannot affect the structure and function of DAT1, but may be involved in the regulation of the gene (Bannon *et al.* 2001; Mill *et al.* 2002).

In a first-depression treatment study (Joyce *et al.* 2002) in which we had particular interests in the impact of personality and personality disorders on treatment outcome (Joyce *et al.* 2003*a*, 2004; Mulder *et al.* 2003), and while undertaking analyses on the association between genetic polymorphisms and personality (Sullivan *et al.* 1997; Joyce *et al.* 2003*b*; Roberts *et al.* 2004), we observed a significant relationship between the 9-repeat allele of DAT1 and BPD. As this association was found in exploratory analyses and as we were undertaking another depression treatment study, we attempted to replicate the initial finding. We also decided to explore how other risk factors for BPD, such as childhood abuse and neglect and temperament influenced any possible association of DAT1 with BDP.

METHOD AND SUBJECTS

Subjects and assessment

For both out-patient depression treatment studies we recruited patients, aged $\geqslant$18 years, with a principal current diagnosis of major depression. Exclusion criteria were minimized but included a history of schizophrenia or mania (a history of hypomania was allowed), a principal current diagnosis of severe alcohol or drug dependence, or severe current medical illness. In addition, patients needed to be free of psychotropic medication for a minimum of 2 weeks, or five drug half-lives, except for an occasional hypnotic for sleep. Patients also could not have received in the past 12 months an adequate treatment trial of one of the trial treatments to which they could be randomized. In the first depression treatment trial, patients were randomized to fluoxetine or nortriptyline (Joyce *et al.* 2002); and in the second trial they were randomized to interpersonal psychotherapy or cognitive behaviour therapy (Joyce *et al.* unpublished observations; Luty *et al.* unpublished observations). The two trials ran sequentially, in the same university-based out-patient Clinical Research Unit, and were the only depression treatment studies being undertaken in the Department at the time. Both treatment studies had been approved by the Canterbury (New Zealand) Ethics Committee. After explanation of the studies all patients provided written informed consent.

Assessment included the Structured Clinical Interview for DSM (SCID; Spitzer *et al.* 1992), which had been expanded to include assessment of all DSM-III-R and DSM-IV melancholic and atypical depression symptoms. Approximately

6 weeks after commencing treatment a trained psychiatrist or clinical psychologist completed the Structured Clinical Interview for Axis II Personality Disorders (SCID-II; Spitzer *et al.* 1987).

During the baseline assessment patients completed a series of self-report questionnaires, including the Parental Bonding Instrument (PBI; Parker *et al.* 1979) and the Temperament and Character Inventory (TCI; Svrakic *et al.* 1993). Patients were also interviewed by a research nurse who systematically enquired about childhood (prior to 16 years) physical, emotional and sexual abuse. DNA was also collected for genetic studies.

Genotyping

Our method for DAT1 genotyping was based on the polymerase chain reaction method of Vandenbergh *et al.* (1992) but with modifications as previously described (Sullivan *et al.* 1997).

Data analysis

All data were entered into a relational database and later transferred to the statistical package SYSTAT for statistical analysis (Systat Inc., 1990). The principal statistical approach was logistic regression. When the association of multiple risk variables with BPD was being analysed, multiple logistic regression was used. In the multiple logistic regression analyses we also examined for gene × environment interaction effects.

For the purposes of this study, childhood neglect was calculated by averaging the maternal and paternal care scales of the PBI. Scores were then divided into quartiles, so that the absence of childhood neglect (score of zero) indicated that a patient reported maternal and paternal care scores in the top quartile. A rating of severe neglect (score of 3) indicated that a patient had reported maternal and paternal care scores in the bottom quartile.

The childhood abuse score was based upon the assessment of both the type and frequency of childhood abuse experiences. A score of zero means that an individual reported no childhood abuse experiences. A score of 3 (severe abuse) represents repeated childhood physical and/or sexual abuse. Scores of 1 or 2 indicate either lesser severity (e.g. sexual touching, but not intercourse) and/or lesser frequency (e.g. one episode of sexual abuse).

The combined childhood abuse plus neglect variable was determined by adding the childhood abuse plus the childhood neglect scores (possible totals were 0–6). The combined variable was assigned a score of zero when the calculated score was zero; the combined variable was assigned a score of 1 when the calculated score was 1 or 2; the combined variable was assigned a score of 2 when the calculated score was 3–5; and the combined variable was assigned a score of 3 when the calculated score was 6. Thus, a childhood abuse plus neglect score of zero implies the patient reported no childhood abuse experiences and rated their parents in the top quartile for care and warmth. A score of 3 implies the patient was in the bottom quartile for care and warmth and reported severe repeated childhood abuse.

Borderline temperament was a quartile score based on the novelty-seeking score multiplied by the harm-avoidance score (reflecting approach-avoidance conflict). The two temperament measures were assessed by self-report on the TCI at the time of entry into the studies.

RESULTS

Table 1 shows the allele and gene frequency for DAT1, the prevalence of BPD and the association of a 9-repeat polymorphism with BPD in each of the two samples. While the association [odds ratio (OR) 3·07, $p = 0{\cdot}018$] in the first sample was found while undertaking exploratory analyses and, therefore, could be ascribed to chance, the association is remarkably similar in the second independent sample (OR 3·15, $p = 0{\cdot}020$). If both studies are combined the OR remains > 3 but the p value is $< 0{\cdot}001$.

Other recognized risk factors for BPD include childhood abuse and neglect (Zanarini *et al.* 1997), a borderline temperament (Svrakic *et al.* 1993; Joyce *et al.* 2003*a*), and a younger age (Zanarini *et al.* 2003). Table 2, in which the separate samples have been combined, shows the significant univariate associations of BPD with age, DAT1 polymorphism, childhood neglect, childhood abuse, a combined variable called childhood abuse and neglect, and borderline temperament.

Table 1. *The frequency of dopamine transporter polymorphisms, the prevalence of BPD, and the association (odds ratio) of a 9-repeat polymorphism with BPD in two independent depressed samples*

	Sample 1	Sample 2
n	157	178
Age (yr)	32·3 (±11·6)	35·5 (±10·1)
% Female	57·0	70·0
DAT1 allele frequency		
% 9-repeat	22·6	24·7
% 10-repeat	76·4	74·7
% 11- or 12-repeat	1·0	0·6
DAT1 genotype frequency		
9-repeat homozygote	5·1%	7·3%
9-repeat heterozygote	35·0%	34·8%
No 9-repeat allele	59·9%	57·9%
% BPD	14·0	11·8
OR (95% CI) [*p*]	3·07 (1·20–7·84) [0·018]	3·15 (1·20–8·24) [0·020]

BPD, Borderline personality disorder; OR, odds ratio; CI, confidence interval.

Table 2. *Univariate associations of age, dopamine transporter polymorphism, childhood experiences and borderline temperament with BPD in the combined depressed samples*

	n	% BPD	OR (95% CI)	*p*
Age group				
<35 years	182	16·5	0·47 (0·24–0·94)	0·032
⩾35 years	153	8·5		
Dopamine transporter				
9-repeat absent	197	7·6	3·09 (1·58–6·04)	0·001
9-repeat present	138	20·3		
Childhood neglect				
Absent	84	4·8	1·55 (1·14–2·12)	0·006
Mild	83	12·0		
Moderate	83	13·3		
Severe	85	21·2		
Childhood abuse				
Absent	157	7·6	1·54 (1·15–2·06)	0·003
Mild	64	17·2		
Moderate	76	11·8		
Severe	38	28·9		
Childhood abuse plus neglect				
Absent	54	3·7	2·62 (1·66–4·13)	<0·001
Mild	122	6·6		
Moderate	138	18·8		
Severe	21	33·0		
Borderline temperament				
Very low	74	2·7	1·84 (1·31–2·57)	<0·001
Low	90	7·8		
High	91	16·5		
Very high	79	21·5		

BPD, Borderline personality disorder; OR, odds ratio; CI, confidence interval.

Table 3. *Results from a multiple logistic regression predicting BPD from a combination of risk factors*

	Adjusted OR	95% CI	*p*
9-repeat allele	3·10	(1·51–6·35)	0·002
Childhood abuse plus neglect	2·64	(1·62–4·29)	<0·001
Borderline temperament	1·66	(1·14–1·07)	0·008
Age group	0·49	(0·22–1·07)	0·074

BPD, Borderline personality disorder; OR, odds ratio; CI, confidence interval.

As the combined variable of childhood abuse plus neglect was the strongest predictor of BPD in univariate analyses, this variable along with borderline temperament, age and the 9-repeat allele of DAT were entered into a multiple logistic regression. Table 3 shows that the adjusted OR for the 9-repeat allele was 3·10 ($p=0·002$), and that childhood abuse plus neglect and borderline temperament and age were all significant independent predictors for the presence of BPD. No significant interaction terms were found.

To demonstrate the effects of the three major risk factors on the prevalence of BPD in the combined depressed sample, the childhood abuse plus neglect and borderline temperament variables were collapsed into dichotomized variables. Fig. 1 shows that the likelihood of BPD is increased by the presence of the 9-repeat allele across all combinations of temperamental and childhood risk factors.

As BPD often remits with age, often during the fourth decade (Zanarini *et al.* 2003), we examined the association of the 9-repeat polymorphism with BPD as a function of age. In those aged <35 years the adjusted OR for the 9-repeat allele was only 2·03 ($p=0·098$), while childhood abuse plus neglect remained the strongest risk factor. However, in those aged ⩾35 years the adjusted OR for the 9-repeat allele increased to 9·18 ($p=0·007$) and was the strongest risk factor. The adjusted OR of >9 in the older depressed patients was also consistent across samples.

Across samples only 21 (6·2%) were homozygous for the 9-repeat allele, and of these 23·8% had BPD; in those with just one copy of the 9-repeat allele the prevalence of BPD was similar at 19·7%. Both these rates of BPD are

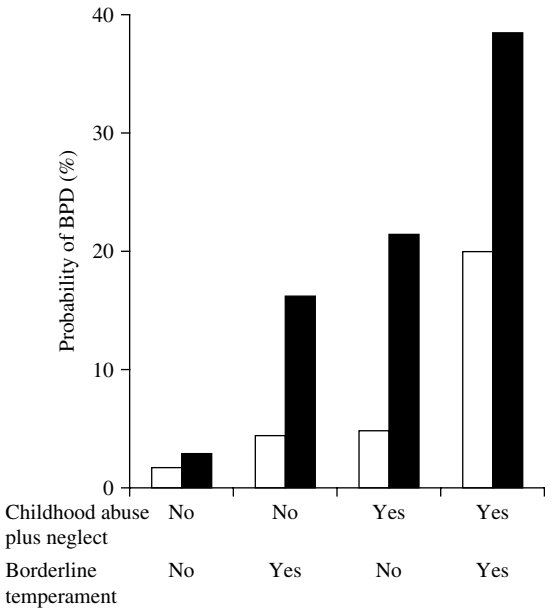

FIG. 1. The probability of borderline personality disorder (BPD) in relationship to different combinations of the dopamine transporter polymorphism, childhood abuse plus neglect and borderline temperament. □, 9-repeat absent; ■, 9-repeat present.

higher than the 7·6% in those without a 9-repeat allele. In both samples more than 95% are caucasians. For residents of Christchurch, New Zealand the vast majority of ancestors came from the United Kingdom. Excluding the few non-caucasians from the sample does not alter the findings.

DISCUSSION

In this paper we have presented a replicated association between the presence of a 9-repeat allele of DAT1 and BPD in two independently recruited depressed out-patient samples. We have also shown that this association remains significant when other potential developmental risk factors for BPD, such as childhood abuse plus neglect and borderline temperament, and age are included in multiple logistic regression. Furthermore, the association is stronger in the older depressed patients, when BPD is less common. This last finding raises the possibility that the 9-repeat allele is associated with a more persistent BPD, rather than a young adult limited variant.

A persistent difficulty in psychiatric genetics has been in the meaning of replication. In our view, it is compelling that we found essentially identical ORs and confidence intervals in two independent clinical samples. From a probabilistic perspective, a significant finding in only one sample may well be a false positive; significant findings in two consecutive samples decrease the probability of a false positive considerably. Critically, the magnitude of this decrease depends on the prior probability of association before the second sample was analysed. Using the approach described by Wacholder *et al.* (2004), the cut-off for the noteworthiness of the association in our second sample is a prior probability of $\sim 0{\cdot}04$. In other words, if the combination of the accumulated literature of the importance of DAT1*9 plus the empirical finding in our first sample increased the prior probability to $p \geqslant 0{\cdot}04$, then the second sample finding would have a false-positive report probability of under 50% (i.e. 'the preponderance of evidence'). Therefore, taken together, our findings suggest (but certainly do not prove) the importance of the association of DAT1*9 and BPD.

One potential limitation of these findings is that the association has been found in clinical samples of depressed patients. In the community, the prevalence of BPD is about 1–2%, but in out-patient samples it is often 10–15% (Hyman, 2002). Mood disorders increase the risk of BPD. Any depression sample is thus an 'enriched' sample, and it is possible that our findings in two depressed samples, may not extend to the minority of BPD patients who do not suffer from depression. It is also of note, that while the population prevalence of BPD is only 1–2%, approximately 40% of the population have a 9-repeat DAT1 allele. Even in our 'enriched' depression samples the prevalence of BPD in those with a 9-repeat allele is only 2·9% in the absence of measured developmental risk factors. It could perhaps be argued that the absence of the 9-repeat allele is protective against the development of BPD when there are other developmental risk factors.

The finding that the 9-repeat allele of DAT1 is a risk factor for BPD supports a dopamine dysfunction hypothesis of borderline personality disorder (Friedel, 2004). Such a possibility is consistent with the tendency for BPD patients

to have brief psychotic episodes when under stress, and the possible role of antipsychotic drugs in the management of some BPD patients (Oldham *et al*. 2001). Animal research suggests that repeated exposure to social stress has long-term effects on dopamine transporter density (Lucas *et al*. 2004) and that DAT1 knock-out mice demonstrate abnormalities of social interaction secondary to a behavioural inflexibility (Rodriguiz *et al*. 2004). These animal findings involving behavioural effects related to DAT1, plus our finding that a polymorphism of DAT1 is a risk factor, suggest new avenues for research into the neurobiology of BPD.

ACKNOWLEDGEMENTS

This research was funded by the Health Research Council of New Zealand. We thank Robyn Abbott and Isobel Stevens for their contributions to patient care and data management.

DECLARATION OF INTEREST

None.

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